# "Some Model Studies for Vitamin $B_{12}$ Dependent Enzymic Reactions."

by

Martin Philip Atkins

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy from the University of Warwick, Department of Chemistry and Molecular Sciences.

## ABSTRACT

Vitamin $B_{12}$ catalyses a variety of important reaction in metabolic pathways. Impairment of vitamin $B_{12}$ by man leads to deficiency diseases e.g. pernicious anaemia. Many mechanistic possibilities have been suggested to account for the transformation of organic substrates to products in these enzymic reactions ranging from purely protein mediated reactions to the existence of discrete ionic or radical intermediates. A crucial point in these rearrangements is the possibility of discrete organocorrin intermediates. To investigate this possibility and to investigate reactions of alkyl groups attached to cobalt a series of alkylcobaloximes were studied. Cobaloximes were used as models for Vitamin $B_{12}$ on account of their similarity, relative ease of synthesis, and easily interpretable spectroscopic data.

The work described in this thesis explores reactions of substituted cyclopropylmethyl- and but-3-enyl- groups attached to cobalt. By use of $^{13}C$ labelling experiments and kinetic studies on the rearrangement of cyclopropylmethyl- to but-3-enylcobaloxime the mechanism of this rearrangement has been postulated to be a unimolecular reaction involving a homoallylic transition state. 1-Methylbut-3-enylcobaloxime was found to equilibrate with the 2-methylbut-3-enyl isomer, the reaction presumably proceeding through the intermediacy of methylcyclopropylmethylcobaloximes. Both cis- and trans-isomers of the postulated 2-methylcyclopropylmethyl-intermediate were synthesised and it was shown by suitable kinetic study that the cyclopropanes were, indeed, plausible intermediates. (R)- and (S)-1-methylbut-3-enylcobaloximes were found to equilibrate stereospecifically with (S)- and (R)-2-methylbut-3-enylcobaloximes, respectively, under catalysis by TFA - and demonstrates the first stereospecific

transformation of an organic ligand attached to a metal atom.

Reactions of alkyl(pyridine)cobaloximes with TFA were explored and were shown to exhibit a general trend. TFA first protonates a dimethylglyoximato ligand and a subsequent molecule removes coordinated pyridine as pyridinium trifluoroacetate. Excess of TFA causes the eventual precipitation of a red crystalline complex characterised as a novel cis-cobaloxime by single crystal X-ray diffraction study.

## ACKNOWLEDGMENT

I would like to thank all members of the department of chemistry and molecular sciences for their help and encouragement during my stay here. In particular, thanks to my supervisor Dr. B.T. Golding, for his enthusiasm, optimism and friendship throughout my stay; and to Dr. P. J. Sellars for his time, many fruitful discussions, and friendship.

I should also like to thank my wife for her understanding and for tolerating the author during the preparation of this thesis.

A special thankyou to Mrs. K. Burton, for producing the typescript for this thesis and her family who were deprived of her presence for many a long hour, during its preparation.

A Postgraduate studentship from the S.R.C. is gratefully acknowledged.

CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| b.p. | Boiling point |
| C.D. | Circular Dichroism |
| c.m. | Centimetre |
| DMG | Dimethylglyoxime |
| e.s.r. | Electron spin resonance |
| g | Gram |
| g.l.c. (G.L.C.) | Gas liquid chromatography |
| I.R. | Infra red |
| J | Joule |
| Mol | Mole |
| mg | Milligram |
| MHz | Mega Hertz |
| ml | Milli litre |
| mmol | Milli mole |
| mp | Melting point |
| MS | Mass spectra |
| nm | Nanometre |
| n.m.r. | Nuclear magnetic resonance |
| T.L.C. | Thin layer chromatography |
| U.V. | Ultra-violet |
| $\delta$ | Chemical Shift |
| $\xi$ | Extinction Coefficient |
| $\lambda$ | Wave length |

Publications submitted, based on work described in this thesis :

1. "Rearrangements of Cyclopropylmethyl- and But-3-enylcobaloximes". M.P.Atkins, B.T.Golding and P.J.Sellars, J.C.S. Chem. Comm., 1978, 954.

2. "Models for Cobalamin-dependent Enzymatic Reactions", M.P.Atkins, B.T. Golding, C.S.Sell and P.J.Sellars; Lecture presented at Autumn Meeting of the Chemical Society held at University of Warwick, Sept. 1978.

3. "Model Systems for Adenosylcobalamin Dependent Enzymatic Reactions", M.P.Atkins, B.T.Golding and P.J.Sellars, Third European Symposium on Vitamin $B_{12}$ , Zurich, March 1979.

4. "Mechanistic Studies using $^{13}C$-Labels", M.P.Atkins, D.C.Billington, B.T.Golding, M.D.Johnson, I.K.Nassereddin and P.J.Sellars; Paper presented at "Symposium on Stable Isotopes", University of Warwick, Sept. 1979.

5. "$^{3}\eta$ -Homoallylcobalt Complexes in the Intramolecular Rearrangements of But-3-enylcobaloximes", M.P.Atkins, B.T.Golding, M.D.Johnson and P.J. Sellars, J.Am.Chem.Soc., 1980, 102, 3630.

6. "2,6,7-trioxabicyclo- 2.2.2. -octane : Application to the Synthesis of Alkylcobaloximes containing Ester and Carboxyl Groups", M.P.Atkins, B.T. Golding, D.A.Howes and P.J.Sellars, J.C.S. Chem.Comm., 1980, 207.

7. "Some Syntheses of Cobaloximes", M.R.Ashcroft, M.P.Atkins, B.T.Golding, M.D.Johnson and P.J.Sellars; J.Inorg. and Nuc.Chem., submitted for publication.

cont.

8. "A mononuclear cis-Cobaloxime : Di-trifluoroacetoxy bis-(butane-2,3-dionedioxime)cobalt(II)", N.W.Alcock, M.P.Atkins, E.H.Curzon, B.T. Golding and P.J.Sellars, J.C.S. Chem.Comm., submitted for publication.

To Mum, Dad and Lauren

Let me but live my life from year to year
With forward face and unreluctant soul;
Not hurrying to, nor turning from the goal;
Nor mourning for things that disappear
In the dim past, nor holding back in fear
From what the future veils; but with a whole
And happy heart, that pays it's toll
To youth and age, and travels on with cheer.
So let the way be up the hill or down
O'er rough or smooth, the journey will be joy;
Still seeking what I sought when but a boy -
New friendship, high endeavor and a crown.
My heart will keep the courage of the quest
And hope the road's last turn will be the best.

Henry Van Dyke.

Let me but live my life from year to year
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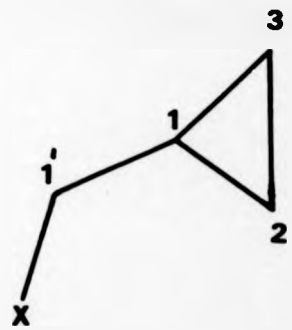
The Numbering System Used Throughout This Thesis for the Cyclopropylmethyl- System




X = Substituent e.g. OH, Br, Co

# Chapter 1 : Introduction

## 1:1 (A) NOMENCLATURE[1]

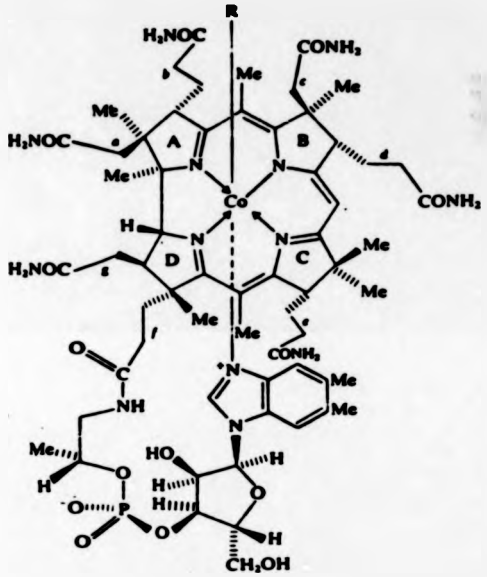
Vitamin $B_{12}$ (cyanocobalamin; fig.1 (a)) is an example of a corrinoid. All corrinoids posses four reduced pyrrole rings joined by links between their α positions into the macrocyclic ring system shown in fig.2. Three of these links are formed by one-carbon units and the other by a direct Cα-Cα' bond. The numbering of the carbon and nitrogen atoms in fig.2 corresponds to that in the porphyrin nucleus, except that corrin lacks C-20 of the latter.

The carboxyl side chains (or derived amides) in corrinoids are assigned letters a,b,c....g as in fig.1. The principal corrinoids (Table 1) are given names based on the prefix cob, which denotes the presence of cobalt. The axial coordination sites of cobalt are labelled α (lower) and β (upper). Since cobalamins, by definition, contain 5,6-dimethylbenzimidazole in the α-position, a convenient shorthand notation is X-Cbl, where X is the ligand in the β-position and Cbl is the remaining cobalamin portion. Examples are given in Table 2.

It is sometimes necessary to specify the formal oxidation state of cobalt e.g. cob(I)alamin ($Cbl^{1}$)(formerly called $B_{12s}$), cob(II)alamin (formerly $B_{12r}$) and cob(III)alamin (e.g. hydroxocobalamin, formerly $B_{12a}$). Modification of an amide function is denoted by adding a specification of the alteration and its position to the basic name of the corrinoid e.g. hydrolysing the d-amide group of CN-Cbl gives a,b,c,e,g,-penta-amide-d-carboxylic acid (abbreviated as CN-Cbl-(d-OH)).

Apart from the above abbreviation, the following representations are often used to designate the "base-on" (fig.3a) and "base-off"

**Figure 1. Structures of Isolated Cobalamins.**




1(a) R = CN

1(b) R = OH

1(c) R = Adenosyl

1(d) R = Me

Adenosyl =

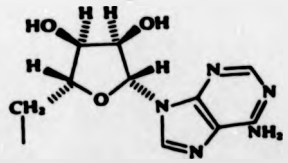


Figure 2. Structure of the Corrin Nucleus

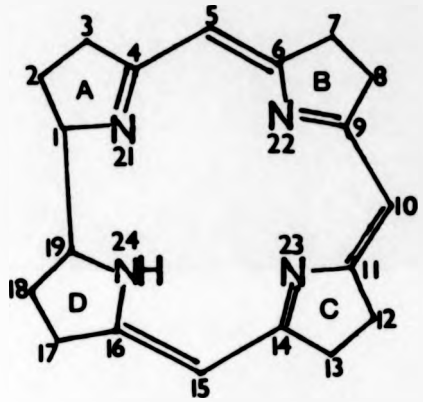



Figure 3a "Base-on" Cobalamin


Figure 3b "Base-off" Cobalamin

**Table 1. Principal Corrinoids.**

| Corrinoid | Abbreviation | Side-chains[a] a-e, g | f[b] |
|---|---|---|---|
| Cobyrinic | — | $CO_2H$ | $CO_2H$ |
| Cobinic acid | — | $CO_2H$ | $CONHCH_2CH(OH)Me$ |
| Cobamic acid | — | $CO_2H$ | $CONHCH_2CH(OR^1)Me$ |
| Cobyric acid | Cby | $CONH_2$ | $CO_2H$ |
| Cobinamide | Cbi | $CONH_2$ | $CONHCH_2CH(OH)Me$ |
| Cobamide | Cba | $CONH_2$ | $CONHCH_2CH(OR^2)Me$ |
| Cobalamin | Cbl | $CONH_2$ | $CONHCH_2CH(OR^3)Me$ |

[a] cf. formula shown in figure 1.

[b] $R^1$ = α-D-ribofuranose-3-phosphoryl; $R^2$ = $R^1$ + base joined to α-glycosidic bond; $R^3$ = $R^1$ + 5,6-dimethylbenzimidazole joined to α-glycosidic bond.

**Table 2. Abbreviations for Some Common Corrinoids.**

| Name | Abbreviation |
|---|---|
| Cyanocobalamin (vitamin $B_{12}$) | = CN-Cbl (figure 1a) |
| Aquocobalamin (vitamin $B_{12a}$) | = OH-Cbl (figure 1b) |
| Hydroxocobalamin (vitamin $B_{12b}$) | |
| Adenosylcobalamin | = AdoCbl (figure 1c) |
| Methylcobalamin | = MeCbl (figure 1d) |
| (Cyano)methylcobinamide | = (CN)MeCbi |
| $Co^{\alpha}$-(5-Methoxybenzimidazolyl)-$Co^{\beta}$-cyanocobamide | = (5-MeOBza)CN-Cba |

(fig.3b) forms of cobalamins.

I: 1(b) HISTORICAL

Cyanocobalamin was first isolated in 1948 by two groups of workers, the Glaxo Company (Smith, Parker and co-workers)[2] and Merck Laboratories (Folkers and co-workers)[3]. Cyanocobalamin is an artefact of the isolation procedure and the corrinoid present in animal tissue is almost exclusively adenosylcobalamin, AdoCbl (fig.1(c)). Cobalamins are the only vitamins which are known to contain a metal. They are also the largest of the vitamins and require a special mechanism for absorption into the body from the gut. Cobalamins are required by humans and animals to perform necessary catalytic roles in metabolism, but cannot be synthesized by mammals and therefore become a dietary inclusion. Thus, any defects by the animal in absorption leads to a deficiency disease. The most widely known example of this is the disease pernicious anaemia - a disease which was first described in 1821 and until 1926 had no known cure. The disease was characterised by loss of energy, weakness, shortness of breath, palpitation and anaemia. The level of normal red blood cells is reduced as is the haemoglobin content, and a varying number of occluded (megoblastic) red blood cells are apparent. The number of white cells in the blood is often reduced.

Early in the twentieth century pioneering work by Eijkmann on beri-beri gave credence to the thought that traces of accessary dietary factors (termed "vitamins" by Casimir Funk in 1913) might cause human disease under restricted dietary conditions - hence the phrase "good food makes good blood".

Whipple[5] studied the ability of various additions to a basal dietary regime to enhance haemoglobin formation in chronically bled dogs, and concluded that raw beef liver was most efficient. Encouraged by this report, Minot and Murphy set out clinical trials for pernicious anaemia patients to include raw liver (120-240g.daily) in their diets and confirmed[6] consistent clinical improvement and gain in red blood cell levels in 45 patients.

Work to isolate the anti-pernicious anaemia (APA) factor began with the early fractionating procedures of Cohn and his associates[7] which led to an extract, Liver Extract 343 (Lilly) being placed on clinical trials. Extract 343 conserved the haematopoietic activity of 300g. of beef liver in a daily oral dose of 12.75g.

Improvements to the fractionation procedures were gradually made by a number of contributors (Gansslen, Dabin, LaLand and Klem) all aiming at further purification of the APA factor. In 1946 Emery and Parker[8] reported a complete haematological remission from a single injection of 1mg in their material. Later, in 1948, West[9] demonstrated the clinical activity of cyanocobalamin in pernicious anaemia patients. This material had been supplied by Merck Laboratories in the United States (Karl Folkers and co-workers)[10] and had been independently isolated by the Glaxo Company in England (Smith and Parker)[11].

The reasons why cyanocobalamin had not been isolated in the pure state for some 22 years after initial studies, were many. Losses during fractionation were so great that vast quantities of starting materials e.g. tons of liver, were required as well as the bulk processing

facilities only large industrial concerns employed. Pre-occupation with the idea that pernicious anaemia was a unique human disease limited testing of fractions to suitable patients and inhibited the search for methods of assay analysis involving micro-organisms or laboratory animals, until almost the end of the $B_{12}$ isolation period. The classical methods (mainly solvent extraction) of fractionating water-soluble substances[12] were inadequate and only with the development of adsorption and partition chromatography could efficient separations be effected[13]. The later stages of Folkers' contributions were aided by the development of a microbial assay for cobalamins, which enabled their detection in beef extract, powdered milk and microbial broths. This finding led to an influx of activity into the potential commercial production of cobalamin by microbial fermentation processes (reviews by Perlman[14] and Mervyn and Smith[15]).

Following the isolation of cyanocobalamin the task of elucidating its structure began. Two complementary approaches were used.

Degradative studies carried out by the groups of Folkers, Smith Petrow and Todd (reviewed by Folkers and Wolf[16], Smith[17], Johnson and Todd[18], and Barnett[19]), identified the nucleotide portion of the molecule, hinted at the nature of the corrin nucleus, and provided evidence for the structure on the periphery of the molecule. The cyanide ligand was identified by smelling the hydrogen cyanide liberated when CN-Cbl was treated with acid (confirmed by infrared spectroscopy C≡N 2130 $cm^{-1}$).

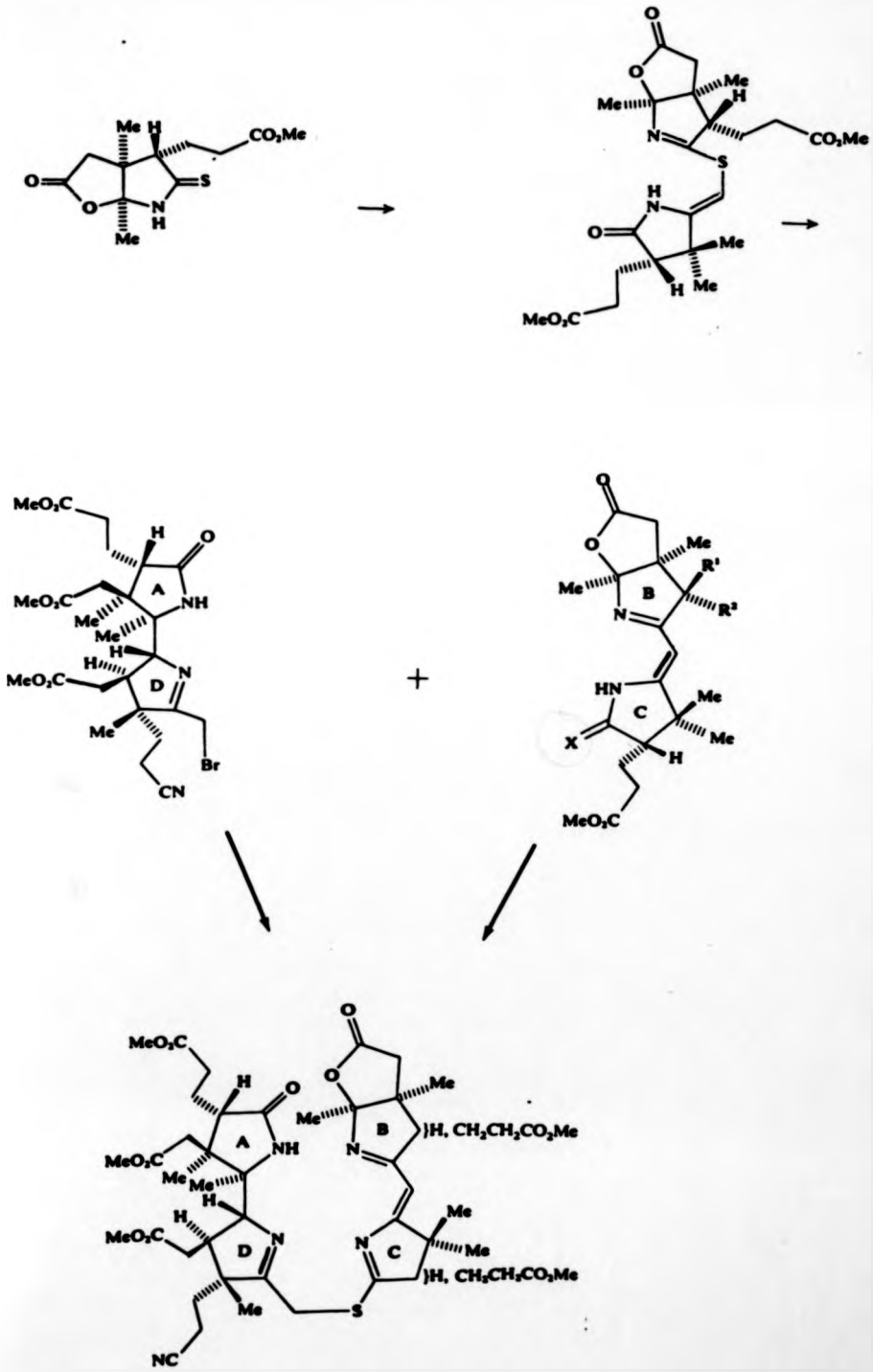
X-ray diffraction studies located the atoms near cobalt in the centre of the corrin ring. Single crystals of CN-Cbl and two of its degradation

Products were given to Dorothy Hodgkin and co-workers for study and the correct structure for CN-Cbl was assembled[20,21], as shown in fig.1(a). The molecule contains a hexacoordinate, diamagnetic, cobalt(III) ion, the donor atoms being the four nitrogens of the planar corrin nucleus, a dimethylbenzimidazole base (donor at N-3) and the cyano group. The corrin nucleus contains four partially reduced pyrrole rings (A-D), two of which are directly linked (the A/D link, C1-C19) whilst A/B, B/C, and C/D are joined in a porphyrin-like manner.

Crystals of the coenzyme, isolated by Barker, were sent to Hodgkin and her collaborater, Lenhert, who deduced[22] its structure shown in fig.1(c). The remarkable feature of the structure is the unique Co-C $\sigma$-bond, a feature which identified adenosylcobalamin (AdoCbl) as the first naturally occuring organometallic compound. All alkylcobalamins are photosensitive compounds readily converted to hydroxocobalamin (OH-Cbl, fig.1(b)) - which subsequently reacts with cyanide ions (e.g. present in charcoal columns originally used to isolate "vitamin $B_{12}$") to give CN-Cbl. Further confirmation of the structure of cobalamin came from the similarity of the single crystal diffraction patterns of synthetic and natural materials. Two independent routes to the total synthesis of $B_{12}$ were devised. Woodward synthesised[23] a portion corresponding to the AD rings of corrin, whereas Eschenmoser synthesised[24] a BC precursor <u>via</u> the "sulphur bridging method". Combination of the thioamide of Eschenmoser's BC moiety with Woodward's AD component gave rise to the corrin precursor (Scheme 1).

The biosynthesis of corrins has been an active area in research. As $\delta$-aminolaevulinic acid was a precursor of the tetrapyrrole porphyrin ring, it was suggested that it might also be a precursor of corrin.

**Scheme 1. Stages in the Synthesis of Vitamin $B_{12}$**



This was confirmed by feeding $^{14}C$-labelled δ-aminolaevulinic acid to a Streptomycete and determining the activity of the cobalamin isolated from the bacterium[25]. Further studies[26-29] revealed that the sequence of events in the biosynthesis of corrinoids starts from δ-aminolaevulinic acid and S-adenosylmethionine to produce porphobilinogen and porphyrino(urogen-III), culminating in cobyrinic acid. $^{13}C$ n.m.r. studies showed that seven of the eight methyl groups on the periphery of corrin are derived from methionine. To cobyrinic acid (fig.4) is then added the nucleotide loop derived from (L)-threonine, guanosine triphosphate, dimethylbenzimidazole and the primary amide functions to produce cobalamin. Cobalt is incorporated in the later stages from urogen-III to cobyric acid. Although the isolation of corrinoids lacking a cobalt atom implies their intermediacy in the biosynthesis of vitamin $B_{12}$ this has not yet been demonstrated experimentally in enzymic studies.

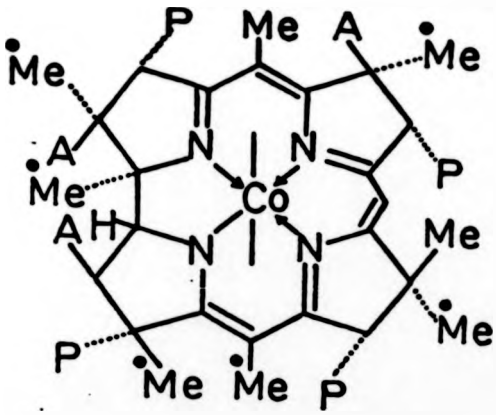
## 1:2 Adenosylcobalamin Dependent Enzymic Rearrangements

### 1:2(a) Introduction

Adenosylcobalamin catalyses a number of enzymic rearrangements shown in Table 3, some of which have no known analogy in organic or organometallic chemistry. The mechanistic pathways for these reactions are currently the subject of much attention and discussion. The enzymic processes of interest are molecular rearrangements in which a group X and a particular hydrogen atom exchange places. This is represented formally by equation 1.


equation 1

Figure 4. Structure of Cobyrinic Acid - the Cobalamin Precursor

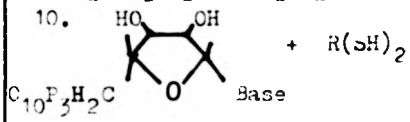
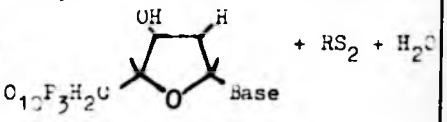



A = $CH_2COOH$

P = $CH_2CH_2COOH$

• = the methyl groups derived from methionine in the biosynthetic pathway to cobyrinic acid.

Table 3. Enzymic Rearrangements Catalysed by AdoCbl

| | | | |
|---|---|---|---|
| 1. | $HO_2CC(H)NH_2CH_2CH_2CO_2H$ | ⇌ | $HO_2CC(H)NH_2C(H)CO_2HCH_3$ |
| 2. | CoA $SCoC(H)CO_2HCH_3$ | ⇌ | CoA $SCoCH_2CH_2CO_2H$ |
| 3. | $HO_2CC{=}CH_2CH_2CH_2CO_2H$ | ⇌ | $HO_2CC{=}CH_2C(H)CO_2HCH_3$ |
| 4. | $CH_3C(H)OHCH_2OH$ | ⇌ | $CH_3CH_2CHO + H_2O$ |
| 5. | $HOCH_2C(H)OHCH_2OH$ | → | $HOCH_2CH_2CHO + H_2O$ |
| 6. | $H_2NCH_2CH_2OH$ | → | $CH_3CHO + NH_3$ |
| 7. | $H_2NCH_2CH_2CH_2C(H)NH_2CO_2H$ | → | $CH_3C(H)NH_2CH_2C(H)NH_2CO_2H$ |
| 8. | $H_2NCH_2CH_2CH_2CH_2C(H)NH_2CO_2H$ | ⇌ | $CH_3C(H)NH_2CH_2CH_2C(H)NH_2CO_2H$ |
| 9. | $H_2NCH_2CH_2C(H)NH_2CH_2CO_2H$ | ⇌ | $CH_3C(H)NH_2CH_2C(H)NH_2CH_2CO_2H$ |
| 10. |  | → |  |

1. = Glutamate Mutase
2. = Methylmalonyl CoA Mutase
3. = α-Methyleneglutarate Mutase
4. = Diol Dehydrase
5. = Glycerol Dehydrase
6. = Ethanolamine Ammonia-Lyase
7. = L-β-Lysine Mutase
8. = D-β-Lysine Mutase
9. = D-Ornithine Mutase
10. = Ribonucleotide Reductase

A key step in these rearrangements is the cleavage of the Co-C bond of AdoCbl. Formally, this bond can be broken in four ways: heterolytically with carbonium ion formation; heterolytically with carbanion formation; heterolytically with olefin formation, and homolytically (shown in fig.5). Corey [30] has proposed a pathway for diol-dehydrase rearrangements in which initial heterolytic cleavage of the Co-C bond of AdoCbl led to alkyl- and hydridocobalt intermediates. Schrauzer postulated heterolytic cleavage[31] of the Co-C bond of AdoCbl to give $Cbl^{I}$, and 4,5-anhydroadenosine (shown in Scheme 2.) as a consequence of the activation of the Co-C bond when bound to enzyme (e.g. diol dehydrase). The 4,5-anhydroadenosine was considered to remain in the vicinity of the active site of the enzyme, whilst $Cbl^{I}$ reacted with the activated substrate to yield product aldehyde. It is known in these rearrangements that the 5' hydrogens of the adenosine become equivalent. Schrauzer accounts for this observation by postulating hydrogen exchange between the 5' - protons of 3 (Scheme 2) and the labile protons of the product aldehyde generated at the active site.

Evidence supporting homolytic cleavage of the Co-C bond of adenosylcobalamin comes mainly from e.s.r. studies[32], which showed two components: a broad low-field peak due to cob(II)alamin and a narrower signal (doublet) attributed to a radical. The adenosyl radical so produced is supposed to abstract a hydrogen atom from the substrate molecule to produce a substrate derived radical (S· see Scheme 3) and 5'-deoxyadenosine. Radical S· rearranges to a product-like radical P· which abstracts a hydrogen from 5'-deoxyadenosine to give the product PH and an adenosyl radical. The hydrogen in PH is derived exclusively from the adenosyl group and no hydrogen exchange with solvent is observed in the rearrangements.

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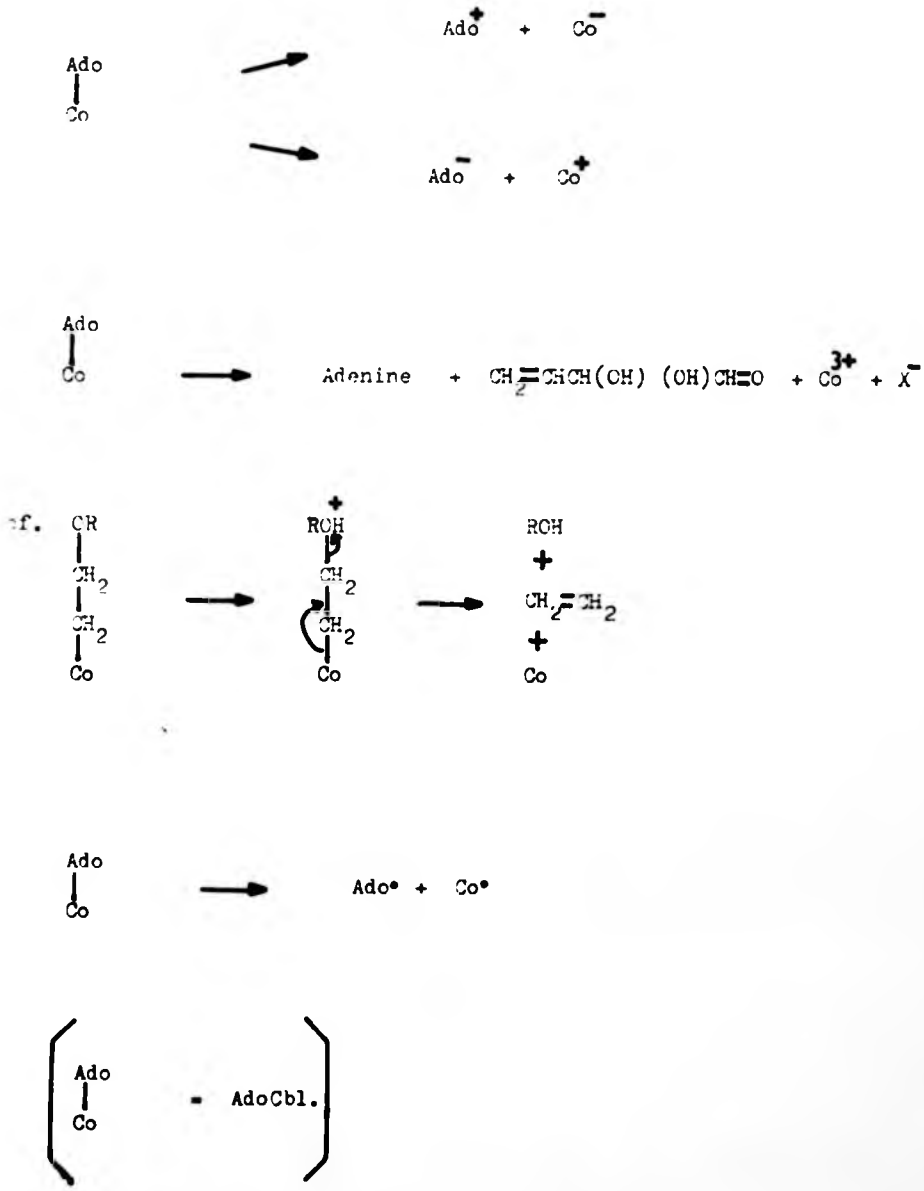
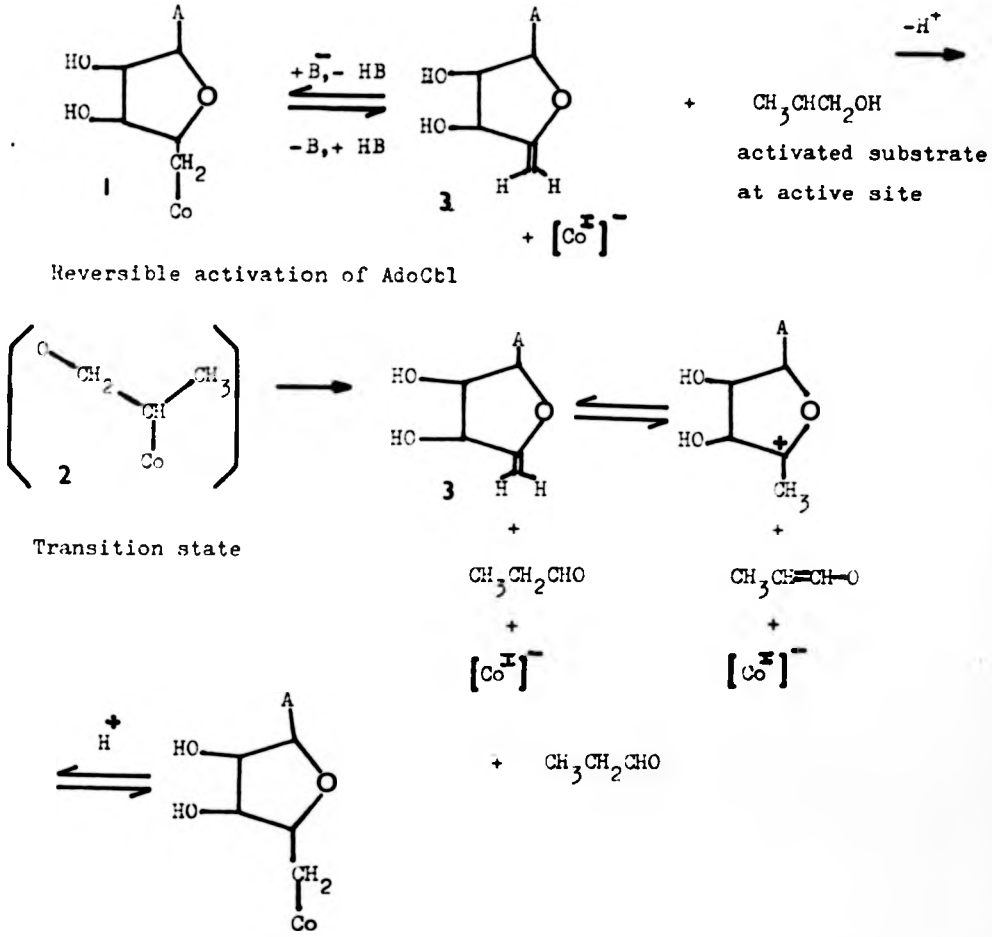
Figure 5. Possible Pathways for the Cleavage of the AdoCbl Co-C $\sigma$-Bond



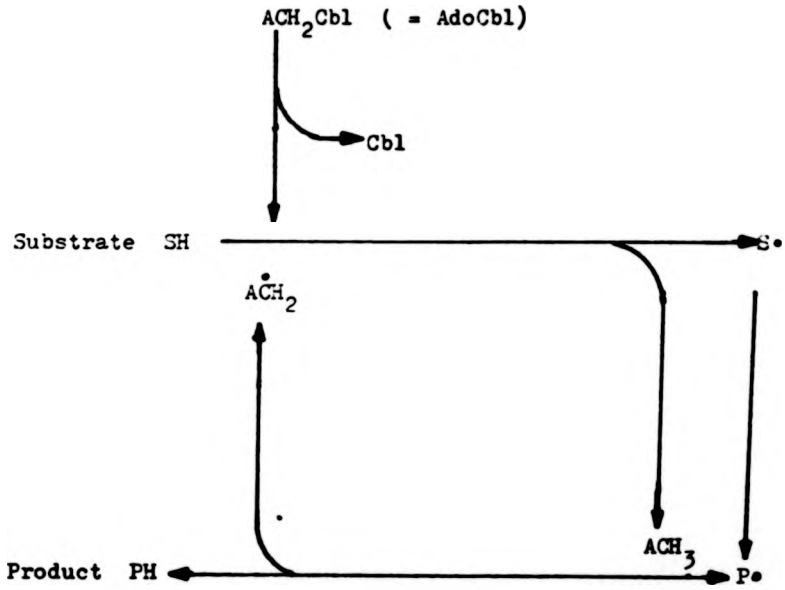
Scheme 2. A Suggested Mechanism for Diol Dehydrase.




Regeneration of AdoCbl and removal of product from active site

A = Adenine.

Scheme 3. Mechanism of AdoCbl - Dependent Enzymic Processes.



The possible modes of adenosylcobalamin dependent rearrangements discussed above, pose some unresolved features concerning the mechanism of rearrangement of the substrates.

(1) The possibility and likelyhood of organo-corrin intermediates.

(2) The role of the active site in binding intermediates which may be subsequently transformed into products via protein-mediated steps.

The results presented in this thesis show that organocorrinoids could be plausible intermediates in some AdoCbl catalysed rearrangements.

I: 2(b) α-Methyleneglutarate Mutase

α-Methyleneglutarate mutase catalyses the reversible interconversion of α-methyleneglutarate and methylitaconate (fig. 6). The reaction involves migration of an acrylyl residue from one carbon to another. The mutase has an absolute requirement for AdoCbl as cofactor for activity but does not require additional metal ions. A number of dicarboxylic acids (e.g. 1-methyl-1,2-*cis*-cyclopropanedicarboxylic acid; 1,2-cyclobutanedicarboxylate) have been found to be competitive inhibitors of the mutase[33].

α-Methyleneglutarate mutase (isolated from *Clostridium barkeri*) is a very unstable enzyme and loses activity after 3 days at $0^{o}C$ at low protein concentrations (1mg protein per $cm^3$), but is more stable at higher protein concentrations. Even storage at $-80^{o}$ results in a 38% loss of activity after 6 days. The addition of substrate does not increase the stability of the enzyme. Gel filtration shows the enzyme to have a molecular weight of *ca.* 170,000. AdoCbl is weakly bound to the mutase and may be readily removed by passage down a DEAE column or by treatment with charcoal. The enzyme has an essential

Figure 7. Stereochemical Course of the Diol Dehydrase Reaction.

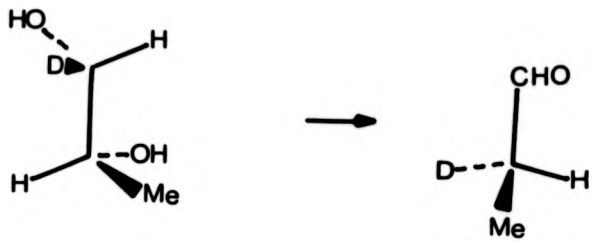
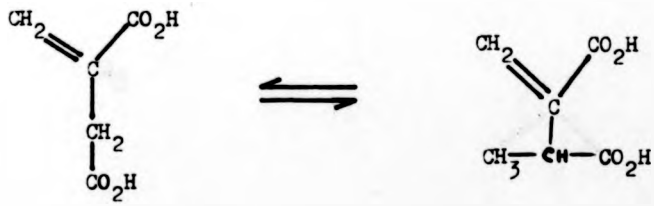



Figure 6. AdoCbl Catalysed Conversion of α-Methyleneglutarate to Methylitaconate.




$$OHCH_2CH_2OH \xrightarrow{OH^{\bullet}} HOCH_2\overset{\bullet}{C}HOH \xrightarrow{H^+} H_2O + \overset{\bullet}{C}H_2CHO$$

equation 2.

sulphydryl group since reaction with iodoacetate inhibits the enzyme. No information is yet available concerning intermediates in this enzymic reaction.

I: 2(c) Diol Dehydrase

Diol dehydrase catalyses the conversion of 1,2-diols to aldehydes. It also catalyses the conversion of butane-2,3-diol to butanone but will not accept diols of five or more carbon atoms as substrates. The stereochemistry of the dehydration of propane-1,2-diol catalysed by diol dehydrase has been completely defined[34,35]. Diol dehydrase will accept either (R)-or(S)-propane-1,2-diol as substrate, with stereospecifically deuterated substances it was shown[35] that the conversion of diol to aldehyde is associated with migration of hydrogen from C-1 of substrate to C-2 of product (see fig.7). With (S)-propane-1,2-diol the pro-S hydrogen at C-1 migrates whilst in the R isomer the pro-R hydrogen migrates. For both, the configuration of the carbon which receives the hydrogen atom undergoes inversion during the course of the reaction. Studies[36] with $^{18}O$-labelled substrates confirmed migration of hydroxyl from C-2 to C-1 to form propane-1,1-diol which yielded propanal upon elimination of water. Many mechanistic pathways have been postulated to explain this labelling experiment. These invoke $\pi$ complexes[37] or consider the intermediacy of protonated bridged species[38] in the interconversion of $S^{\bullet}$ to $P^{\bullet}$. Model studies employing cobaloximes[39] showed that primary radicals could initiate reactions identical to those encountered in the conversion of 1,2-diols to aldehydes by diol dehydrase (equ.2).

For activity, diol dehydrase requires adenosylcobalamin and a unipositive cation (eg. $K^+$, $Na^+$, $Li^+$). The requirement for unipositive

cations is due to their ability to stabilise the enzyme-coenzyme complex. Diol dehydrase has a molecular weight of ca.250,000 and possesses one active site; it comprises of two sub-units. Sulphydryl reagents inhibit diol dehydrase, but protection can be afforded by binding of AdoCbl with or without a substrate. As butene-diols[40] are known to inhibit diol dehydrase, preliminary studies were undertaken with 2',2'-dichloro-cyclopropylethane-1,2-diol and cyclopropylethane-1,2-diol with the aim of investigating their properties as inhibitors, substrates or suicide substrates (Chapter 3).

## 1:3 Reactions of Cobalamins

### 1:3(a) Hydrolysis of Peripheral Amide Groups

Acid hydrolysis of cobalamins yields mixtures of mono- to heptacarboxylic acids. The acetamide residues are more resistant to both acidic and basic hydrolysis than the propionamide groups. Preferential cleavage of a particular amide function is possible by exploiting neighbouring group participation e.g. the e-propionamide grouping is susceptible to hydrolysis with the aid of the neighbouring phosphate grouping. Mild acid hydrolysis yields predominantly a monocarboxylic acid, shown to be CN-Cbl(e-OH) by X-ray diffraction studies[41]. Concentrated hydrochloric acid selectively hydrolyses the f-amide group of CN-Cbl giving rise to a 10% yield of cobyric acid after column chromatographic purification[42]. The course of these hydrolytic reactions depends on the ligands attached to cobalt in the $\alpha$- and $\beta$-positions e.g. the order of acetamide hydrolysis is different between aquo- and cyanocobalamin.

Alkaline hydrolysis of cyanocobalamin with 30% aqueous sodium hydroxide at 150° gives a mixture of corrinoids, predominantly the nucleotide-free penta- and hexacarboxylic acids. The purified hexacarboxylic acid

crystallises as red prisms and X-ray diffraction data shows the presence of four propionic acid and only two acetic acid residues. The third acetamide residue has undergone cyclisation at C-8 to yield a γ-lactam.

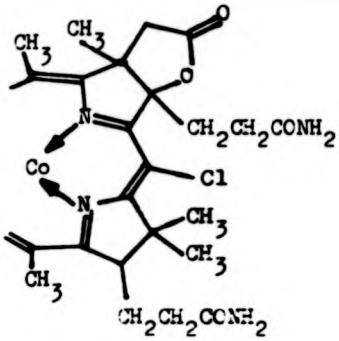
I: 3(b) Reactions with Electrophilic Reagents

Treatment of cyanocobalamin with equimolar amounts of chloramine-T or bromine water (pH4) gives a crystalline compound characterised[21] as cyano(8-hydroxy-10-chloro-α-(5,6-dimethylbenzimidazolyl)cobamic acid - a,b,d,e,g-pentaamide-c-lactone)(fig.8). The lactone can be hydrolysed to the hydroxy acid under mild conditions. Vigorous alkaline hydrolysis yields a heptacarboxylic acid. The extent of lactone or lactam formation depends on the β-coordination ligand e.g. methyl and adenosylcobalamin (0.1M NaOH/100$^0$/10min.) yield no lactam, whereas under identical conditions cyano and aquocobalamin yield the lactam. Use of an excess of halogenating agent gives rise to halo-containing lactones. Halogenation was assumed to occur at C-10 by considering electron availability throughout the corrin ring[19]. Treatment of the γ-lactam of cyanocobalamin with one equivalent of halogenating agent leads to substitution at C-10. Similar reactions with N-bromosuccinimide lead to C-10 brominated corrins. Reaction of cyanocobalamin with two equivalents of nitrosyl chloride gives rise to a new deep-red corrinoid suggested to be nitrated at the C-10 position as evidenced by spectral and chemical data[43].

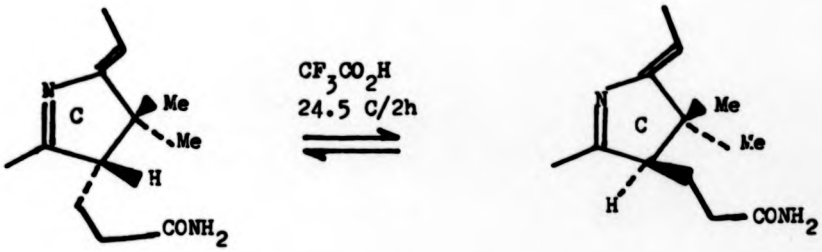
I: 3(c) Epimerisations[44]

Treatment of cyanocobalamin with trifluoroacetic acid (room temperature 2/h) yields a mixture of cyanocobalamin, cyanocobinamide, and two epicorrinoids (C-8 and C-13 epicorrinoids). The epicorrinoids are virtually indistinguishable from the corrinoids on the basis of electrophoretic behavior and infra-red spectra. Significant differences

Figure 8. Partial Structure of Cyano 8-hydroxy-10-chloro-α-(5,6-dimethylbenzimidazolyl)cobamic acid-a,b,d,e,g-pentamide-c-lactone .




Scheme 4. Epimerizations of Corrinoids.



are however, observed in both ORD and CD spectra. The formation of epicorrinoids is caused by an acid-catalysed equilibrium shown in Scheme 4.

1:3(d) Redox Reactions

It is a property of the corrin ring to stabilise equally the three formal oxidation states of cobalt, (Co(I), Co(II) and Co(III). Cob(II)alamin is prepared by the reduction of cob(III)alamin with hydrogen and a platinium catalyst, the colour of the solution changes from red to brown during reduction. Reduction has been confirmed by controlled potential reduction[45] and polarography[46]. Cob(II)alamin is also formed when aquocobalamin is treated with carbon monoxide or monothiols[47]. Solutions of cob(II)alamin are oxidised to aquocobalamin in the presence of air, but solid cob(II)alamin is stable even in the presence of oxygen. Co(II)corrinoids are also formed in the photolysis of alkylcobalamins under anaerobic conditions[48].

With more powerful reducing agents (e.g. sodium tetrahydroborate, chromium(II) chloride, zinc and acetic acid), Co(I) can be generated from Co(III) or Co(II)corrinoids. Originally, cob(I)alamin was formulated as a hydride, but it has been shown[49] to exist predominantly as the unprotonated species on the basis of isotope exchange reactions on cob(I)alamin in $D_2O$/NaOD media. Cob(I)alamin is also formed by disproportionation of $Cbl^{II}$ in strong alkali. Aqueous solutions of $Cbl^{I}$ decompose to $Cbl^{II}$ and hydrogen, the rate being dependent on the pH and nature of the buffer anion (e.g. half-life for Co(I) 355 mins. at pH10; 87 mins. at pH8). Cobalt(I)corrinoids are extremely sensitive to oxygen being oxidised almost instantaneously to cob(II)corrinoids. Co(I)corrinoids exhibit a green/grey colour in solution(for visible absorption spectra of Co(III), Co(II) and Co(I)

see fig 9).

I: 3(e) Synthesis of Organocorrinoids

Good yields of alkylcobalamins are obtained by reacting $Cbl^{I}$ with standard alkylating agents (e.g. alkylhalides, O-toluene-p-sulphonates and epoxides), because this Co(I) species is one of the most powerful nucleophiles known. The reaction of Cob(I)alamin with alkylhalides is thought to proceed by the classical $S_N2$ pathway, although there is evidence to suggest electron transfer pathways especially with alkyl iodides[49]. Nucleophilic addition of $Cbl^{I}$ to alkenes occurs only if the alkene is activated by electron-withdrawing substituents (e.g. COR). Additions to alkynes occurs directly. A summary of synthetic routes is shown in Table 4. The reaction of $Cbl^{I}$ with secondary alkylhalides is fast but the resulting alkylcobalamins are often too unstable to be isolated. Schrauzer has recently prepared[50] isopropyl-cobalamin from the reaction of hydridocobalamin with propylene. Alkylcobalamins may also be prepared by reaction of Co(III)corrinoids with nucleophiles[51] and from Co(II)corrinoids and radicals[52].

1:4 Models for Cobalamins

1:4(a) Criteria for a Model System

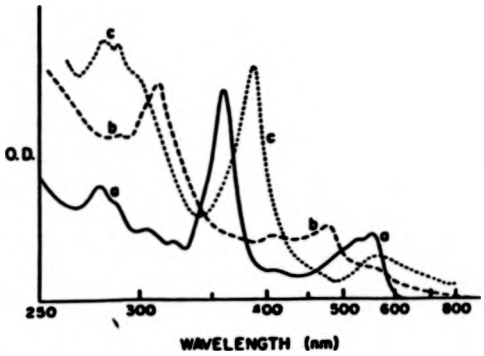
A model system may be developed using the following criteria:

(1) The model must bear some structural resemblance to the system being modelled.

(2) The model system has to parallel the behavior of the system modelled in some way.

(3) The model system must be so constructed such that some property of the model may be exploited to obtain information which cannot be so readily undertaken in the system being modelled.

Figure 9. Absorption Spectra of Cob(III),Cob(II), and Cob(I)alamin.




(a) = cyanocobalamin

(b) = cob(II)alamin

(c) = cob(I)alamin

Table 4. Synthetic Routes to Alkylcobalamins.

| | | | |
|---|---|---|---|
| CoI | + | RX | $\longrightarrow$ Co—R + $X^-$ |
| | | RCOX | $\longrightarrow$ Co—COR + $X^-$ |
| | | RC≡CX | $\longrightarrow$ Co—C≡CR + $X^-$ |
| | | $H_2C{=}CH{-}COR$ + $H^+$ | $\longrightarrow$ Co—$CH_2CH_2COR$ |
| | | HC≡CR + $H^+$ | $\longrightarrow$ Co—CH=CHR |
| | | $H_2C{-}CH_2$ (O) + $H^+$ | $\longrightarrow$ Co—$CH_2$—$CH_2OH$ |

Figure 10. Other Models for Cobalamins.

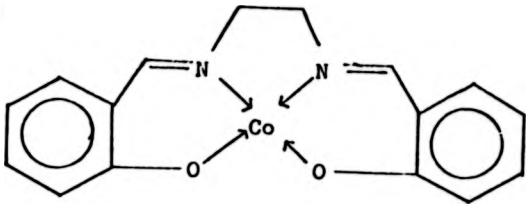



Fig.10b SalenH$_2$ Complexes.

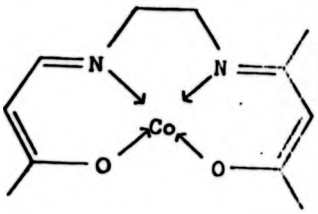



Fig.10a The BAE Complexes.

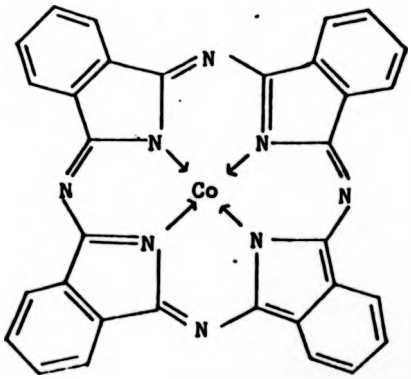



Fig.10c Aetioporphyrin(I) Complex.

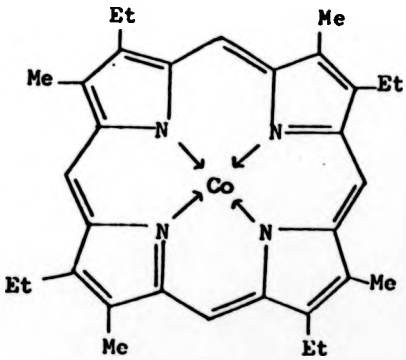



Fig.10d Cobalt Phthalocyanin Complex.

(4) The information gained from (3) should preferably be capable of unambiguous interpretation.

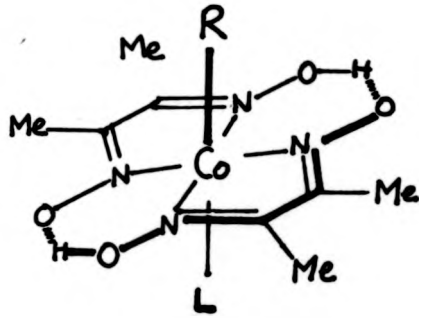
When considering models for cobalamins, there are many features for which a particular model could be designed. A model designed to represent the molecular structure of an alkylcobalamin would require a Co-C $\sigma$ bond, a planar Co(N4) system and an axial N-donor. The chemical constitution of the particular model system used is chosen from consideration of the type of information required. Thus, for cobalamin many types of systems have been employed as chemical, biochemical or purely structural models. Some of these are illustrated in fig. 10.

For biological studies (membrane solubility etc.) where lipophilicity is a major consideration, the more bulky models e.g. cobalt phthalocyanin or aetioporphyrin(I)cobalt may be preferable. For chemical study of the characteristics of an alkyl cobalt group, the less bulky and cumbersome the models the better. Here, the feature of importance is an alkyl group attached to cobalt; the reactions of this group should be capable of being followed by physical techniques such as n.m.r. spectroscopy. Amongst the most well studied model compounds for cobalamins are the alkyl-bis(butane-2,3-dionedioximato)cobalt(III) complexes (alkylcobaloximes), fig.11.

1: 4(b) Cobaloximes as Models for Cobalamins

(1) Structural relations to cobalamin. The structure of several alkylcobaloximes have been determined by X-ray diffraction studies[54,55]. A comparison of key bond lengths and angles between methylcobaloxime and AdoCbl (Table 5) shows many similarities, a noticable difference

Figure 11. Structure of Alkyl-bis(butane-2,3-dionedioximato)cobalt-(III) Complexes (Alkylcobaloximes).



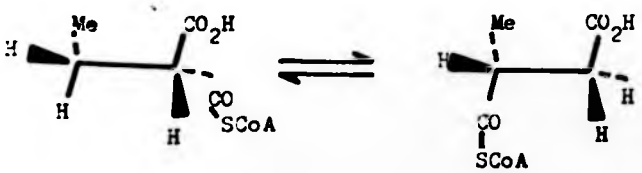

ALKYLCOBALOXIME

R = Alkyl Group L = Lewis Base e.g. Pyridine.

Table 5. Comparison of Key Bond Lengths and Angles for Methylcobaloxime and Adenosylcobalamin

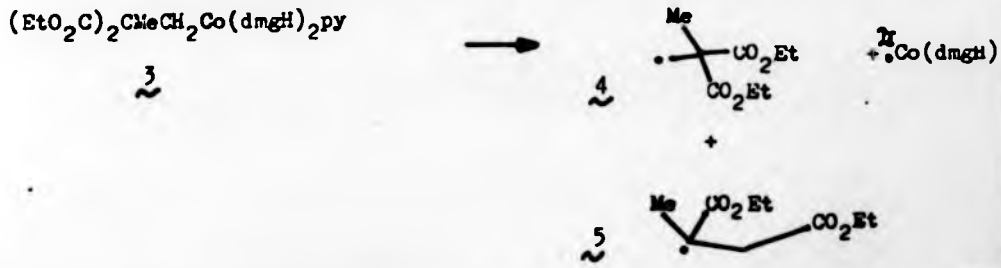
| Methylcobaloxime[1] | | Bond Lengths | | Adenosylcobalamin[2] |
|---|---|---|---|---|
| Co—C (Methyl) | | 1.998 | 2.05 | Co—C (Adenosyl) |
| Co—N (dmgH) | N1 | 1.877 | 1.92 | Co—N (corrin) N21 |
| | N2 | 1.918 | 1.91 | Co—N22 |
| | N3 | 1.887 | 1.97 | Co—N23 |
| | N4 | 1.905 | 1.98 | Co—N24 |
| Co—N (pyridine) | | 2.068 | 2.23 | Co—N (benzimid.) |
| | | Bond Angles | | |
| N1—Co—N2 | | 176.7 | 171 | N21—Co—N23 |
| N1—Co—N(py) | | 90.7 | 92 | N21—Co—N(benz.) |
| N4—Co—C(Methyl) | | 89.3 | 95 | N24—Co—C(Adenosyl) |

1 = cf. figure 11.
2 = cf. figure 1.




equation 3.

Scheme 5. Anaerobic Photolysis of 2,2-Diethoxycarbonylpropylcobaloxime



is shown in the Co-N axial bond length which is somewhat shorter in the cobaloximes than in Ado-Cbl. From this finding it was suggested that the cobalt in cobaloximes carries a slightly greater positive charge than the cobalamins; this suggestion was substantiated by LCAO-molecular orbital calculations[56].

Structurally therefore, cobaloximes are good models for cobalamins by virtue of the similar environments around their central cobalt ions. They are bad models for cobalamins in that they do not contain a complex periphery surrounding the planar N4 system, have an N-axial donor that is not connected to the planar N4 system, and have no chiral centres with exception to those present in axial alkyl groups.

(2) Properties and reactions of cobaloximes. Alkylcobaloximes are readily synthesised stoichiometric compounds containing formally Co(III), that are diamagnetic and intensely coloured. They are usually slightly soluble in water but are often soluble in relatively polar organic solvents e.g. $CH_2Cl_2$, MeOH. In many ways cobaloximes are chemically similar to cobalamins e.g. their photolability, redox behavior, thermal stability (alkylcobaloximes melt with decomposition $<200^{\circ}$.) Their $^{1}H$ and $^{13}C$ n.m.r. spectra are relatively simple; this is a major asset in structural elucidation and mechanistic studies. The transmission of electronic effects through cobalt in cobalamins[57] (cis and trans effects) are also observed in cobaloximes. In cobalamins the observed cis effect may be a manifestation of distortions in the corrin ring consequent of the alkyl ligand, rather than an electronic effect transmitted through cobalt[58] but the latter may be true for cobaloximes. Costa reviewed cis and trans effects in cobalt chelates and concluded[59] that the two

effects could facilitate Co-C bond fission by increasing electronic charge on cobalt.

Of all the model systems studied, cobaloximes are the only models which substitute for cobalamin in certain biological systems e.g. methane biosynthesis by Methanobacillus omelianskii where methylcobaloxime has been used in the presence of catalytic amounts of MeCbl[60]. The role in this biosynthetic pathway is believed to be methyl transfer participation. Cobaloximes cannot substitute for AdoCbl.

(3) Identification of Cobaloximes It is possible to characterise alkylcobaloximes uniquely by a combination of combustion microanalysis, visible/ultraviolet absorption spectra and n.m.r. spectroscopy. The $^{1}H$ n.m.r. spectra of alkylcobaloximes are often very simple. The dimethylglyoximato methyls (12H) give rise to a singlet (ca $\delta$2.1) if the $\sigma$-alkyl group is achiral. It is presumed that rapid rotation of the alkyl group about the Co-C bond axis renders the magnetic environment about each methyl group equivalent. The two intramolecularly bonded -OH groups give rise to a broad singlet at ca $\delta$18. The pyridine resonances are at $\delta$7.3 (2H,t), $\delta$7.7 (1H,t) and $\delta$8.55 (2H,d). The alkyl resonances are usually clearly visible. Substituents $\alpha$ and to $\beta$ cobalt are affected by shielding from the cobalt e.g. ethylcobaloxime $CH_3$ resonates at $\delta$0.33 and the $CH_2$ at $\delta$1.7.

I: 4(c) Development of Models for Enzymic Processes.

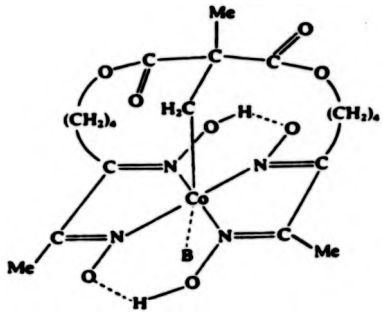
Development of a realiable model for an enzyme presents a difficult problem. Enzymes operate under the mildest of conditions, using only a few simple functionalities e.g. hydroxy, sulphydryl, carboxyl, amino and imidazole. They carry out specific functional group interconversions

on molecules possessing other functionalities without the need of protecting groups. Enzymic reactions can exhibit 100% stereospecificity. Enzymes have the ability to select a single substrate from a mixture of many compounds in their environment.

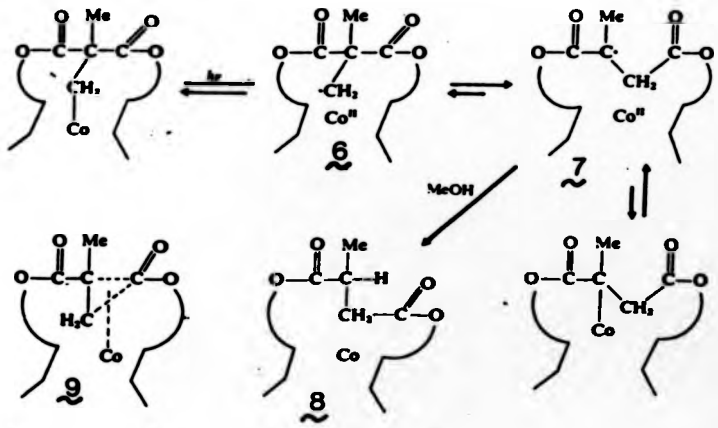
One approach to modelling an enzymic reaction is to try to simulate the chemistry that appears to take place during interconversions carried out by the enzyme. This is where the majority of model studies of the reactions catalysed by AdoCbl is aimed.

The development of a model for an AdoCbl rearrangement and its subsequent modification in view of experimental observations could be illustrated by many examples. One particular elegant example is that due to Rétey, who was concerned with models for methylmalonyl-CoA mutase. This enzyme catalyses the reversible conversion of methylmalonyl CoA (1) into succinyl CoA(2), equ.3. Anaerobic photolysis of an aqueous solution of 2,2-diethoxycarbonylpropyl (pyridine)cobaloxime[61](3) gives dimethyl diethylmalonate and the rearrangement product diethyl methylsuccinate from the alkyl side-chain (Scheme 5). After initial homolysis of the Co-C bond of the cobaloxime (3) the resulting alkyl radical(4) may rearrange to radical (5). The yields and ratios of products from this reaction were irreproducible. Variation in yields was explained by considering that soon after homolysis of the Co-C bond, the substrate-derived radical moves away from the central cobalt atom, and devoid of the catalytic influence of cobalt, is unable to rearrange. To test this hypothesis, Rétey produced a modified model[62] in which the σ-alkyl group was covalently attached to the dioximato ligands (Scheme 6). On photolysis, the substrate-derived radical (6) cannot now leave the vicinity of cobalt and rearrangement is possible. Indeed, 2-methylsuccinic

Scheme 6. Modified Model for Methylmalonyl-CoA Mutase.



Modified model due to Rétey, in which the σ-alkyl group is covalently attached to the dioximato ligands, cf. figure 11.



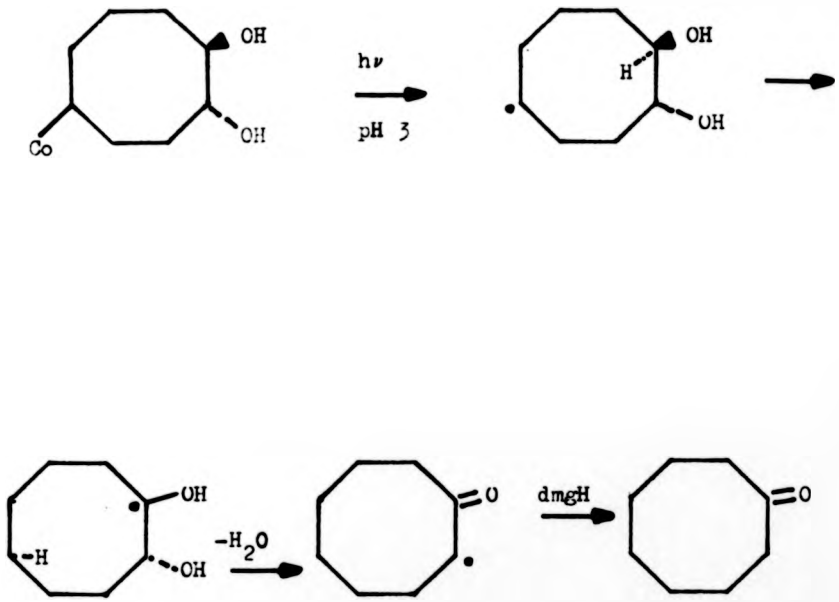
acid, the expected rearrangement product was isolated from the reaction mixture, after alkali treatment, in 83% yield. The initially formed radical (6), under the catalytic influence of cobalt, rearranges reversibly to (7). Recombination with Co(II) would lead to the unstable tertiary-alkylcobaloxime. Radical (7) can be stabilised by H-abstraction from solvent to yield the succinic acid precursor (8). A possible intermediate in this reaction is the cobalt-stabilised species (9).

A model system for diol dehydrase devloped by Golding, has been interpreted in terms of a series of radical reactions which do not necessarily invoke the intermediacy of organocobalt entities. Thus, it was demonstrated that methyl radicals (derived from the photolysis of methyl(aquo)cobaloxime) caused the conversion of ethane-1,2-diol to ethanal[63] in a manner paralleling the conversion of 1,2-diols to aldehydes catalysed by diol dehydrase. As a development of this type of model, 4,5-dihydroxycyclooctyl (pyridine)cobaloxime was synthesised[64]; upon anaerobic photolysis of this cobaloxime, cyclooctanone was isolated in 30% yield. It was proposed that the 4,5-dihydroxycyclooctyl radical released from cobalt (Scheme 7) undergoes a transannular 1,5-H shift to give the 1,2-dihydroxycyclooctyl radical which is converted to the 2-oxocyclooctyl radical and subsequently to cyclooctanone after hydrogen atom abstraction from dimethylglyoxime (OH).

## I: 4(d) Other Models for Cobalamins

The bis(acetylacetone)ethylenediamine cobalt(III) chelates (BAE complexes) (fig 10a) were considered as models for cobalamin[65]. They are usually isolated as the cationic salts $(Co^{III}(BAE)(NH_3)_2)^+$. One problem associated with these complexes is that mixtures of optical isomers are produced which are difficult to separate. Alkyl$Co(BAE).H_2O$ complexes

Scheme 7. A Model for Diol Dehydrase : The Production of Cyclooctanone via the Photolysis of 4,5-Dihydroxycyclooctyl(pyridine)cobaloxime




30% yield

are prepared by reaction of the cationic salts of $(Co(BAE)L_2)^+$ with Grignard reagents to yield red crystalline complexes. These complexes dehydrate at 100° to give the green coloured 5-coordinate alkyl complexes. The bis(salicylaldehyde)ethylenediamine complexes (salen$H_2$complexes) (fig.10b) are similar to the BAE complexes. Alkyl Co(salen).$H_2O$ complexes are prepared as yellow crystals by reaction of $(Co(salen)L_2)^+$ with the corresponding Grignard reagent. The water ligand is very easily displaced from the alkylCo(salen).$H_2O$ complex by e.g. pyridine. The salen complexes are planar as confirmed by X-ray crystallographic studies. BAE and salen complexes are photolabile. The macrocyclic models e.g. the Aetioporphyrin(I) complexes (fig.10c) are prepared by reacting the corresponding bromo(pyridine)cobalt complex with Grignard reagents. The alkyl complexes are isolated as photosensitive red prisms.

The work described in this thesis utilises alkylcobaloximes, because an important feature of the study was the necessity to monitor reactions of the cobaloximes. The relatively simple n.m.r. spectra of cobaloximes has been exploited to follow the rearrangement of several alkylcobaloximes. The model reactions discussed relate to the possible intermediacy of organo-cobalt species in the rearrangement catalysed by $\alpha$-methyleneglutarate mutase.

# Chapter 2. Instrumentation and Materials

## 2:1 Instrumentation

Unless otherwise stated, $^{1}H$ n.m.r. spectra were recorded using either a Perkin Elmer R12 instrument operating at 60 MHz and 37°C or a Perkin Elmer R34 instrument at 220 MHz and ambient temperature (22°C).

$^{13}C$ N.m.r. spectra were recorded using a Bruker WH-90 instrument using the Fourier transform technique and operating at 22.63 MHz, and ambient temperature (22°C) unless otherwise stated. All spectra are proton decoupled unless otherwise stated.

$^{19}F$ N.m.r. spectra were also recorded on this instrument at 84.6 MHz and ambient temperature (22°C) unless otherwise stated.

The known frequency separation of the resonances of either methanol or ethane-1,2-diol was employed to determine the probe temperature where necessary.

G.l.c. traces were recorded using a Perkin Elmer F.11 instrument fitted with a flame ionisation detector. Columns were constructed of stainless steel coils of total length 2m and internal diameter 2mm. The carrier gas was nitrogen.

Infrared spectra were recorded using a Perkin Elmer 257 instrument (4000-625cm$^{-1}$) either as mulls in Nujol, liquid films or solutions.

Visible and ultraviolet spectra were recorded using a Cecil CE500 spectrophotometer.

Mass spectra were recorded using a VG micromass / 2 instrument.

Melting points were recorded using a Gallenkamp instrument and are uncorrected.

Combustion microanalyses were carried out by CHN Laboratories, Leicester.

Optical rotations were recorded using a Bendix-NPL automatic polarimeter type 143D, using sodium filter 589 nm. Values are reported as,

$$\left[\alpha\right]_D \cdot c, \text{ (where c = concentration of solution in g cm}^{-3}\text{)}$$

Circular dichroism spectra were recorded by Dr P M Scopes, Westfield College, University of London, using a Cary 6 instrument.

2:2 Reagents.

All reagents were of the purest available grade. Solvents were redistilled before use. The following special reagents were prepared as required. The procedures were taken from D. D. Perrin, W. F. L. Armarego and D. R. Perrin, 'Purification of Laboratory Chemicals', 2nd. ed., Permagon, Oxford, 1980, unless otherwise stated.

Acetaldehyde (b.p.20°) was purified by fractional distillation through a Hempel column under nitrogen.

Acetic Anhydride (b.p.138°) was purified by fractional distillation discarding the first 20 $cm^3$ fraction.

Ammonia was purified by drying with sodium (until blue colouration persists) and distilling directly into the reaction vessel.

N-Bromosuccinimide (m.p.108°). 30 g of commercial N-bromosuccinimide was dissolved rapidly in 300 $cm^3$ of boiling water and filtered through a fluted filter paper into a flask immersed in an ice-bath. After 3h, the white crystals were filtered under suction, washed with 200 $cm^3$

ice-cold water, and then air was drawn through the material with suction for 1h. Final drying was achieved in a vacuum dessicator over phosphorus(V)oxide.

<u>1-Bromobutane</u> (b.p. 101-103°): 10cm$^3$ of commercial material was washed successively with 5cm$^3$ portions of conc.(18M)$H_2SO_4$, water, 10% aqueous $Na_2CO_3$ and water. The organic layer was dried (anhydrous $K_2CO_3$) and distilled to give 1-bromobutane that was stored over activated neutral alumina.

<u>Carbon tetrachloride</u> (b.p. 77°). Commercial $CCl_4$ was heated under reflux with phosphorus(V)oxide for 2h. The apparatus was arranged for downward distillation and the carbon tetrachloride was collected and stored over powdered potassium hydroxide.

<u>Chloroform(ethanol-free)</u> b.p. 61.5°. Commercial chloroform (250cm$^3$) containing 1% ethanol was passed down an alumina column (basic grade, activity 1,50g, 50cm x 2.5cm column). The eluate was used immediately.

<u>Cobalt acetate tetrahydrate</u> was prepared from basic cobalt carbonate and aqueous acetic acid. The solid was obtained by precipitation with acetone[66].

<u>Crotonaldehyde</u> (b.p. 104-5°): Commercial crotonaldehyde was fractionally distilled under nitrogen, through a short Vigreux column to give aldehyde that was stored in a sealed ampoule at 0°C.

<u>4-Cyanopyridine</u> (m.p. 76-79°): 10g of 4-cyanopyridine was dissolved in 30cm$^3$ of dichloromethane and ethoxyethane was added to give a precipitate.

The 4-cyanopyridine was filtered off, washed with ethoxyethane and was air-dried.

Cyclohexane (b.p. 81°): 500cm$^3$ commercial cyclohexane was washed with conc.(18M)$H_2SO_4$ until washings were colourless (9x20cm$^3$), followed by water (50cm$^3$), aqueous $Na_2CO_3$(25cm$^3$), and water (25cm$^3$). The resulting cyclohexane was heated under reflux with phosphorus(V)oxide for 1h, distilled and stored over 4A molecular sieves.

Diethyl ether(ethoxyethane) was distilled from $LiAlH_4$ and stored over sodium wire.

Diiodomethane (m.p.6°, b.p. 66-70° at 12 mm Hg) was fractionally distilled at reduced pressure and then fractionally crystallised by partial freezing at -76°.

Dimethylglyoxime(Butane-2,3-dionedioxime) (m.p. 240° (decomposes)) was recrystallised from ethanol (10cm$^3$/g).

Ethanol (b.p. 78°): clean dry magnesium turnings (5g) and iodine (0.5g) were placed in a 2-litre round bottomed flask, followed by 50-75cm$^3$ of commercial absolute ethanol. The mixture was warmed until the iodine had disappeared and all the magnesium had been converted into ethanolate. 900cm$^3$ of commercial absolute ethanol was added and the mixture heated under reflux for 30 minutes. The ethanol was distilled and stored over 4A molecular sieves.

n-Hexane (b.p. 69°): 250cm$^3$ commercial n-hexane was shaken with portions of conc (18M) $H_2SO_4$ until the acid layer was colourless (5 x 25cm$^3$).

The hexane was then washed successively with water ($25cm^3$), aqueous 10% $Na_2CO_3$ ($25cm^3$), water ($25cm^3$), dried ($MgSO_4$) and was distilled from sodium.

Malonic Acid (m.p. 136°) was recrystallised from toluene-ethoxyethane (1:1) containing 5% v/v petroleum ether (60-80) and was then washed with ethoxyethane and recrystallised from acetone. It was then dried *in vacuo* over conc. (18M) sulphuric acid.

Methanol (b.p. 65°) was purified in a manner analogous to that employed for ethanol.

N-Pentane (b.p. 36.5°): $500cm^3$ of commercial n-pentane was shaken with portions of conc.(18M) $H_2SO_4$ until the acid layer was colourless (3 x $50cm^3$). The organic layer was then washed with aqueous $NaHCO_3$ ($25cm^3$) and water ($25cm^3$). After drying ($MgSO_4$) it was heated under reflux with phosphorus(V)oxide for 1h and distilled.

Pentan-1-ol (b.p. 138°) was dried over anhydrous $K_2CO_3$, filtered and was fractionally distilled.

Potassium cyanide $K\left[{}^{13}CN\right]$ was provided as a gift by Prochem.

Pyridine (b.p. 115-116°) was heated under reflux with solid KOH, followed by fractional distillation. The pure material was stored over KOH pellets.

Silica gel The stock material (100g) was treated on a boiling water bath with conc.(10M) hydrochloric acid ($200cm^3$) for 2h. The acid layer

was then decanted and replaced by a fresh aliquot ($200cm^3$) of acid, and the mixture re-heated (2h). The acid was decanted and the solid was washed with distilled water and was separated by filtration. Washing with water was continued until the washings were neutral (ca $2dm^3$ water). The solid was then washed successively with methanol ($200cm^3$) and chloroform ($200cm^3$), dried in air, then at $120^\circ$ for 24h before use.

Tetrahydrofuran (b.p. $65-66^\circ$) was heated under reflux with $LiAlH_4$ for 4h and then fractionally distilled. The purified material was stored over sodium wire.

Toluene (b.p. $110-111^\circ$) was dried with $CaCl_2$, heated under reflux with phosphorus(V)oxide for 1h and was fractionally distilled.

Toluene-4-sulphonyl chloride (m.p. $69^\circ$): 20g of commercial toluene-4-sulphonyl chloride was recrystallised by dissolving in chloroform (60-65 $cm^3$) and petroleum ether (40-60, $400cm^3$), followed by 1-2g animal charcoal. The mixture was swirled for ca 3 minutes, and was filtered through a fluted filter paper. The solvent was evaporated to yield pure white crystals.

Triethylamine (b.p. $89-90^\circ$) was dried with KOH and distilled. The purified material was stored over powdered KOH.

Trifluoroacetic acid (f.p.$-15.3^\circ$, b.p. $72.4^\circ$) was heated under reflux with and distilled from phosphorus(V)oxide. It was further purified by fractional crystallisation by partial freezing and was redistilled. (ref. I. A. Conway and G. N. Novak, J.Phys.Chem., 1977,81,1459).

# CHAPTER 3. Cyclopropanes: Their Use in Mechanistic and Model Studies

## 3: 1 Introduction

Substituted cyclopropanes have been used in three areas of study described in this thesis.

(i) In an attempt to investigate the binding of cyclopropane diols to diol dehydrase and to evaluate their properties as substrates or inhibitors, (1′,1′-dichlorocycloprop-2′-yl)ethane-1,2-diol was synthesised. Enzymological assays were carried out by A. Karagiorgas and Dr. M.Foster.

(ii) Chemally and Pratt reported[67] the thermal rearrangement of cyclopropylmethyl cobalamin to but-3-enyl cobalamin. The reaction was monitored by t.l.c. but no attempt was made either to define the mechanism of the rearrangement or properly characterise the reactant and product. The corresponding cobaloximes were therefore synthesised and used to monitor the rearrangement. A specifically labelled $^{13}C$ cyclopropylmethylcobaloxime was prepared and used to investigate aspects of the mechanism of the rearrangement.

(iii) In the reaction catalysed by α-methyleneglutarate mutase, cyclopropanes are postulated as intermediates in the conversion of α-methyleneglutarate to methylitaconate. A model study was undertaken to test the feasibility of this suggestion. The simplest member of the family of cyclopropylmethyl(pyridine)cobaloximes discussed in (ii) above was used to explore the chemistry of the rearrangement process. The results obtained for the substituted methylcyclopropyl(pyridine)cobaloximes were correlated with the known chemistry from (ii).

A brief summary of the preparative routes to cyclopropanes is given over page.

## Synthesis of Cyclopropanes with the Simmons-Smith reagent

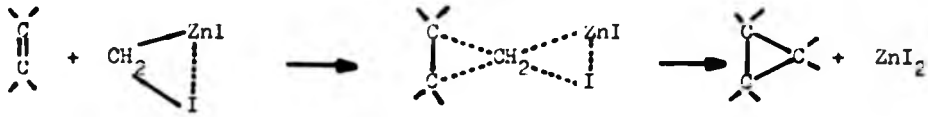
The Simmons-Smith reagent[68] (a zinc-copper couple) and its modified counterparts[69,70] react with diiodomethane and a substituted unsaturated compound to provide a versatile and convenient synthesis of cyclopropanes (equation 4). The synthesis is stereospecific with respect to the stereochemistry of the unsaturated compound and is usually free from competitive side reactions. It can be carried out under mild conditions (ethoxyethane, 35°C) to give cyclopropanes in reasonable yield. The quasi-trigonal methylene group of an intermediate methylenezinc species adds to the olefin $\pi$ bond such that both new carbon-carbon bonds of the cyclopropane are formed essentially simultaneously (equation 5)[68].

A variation of the Simmons-Smith procedure, used for the preparation of a mixture of *cis* and *trans*-methylcyclopropanes, is to react an olefin with diethylzinc and 1,1-diiodoethane[71].

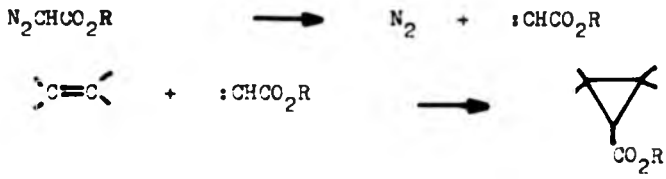
## Synthesis of Cyclopropanes from Olefins and Carbenes

Diazoacetates form carboxylate-substituted cyclopropanes and cyclopropenes by reaction with alkenes and alkynes, respectively[72]. The most probable mechanism is shown in equation 6, in which the diazoacetate loses nitrogen under the influence of heat, light or metal catalysis[71] to produce a carbalkoxycarbene which adds to the alkene (or alkyne) giving a cyclopropane (or cyclopropene) carboxylate. A very simple method of generating cyclopropanes is *via* the reaction between alkenes and dichlorocarbene, the latter being produced by phase-transfer catalysed decomposition of chloroform with hydroxide ion[73].


equation 4

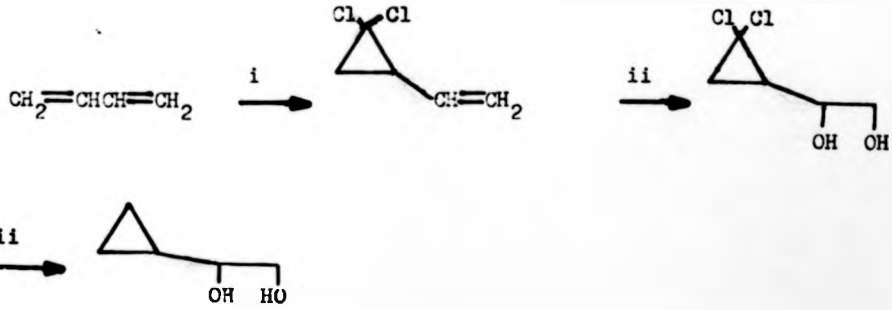



equation 5




equation 6

Scheme 8. Synthesis of (1′,1′-Dichlorocycloprop-2′-yl)ethane-1,2-diol




i = $:CCl_2$;
ii = $OsO_4$/N-Methylmorpholine-N-oxide;
iii = $Na/NH_3$

## 3:2 Synthesis of Diol Substrates for Diol Dehydrase

### 3:2 (a) Introduction

The (1,1′-dichlorocycloprop-2′-yl-)ethane-1,2-diol was synthesised as shown in Scheme 8 from buta-1,3-diene and was converted to cyclopropylethane-1,2-diol by a sodium/liquid ammonia reduction.

### 3:2 (b) Experimental

1,1-Dichloro-2-vinylcyclopropane

To a 100 $cm^3$ three-necked round-bottomed flask fitted with dry ice/acetone condenser, silica gel guard tube and a gas-inlet system was added ethanol-free chloroform ($8cm^3$;100 mmol), benzyl tri-n-butylammonium bromide (0.8g; 2.25 mmol) and aqueous sodium hydroxide ($20cm^3$; 50% w/v solution). The flask was cooled in an ice-salt mixture and buta-1,3-diene (5.4g; 100 mmol) was bubbled into the reaction mixture. The mixture was stirred at 45-50° for 6h. Periodically samples were taken from the chloroform layer to monitor the progress of the reaction by $^1H$ n.m.r. spectroscopy. When the reaction was judged complete, the flask was cooled in ice, and the contents were diluted with water ($60cm^3$). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x $20cm^3$). The combined organic layers were dried ($MgSO_4$), solvent was evaporated and the residue was fractionally distilled to yield pure product, b.p. 123° at 760 mm Hg (lit.b.p.125°)[74],7.1g; (52%).
$^1H$ n.m.r. ($CCl_4$)δ1.65(m,2H), 2.2(m,1H), 5.5(m,3H) p.p.m.
G.l.c. of a sample (3% E301/Chromosorb HMDS, 95°C) showed a single component.

(1′,1′-Dichlorocycloprop-2′-yl)ethane-1,2-diol

To a three necked 100 $cm^3$ round-bottomed flask equipped with pressure-equalising dropping funnel, silica gel guard tube and nitrogen inlet system was added N-methylmorpholine-N-oxide[75] (9.1g; 53 mmol), water (25$cm^3$), acetone (10$cm^3$) and osmium tetroxide (40mg; 0.16 mmol in 8$cm^3$ 2-methylpropan-2-ol). To the stirred reaction mixture was added dropwise 1,1-dichloro-2-vinylcyclopropane (6.8g; 50 mmol) giving a slightly exothermic reaction. The mixture was stirred at room temperature, under nitrogen for 12h. The crude reaction mixture was filtered through a slurry of $Na_2S_2O_4$ and Celite (prepared by treating $Na_2S_2O_4$ (0.75g) with Celite (9g) in methanol (45$cm^3$)). Evaporation of solvent gave the crude product 7.3g (87%).

This product was purified by silica gel chromatography (80g silica gel, 50cm x 4 cm column) eluting with 13% methanol in chloroform. Solvent was evaporated off and the crude material was dissolved in the minimum volume of hot ethyl acetate, and hexane was added dropwise until faint opalescence was observed. The mixture was allowed to stand overnight (15h) at 0°C and the white crystalline material was filtered off and dried in air: m.p.94°C., 5.8g, (69%).

<u>$^1$H n.m.r. ($CDCl_3$)</u> δ1.5(m,2H), 2.3 (m,1H), 3.65 (m,2H), 3.8 (m,1H) p.p.m.

<u>$^{13}$C n.m.r. ($CD_3OD$)</u> δ25.7(C4), 33.3(C3), 49.9($CD_3OD$), 66.5(C1), 73.8(C2)p.p.m.

<u>Elemental Analysis</u> <u>Found</u> C 35.18, H 4.67, Cl 41.73%; <u>calculated</u> for $C_5H_8Cl_2O_2$ C 35.11, H 4.72, Cl 41.65%

<u>Cyclopropylethane-1,2-diol</u>

To a 250$cm^3$ three necked round-bottomed flask fitted with dry ice/acetone condenser, gas inlet system and magnetic follower was added (1,1-dichlorocycloprop-2-yl)ethane-1,2-diol (3.0g; 17.6 mmol). Ammonia

($150cm^3$) was distilled into the flask *via* a gas inlet tube. Sodium (4.5g; 196 mmol) was added in small pieces until a permanent blue colouration was observed in the reaction flask. The mixture was stirred at room temperature overnight (16h) allowing the ammonia to evaporate slowly from the flask, and the residue was dispersed in methanol ($50cm^3$). The mixture (containing a solid, NaCl) was neutralised with 5M hydrochloric acid. The aqueous layer was continuously extracted with dichloromethane (20h). The extract was dried ($MgSO_4$) and solvent was evaporated to yield 1.8g (80%) crude material. This was purified by silica gel chromatography (50g silica gel, 25cm x 2.5cm column) using 13% v/v methanol in chloroform as eluting solvent, to give pure material 1.35g (60%).
$^1H$ n.m.r. ($CDCl_3$) 0.35(m,2H), 0.55(m,3H), 3.65(m,2H), 3.0(m,1H) p.p.m.

### 3:2(c) Summary of Enzymological Assays

The enzymological assays were performed by Mr. A. Karagiorgas and Dr. M.Foster. Details of these procedures are described elsewhere[76]. It was concluded that the cyclopropyl diols were not substrates for diol dehydrase. Competitive inhibition studies revealed that the cyclopropyl diols were however, weak inhibitors of diol dehydrase. This suggests that they are bound weakly at the active site of the enzyme and must, in some way, be prevented in achieving the conformation required for them to function as substrates at the active site. The enzyme used in these studies was only *ca* 20% pure, and therefore, definitive conclusions were not possible at that stage. Currently, efforts are being made by Dr. Foster in Oxford to obtain the enzyme in a pure state.

## 3:3 Synthesis of Cyclopropylmethylcobaloximes: their Kinetics and Mechanism of Rearrangement

The synthesis of cyclopropylmethyl(pyridine)cobaloxime is outlined in Scheme 9. For $^{13}C$ labelled compounds K[$^{13}CN$] (96.5 atom %) was used, for natural abundance samples KCN was employed.

### 3:3(a) Experimental

**Preparation of [$^{13}CN$]-1-chloro-3-cyanopropane**

To a homogenous solution of K[$^{13}CN$] (5.25g; 75 mmol) in water ($6.25cm^3$; 350 mmol) at 45°C, was added absolute ethanol ($21.9cm^3$) followed by 1-bromo-3-chloropropane (9.88g; 62.5 mmol) and the mixture was heated under reflux for 1.5h. The mixture was cooled, diluted with water ($28cm^3$), and the oily layer was extracted into dichloromethane ($5cm^3$). The aqueous phase was extracted with dichloromethane (2 x $5cm^3$). The combined organic extracts were washed with saturated aqueous calcium chloride ($9cm^3$) and water ($9cm^3$), and were dried ($MgSO_4$) and solvent was evaporated off. The resulting oil was fractionally distilled (b.p.79-81° at 9 mm Hg) to yield [$^{13}CN$]-1-chloro-3-cyanopropane, 3.4g (53%) of pure material.

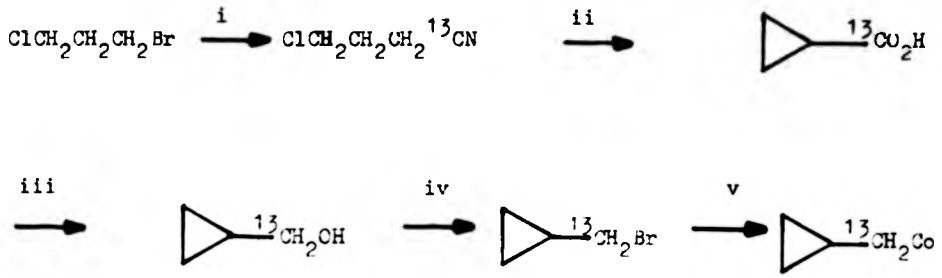
$^1H$ n.m.r. ($CDCl_3$) 2.6 (t,2H), 2.25 (m,2H), 3.7 (t,2H) p.p.m.

$^{13}C$ n.m.r. ($CDCl_3$) 43(C3), 14.7(C2), 28.3(C1), 119 ($^{13}CN$) p.p.m.

**Preparation of [$^{13}CO_2H$] Cyclopropanecarboxylic Acid**

Powdered sodium hydroxide (30g; 750 mmol) was mixed with [$^{13}CN$]-1-chloro-3-cyanopropane (diluted with unlabelled material to 32 atom % $^{13}C$ enrichment) (20.8g; 200 mmol) and the mixture was heated on a steam bath for 1h.

Scheme 9. Synthesis of $[^{13}CH_2Co]$ Cyclopropylmethyl(pyridine)cobaloxime




where Co = $Co(dmgH)_2py$

i. $K[^{13}CN]$
ii. $H_2O/NaOH$
iii. $LiAlH_4$/ethoxyethane
iv. $PBr_3$/pyridine/ethoxyethane
v. (Pyridine)cobaloxime(I)/ethanol

NB. For unlabelled cobaloxime KCN was used in place of $K[^{13}CN]$

Water (10 x 10cm$^3$) was added in portions over a 2h. period, and the mixture heated for a further 1.5h. The resulting suspension was cooled in ice and added to a mixture of concentrated sulphuric acid (23cm$^3$) and ice (60g.). The dark brown upper layer containing cyclopropanecarboxylic acid was removed and the aqueous layer extracted with ethoxyethane (200cm$^3$). The combined organic extracts were dried ($MgSO_4$) and solvent was evaporated off. The acid distilled (b.p. 84° at 15 mm Hg) to yield 15.1g (88%) of pure material.

$^1$H n.m.r. ($CDCl_3$) δ1.2 (m,4H), 2.8 (m,1H) p.p.m.

$^{13}$C n.m.r. ($CDCl_3$) δ181.9 ($^{13}CO_2H$), 12.9 (C1), 9.2 (C2,C3 equivalent) p.p.m.

Preparation of [$^{13}CH_2OH$] Cyclopropylmethanol

To a suspension of lithium tetrahydroaluminate (4.408g; 116 mmol) in ethoxyethane (25cm$^3$) was added dropwise [$^{13}CO_2H$] cyclopropanecarboxylic acid (10g; 116 mmol) in ethoxyethane (50cm$^3$) over 2h. The mixture was heated under reflux for 3h, then water (25cm$^3$) was added cautiously followed by 10% sulphuric acid (50cm$^3$). The ethoxyethane layer was separated and the aqueous layer extracted with ethoxyethane (2 x 100cm$^3$). The combined ethereal extracts were dried ($MgSO_4$), solvent was evaporated, and the oil distilled to yield 8.0g (95%) pure [$^{13}CH_2OH$] cyclopropylmethanol (b.p. 122-126° at 760 mm Hg).

$^1$H n.m.r. ($CDCl_3$) δ0.35 (m,2H), 0.9 (m,2H), 1.1 (m,1H), 3.35 (d,2H) p.p.m.

$^{13}$C n.m.r. ($CDCl_3$) δ2.8 (C2 and C3 equivalent cyclopropane), 13.5 C1 cyclopropane), 67.5 ($^{13}CH_2OH$) p.p.m.

Preparation of $[^{13}CH_2Br]$ Cyclopropylmethyl bromide

To a stirred solution of $[^{13}CH_2OH]$ cyclopropylmethanol (2.51g; 34.8 mmol), pyridine (6.26g; 69.6 mmol) and ethoxyethane (22cm$^3$) was added phosphorus tribromide (3.76cm$^3$; 40 mmol) in ethoxyethane (9cm$^3$) over 1h. at -25°C. The mixture was stirred at -10° for 1h. and finally in a cold room (0-3°C) for 2 days. The excess of phosphorus tribromide was destroyed using ice (5g), the ethoxyethane was separated and washed successfully with 10cm$^3$ portions of ice/water, 80% orthophosphoric acid, ice-cold saturated aqueous sodium bicarbonate, ice/water, and finally dried ($MgSO_4$). The ethoxyethane was evaporated off and the $[^{13}CH_2Br]$-cyclopropylmethyl bromide distilled (b.p. 102-110° at 760 mm Hg) to yield 2.6g (55%) pure material.

$^1$H n.m.r. ($CCl_4$) $\delta$ 0.35 (m,2H), 0.18 (m,2H), 1.25 (m,1H), 3.25 (d,2H) p.p.m.

I.R. (liquid film) 3080,3000,2950,2850,1430,1220 cm$^{-1}$.

Preparation of $[^{13}CH_2Co]$ Cyclopropylmethyl(pyridine)cobaloxime

Bromo(pyridine)cobaloxime (2.25g; 5 mmol) and absolute ethanol (50cm$^3$) were stirred under nitrogen at 0°C, in a Schlenk tube for 45 minutes. Sodium borohydride (0.57g; 5 mmol) and $[^{13}CH_2Br]$ cyclopropylmethylbromide (0.675g; 5 mmol) were added and the reaction mixture was stirred at 0°C for 4h. Water (40cm$^3$) containing 2% pyridine was added and air was blown through the reaction mixture for 30 minutes. The precipitated cobaloxime was washed successively with 50cm$^3$ portions of water, absolute ethanol and ethoxyethane, and dried *in vacuo* to yield 1.8g; (41%) pure material.

$^1$H n.m.r. ($CDCl_3$) $\delta$ 0.15 (d.d.,2H), 0.55 (d.d.,2H), 0.85 (m,1H), 1.9 (d,2H) 2.35 (s,12H), 7.7 (t,2H), 8.15 (t,1H), 9.1 (d,2H) p.p.m.

$^{13}C$ n.m.r. ($CDCl_3$) δ6.43 (2C), 11.96, 13.96, 37.83, ($^{13}CH_2$-Co), broad due to coupling to $^{59}Co$,(I=7/2), 125.25, 137.53, 149.29, 149.81 p.p.m.

Stability of Cyclopropylmethyl(pyridine)cobaloxime

Cyclopropylmethyl(pyridine)cobaloxime rearranges with a half-life of 3h at 37°C. The rearrangement can be suppressed by addition of pyridine; 1 mole equivalent of pyridine completely arrests the rearrangement (heating at 60°C for 1 week shows no rearrangement product, but-3-enyl-(pyridine)cobaloxime). The addition of trifluoroacetic acid increases the rate of rearrangement (effectively removing coordinated pyridine as pyridinium trifluoroacetate).

Preparation of But-3-enyl(pyridine)cobaloxime

To a Schlenk tube was added $CoCl_2.6H_2O$ (2.38g; 10 mmol) and dimethylglyoxime (2.32g; 20 mmol) in methanol (30cm$^3$). The mixture was stirred for 45 minutes under nitrogen. Aqueous sodium hydroxide (10M, 2.0cm$^3$, 20 mmol) was added followed by pyridine (0.806cm$^3$; 10 mmol) and the reaction mixture was cooled at -15°C. After 15 minutes, potassium hydroborate (0.135g; 2.5 mmol) dissolved in sodium hydroxide (10M; 1.0cm$^3$; 10 mmol) plus 0.2cm$^3$ water was added and the mixture was left for 5 minutes, after which it had assumed a dark blue colouration. 1-Bromo-but-3-ene (0.98cm$^3$; 10 mmol) was added and the reaction was stirred overnight at room temperature. Air was blown through the reaction mixture for 30 minutes. Ice water (30cm$^3$) containing 2% pyridine was added and the precipitated cobaloxime was filtered off.

For purification of alkylcobaloximes by silica gel chromatography a standard procedure is used. The cobaloxime (0.5g) is dissolved in 2cm$^3$

of dichloromethane containing 2 drops of pyridine. The mixture is placed onto a silica gel column (25cm x 2.5cm; 20g silica gel) and is eluted with dichloromethane/methanol/pyridine (180: 10: 1). The alkylcobaloxime moves as a orange band leaving impurities (e.g. cobaloxime(II)species) at the origin. This band is collected and solvent is evaporated to yield the pure alkylcobaloxime.

$^{1}H$ n.m.r. ($CDCl_3$) $\delta$ 1.9 (d,2H), 2.35 (d,12H), 5.0 (d.d.,2H), 5.9 (m,1H), 7.7 (t,2H), 8.15 (t,1H), 9.1 (d,2H) p.p.m.

$^{13}C$ n.m.r. ($CDCl_3$) $\delta$12.09, 29.25 ($Co-CH_2$, broad due to coupling to $^{59}Co$,I-½) 34.51, 112.90, 139.09, 125.25, 137.53, 149.30, 149.82 p.p.m.

Preparation of Bromo(base)cobaloximes

These compounds were prepared by one of two methods[77].

1. To a hot solution of $CoBr_2.6H_2O$ (6.86g; 21 mmol) and dimethylglyoxime (4.88g; 42 mmol) in ethanol (200cm$^3$) was added the base ligand required e.g. dimethylaminopyridine (420 mmol). After cooling to 20°, a stream of air was blown through the mixture for 30 minutes. The reaction was allowed to stand at room temperature for 1h., during which time the product precipitated. The crystals were filtered off and were washed successively with 50cm$^3$ portions of water, ethanol and ethoxyethane, and were dried at room temperature under vacuum. This method failed to yield a bromo(4-cyanopyridine)cobaloxime. It was however, successful for the preparation of cobaloximes containing 4-nitropyridine, 4-dimethylaminopyridine, and 2-and 4-methylpyridine.

2. To a hot (ca 60°C) solution of $Co(AcO)_2.4H_2O$ (1.53g; 6.15 mmol) in ethanol (100cm$^3$) under nitrogen was added dimethylglyoxime (1.43g; 12.3 mmol). The axial base e.g. 4-cyanopyridine (1.28g; 12.3 mmol) was added and the solution was cooled to room temperature. Sodium bromide (0.65g; 6.15 mmol) was added and air was blown through reaction mixture for 30 minutes. After standing at room temperature for 1-2h. the product crystallised and was removed by filtration. It was washed successively with 50cm$^3$ portions of water, ethanol, ethoxyethane and dried *in vacuo*.

Bromo(4-dimethylaminopyridine)cobaloxime $^1$H n.m.r. ($CDCl_3$) δ2.50(s,12H), 3.08(s,6H), 6.45(d,2H), 7.7(d,2H) p.p.m.

Bromo(4-cyanopyridine)cobaloxime $^1$H n.m.r. ($CDCl_3$) δ2.55(s,12H), 7.65 (d,2H), 8.65(d,2H) p.p.m.

Bromo(4-methylpyridine)cobaloxime $^1$H n.m.r. ($CDCl_3$) δ2.35(5,3H), 2.55 (S,12H), 7.15(d,2H), 8.15(d,2H) p.p.m.

Bromo(4-nitropyridine)cobaloxime $^1$H n.m.r. ($(CD_3)_2CO$) 2.45(s,12H), 8.1(d.2H), 8.8(d,2H) p.p.m.

Bromo(2-methylpyridine)cobaloxime $^1$H n.m.r. ($CDCl_3$) δ2.35(s,12H), 7.5(m,2H), 7.7(m,1H), 8.5(d,2H).

Preparation of Diaquocobaloxime(II)

A Schlenk tube was filled with 100cm$^3$ methanol and flushed with nitrogen for 1h. $Co(AcO)_2.4H_2O$ (6.225g; 25 mmol) and dimethylglyoxime (5.8g; 50 mmol) were added and the mixture was stirred under a fast stream of nitrogen for 1-2h, to yield an orange crystalline product. The Schlenk tube was transferred to a nitrogen dry box and the precipitate was filtered under suction, washed with degassed water (25cm$^3$) and dried *in vacuo*, to yield 5.6g (70%) diaquocobaloxime(II),

which turns black on exposure to air.

Monitoring the Rearrangement of Cyclopropylmethyl(pyridine)cobaloxime

Cyclopropylmethyl(pyridine)cobaloxime rearranges to but-3-enyl(pyridine)-cobaloxime as the only detectable product. The rearrangement is conveniently monitored by n.m.r. spectroscopy for temperatures 298K < T > 320K. $^{1}H$ n.m.r. spectroscopy was used exclusively to test the purity of samples of cyclopropylmethyl(pyridine)cobaloxime.

$^{13}C$ Labelling Study

The sample of $[^{13}CH_2]$cyclopropylmethyl(pyridine)cobaloxime (30mg; mmol) was purified by silica gel chromatography and dissolved in $CDCl_3$ ($1cm^3$) containing 5% v/v TMS as internal standard. To this solution was added four drops of pyridine (to suppress rearrangement of the $[^{13}CH_2Co]$-cyclopropylmethyl(pyridine)cobaloxime. The solution was transferred to a 10mm external diameter n.m.r. tube and the $^{13}C$ n.m.r. spectrum recorded (s.w. 6000, no. of scans 5000, T=240K). The sample was then evaporated at 0°C to dryness in vacuo (to remove all traces of pyridine), the residue was dissolved in $CDCl_3$ ($1cm^3$) containing TMS, and the solution was incubated for 20 minutes at 37°C. Then, the solution was cooled to - 33°C and its $^{13}C$ n.m.r. spectrum recorded. Incubation at 37°C and recording of spectra at -33°C was repeated until the rearrangement was judged complete. A $^{13}C$ n.m.r. spectrum of but-3-enyl(pyridine)-cobaloxime was also recorded.

$^{1}H$ n.m.r. Spectral Measurements

$^{1}H$ n.m.r. spectroscopy was employed to determine the rate constant for the rearrangement of cyclopropylmethyl- to but-3-enylcobaloximes and

activation parameters, $\Delta H^{+}$ and $\Delta S^{+}$. Samples of cyclopropylmethylcobaloxime were purified by silica gel chromatography at $0^{o}C$ prior to use. A sample of the cobaloxime (60mg; 0.14 mmol) was dissolved in $CDCl_3$ ($0.5cm^3$) and its rearrangement to but-3-enylcobaloxime was followed by $^1H$ n.m.r. spectroscopy. The $^1H$ n.m.r. spectra of cyclopropylmethyl- and but-3-enylcobaloxime, and a sample that is approx.50% rearranged, are shown in fig.12. The useful features of the spectrum of cyclopropylmethylcobaloxime are the 5 H'S of the cyclopropane ring $\delta$ 0.3 (m,2H); $\delta$ 0.65 (m,2H); $\delta$ 0.95 (m,1H). The salient change during the rearrangement is the diminution in intensity of these cyclopropane H resonances with concurrent formation of new resonances at $\delta$ 5.35,(d.d,2H), $\delta$ 6.20, (m,1H); due to the allyl group in but-3-enylcobaloxime.

To follow the kinetics of the rearrangement, a sample of cyclopropylmethyl-(pyridine)cobaloxime (60mg; 0.14 mmol) was dissolved in the solvent ($CDCl_3$, $CD_2Cl_2$, $CD_3OD$, $C_6D_6$), ($0.5cm^3$) and placed in an n.m.r. tube. The rearrangement was followed by $^1H$ n.m.r. spectroscopy in a thermostated probe. The extent of the rearrangement was estimated by a comparison of the areas under the peaks of the cyclopropyl H resonances and the but-3-enyl alkene H resonances. The rearrangement was first order w.r.t. [cobaloxime] and a graph log [a-x(t)] was linear with slope = - k/2.303, where [a-x(t)] = % cyclopropylmethylcobaloxime remaining at time t.

A representative calculation for the estimation of cyclopropylmethyl- and but-3-enylcobaloxime at time t is appended (e.g. rearrangement in $CD_2Cl_2$ at 298K for t = 242s). From the integrated spectrum, the area due to the cyclopropane ring H's is equivalent to 68.0cm (5H); for the butenyl H's, the total area under the peaks $\delta$ 5.4 is equivalent to 30.8cm (2H).

Therefore, for a direct comparison of the relative concentration of cyclopropylmethyl- to but-3-enylcobaloxime, the relative step height of the but-3-enyl peak is multiplied by 5/2.

i.e.

$$\text{Step height for but-3-enylcobaloxime} = \frac{30.8 \times 5 \text{ cm}}{2}$$

$$= \underline{76.9 \text{ ( 5H)}}$$

$$\text{\% cyclopropylmethylcobaloxime} = \frac{68.0}{68.0+76.9} \times 100\%$$

$$= \underline{46.9\%}$$

A specimen kinetic plot is shown in fig.13. Kinetic measurements were performed under various conditions e.g. variable temperatures, differing solvents, both aerobically and anaerobically, and in the presence of added cobaloxime(II). The slopes of the graphs were calculated using an unweighted least squares procedure with the aid of a computer program (WLSAPROG).

## 3:4 RESULTS AND DISCUSSION

### 3:4(a) $^{13}C$ labelling Study of the Rearrangement of Cyclopropylmethyl- to But-3-enyl(pyridine)cobaloxime.

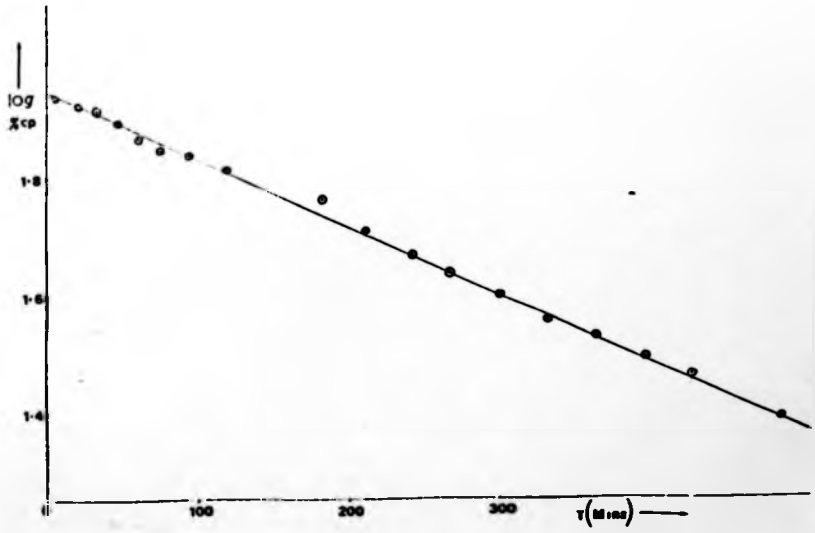
The aim of the experiment was to distinguish between some of the possible mechanisms for this rearrangement shown in Scheme 10. From the Scheme, it can be deduced that if this rearrangement proceeds via the cyclobutyl intermediate (pathway b), scrambling of the $^{13}C$ label would be observed

Figure 13. Kinetic Data for the Rearrangement of Cyclopropylmethyl- to But-3-enyl(pyridine)cobaloxime in $CD_2Cl_2$ at 298K

| Time | cp | Log %cp | Time | cp | Log %cp |
|---|---|---|---|---|---|
| 4.3 | 70.0 | 1.940 | 242.0 | 68.0 | 1.672 |
| 20.5 | 65.5 | 1.928 | 266.5 | 64.6 | 1.642 |
| 32.75 | 62.0 | 1.920 | 299.5 | 58.3 | 1.602 |
| 45.75 | 59.3 | 1.898- | 329.0 | 53.0 | 1.561 |
| 60.25 | 57.5 | 1.870 | 360.0 | 46.5 | 1.536 |
| 75.5 | 55.75 | 1.853 | 392.0 | 45.5 | 1.497 |
| 93.25 | 99.5 | 1.846 | 421.5 | 40.3 | 1.466 |
| 120.5 | 87.0 | 1.819 | 479.5 | 36.3 | 1.391 |
| 183.5 | 73.5 | 1.768 | 513.5 | 30.75 | 1.317 |
| 211.5 | 69.0 | 1.710 | | | |

Time = mins.

cp = Area under integral spectra associated with the cyclopropylmethylcobaloxime.



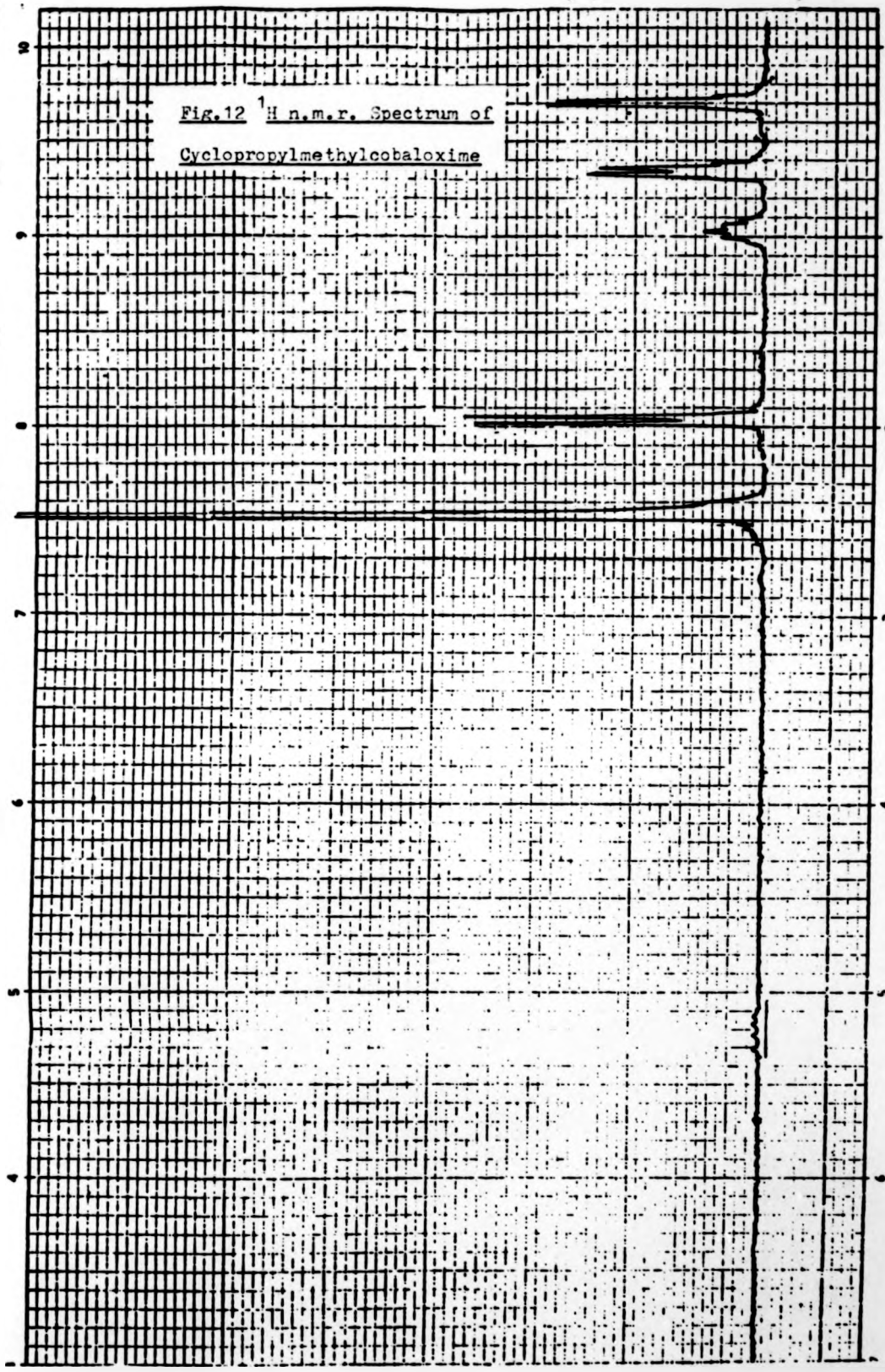


Fig.12 $^{1}H$ n.m.r. Spectrum of Cyclopropylmethylcobaloxime

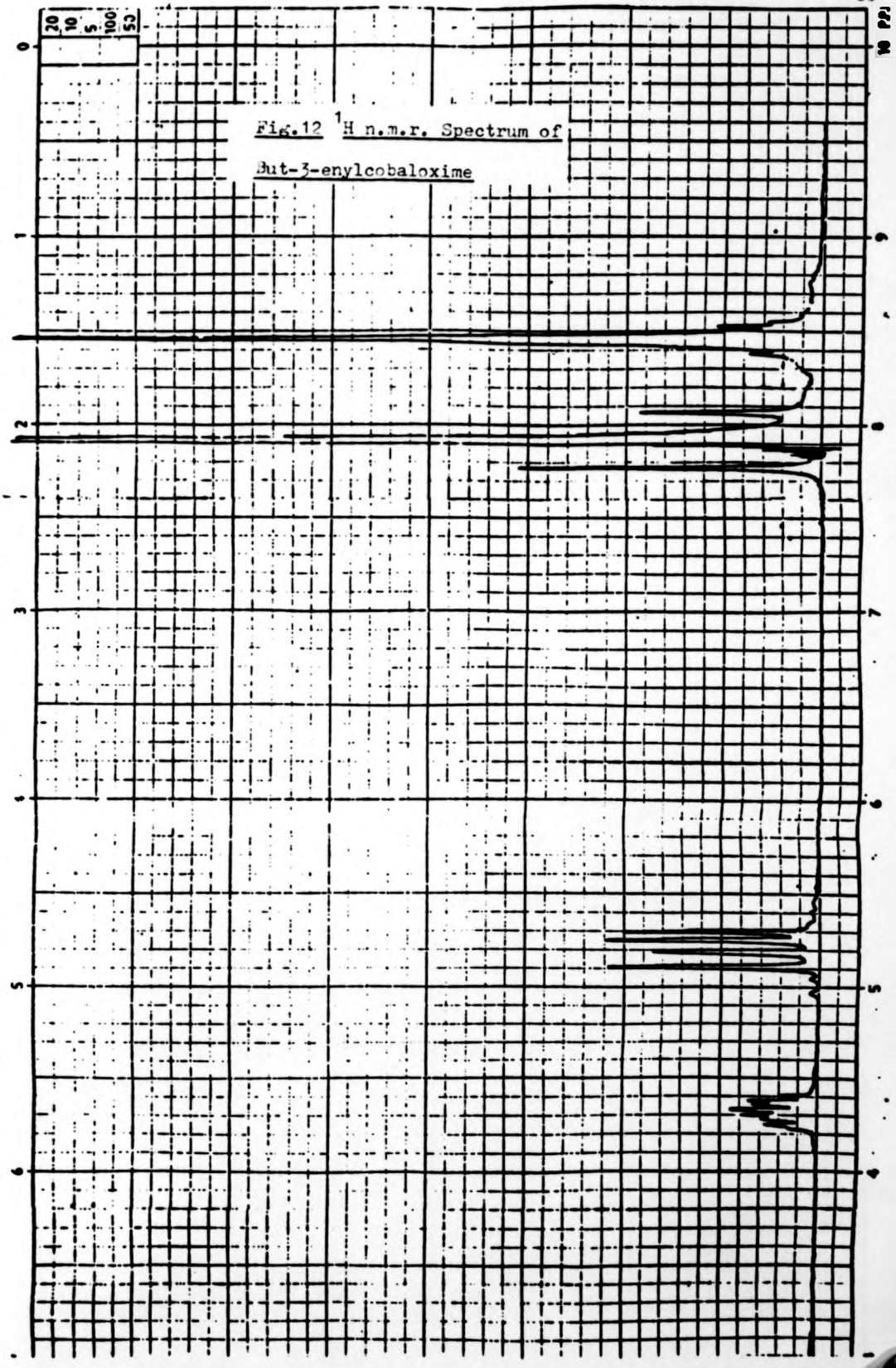



Fig.12 $^{1}H$ n.m.r. Spectrum of

But-3-enylcobaloxime

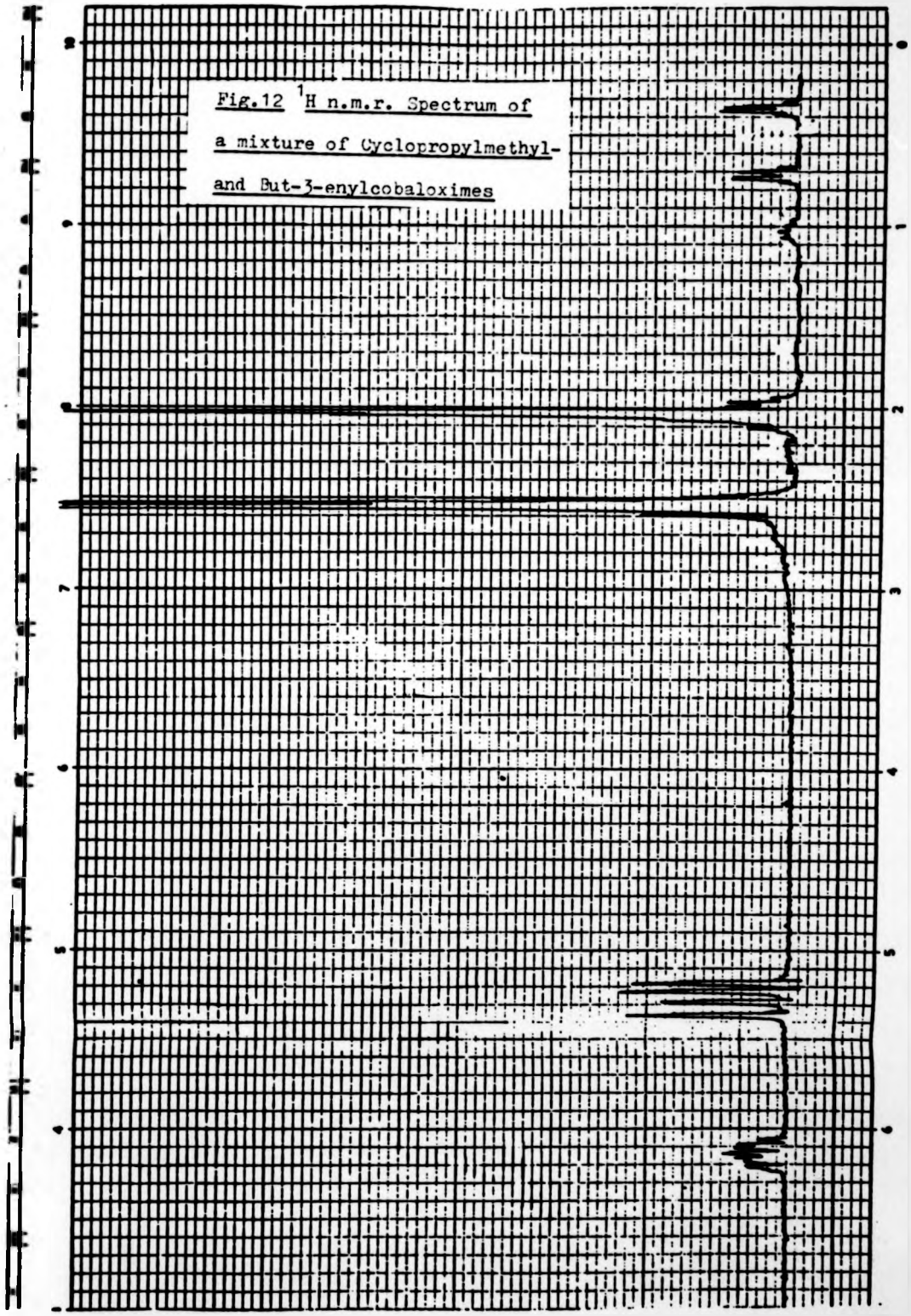
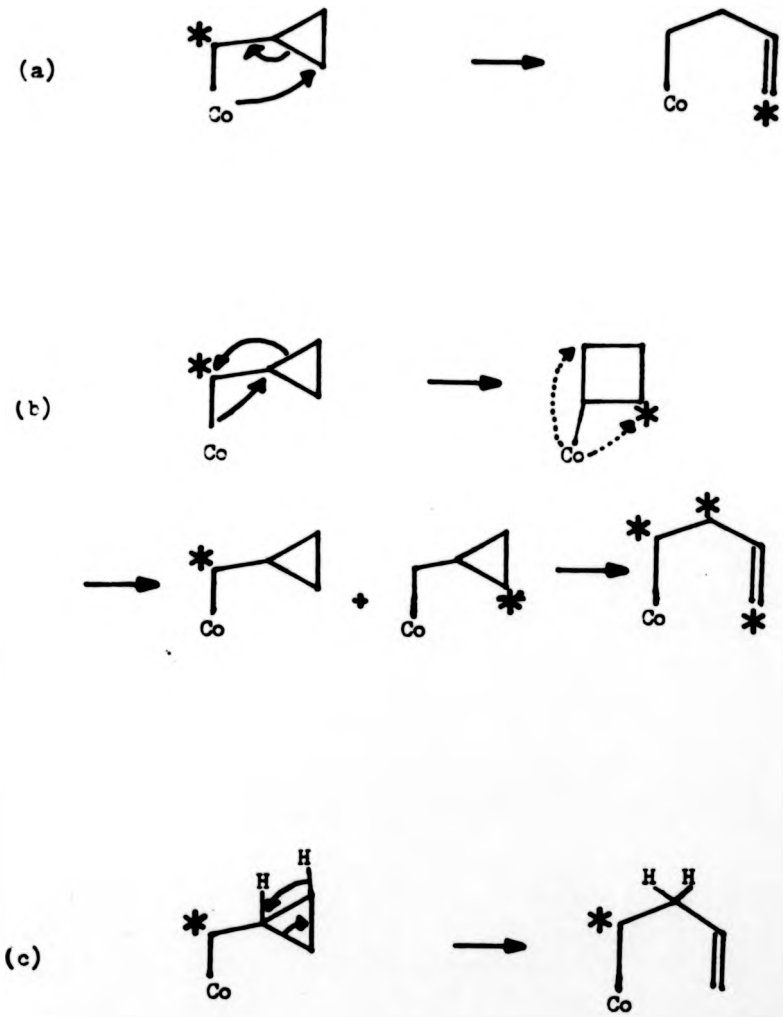


Fig.12 $^{1}H$ n.m.r. Spectrum of a mixture of Cyclopropylmethyl- and But-3-enylcobaloximes

Scheme 10. Some Possible Mechanisms for the Rearrangement of Cyclopropylmethyl- to But-3-enyl(pyridine)cobaloxime



between C1,C2 and C4 of the product butenylcobaloxime. If a mechanism involving a 1,2-hydride shift were operative (pathway C), the label would appear exclusively at C1 of the but-3-enylcobaloxime. If a 1,3-cobalt shift mechanism were operative (pathway a), the label would register at C4 of the but-3-enylcobaloxime.

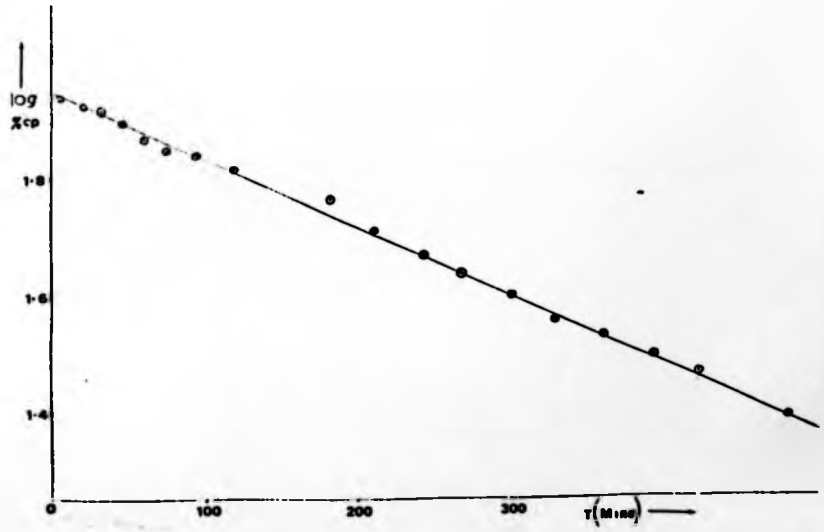
Key $^{13}C$ n.m.r. spectra are shown in fig. 14 and 15. These correspond to the labelled and unlabelled cyclopropylmethylcobaloximes(a) and (b) respectively fig.14. The spectra of fig.15 correspond to the labelled and unlabelled but-3-enylcobaloximes (c) and (d), respectively. Assignments of the resonances were made from comparisons with known compounds[78], the method of synthesis and the presence of adjacent $^{59}Co$ nuclei. These are, $\delta$ 6.50 (A, 2 x cyclopropyl $\underline{C}H_2$), 11.96 (B, 4 x dmgH $\underline{Me}$), 14.04(C, cyclopropyl $\underline{C}H$), 38.09(D, Co-$\underline{C}H_2$ broad, caused by coupling to $^{59}Co$,I = 7/2) and 125.25, 137.47, 149.23 and 150.01 p.p.m. (4 x dmgH $\underline{C}$=N and pyridine carbon atoms). Particularly important are those peaks labelled A. and D. In the spectrum of $^{13}C$ labelled cyclopropylmethylcobaloxime (fig.14) only the signal from the cobalt-bonded carbon atom in the enriched cobaloxime is of significantly enhanced intensity. During the rearrangement signals due to the cyclopropylmethylcobaloxime are replaced by signals due to the but-3-enylcobaloxime,and the $^{13}C$ n.m.r. spectrum after complete conversion (48h) is shown in fig. 15c. This spectrum showed no change after further incubation (7 days at 310K, then 3h at 333K). Comparison of this latter spectrum with that of authentic unlabelled but-3-enylcobaloxime (fig.15d), shows that only one signal is significantly enhanced in intensity. This is due to the olefinic methylene carbon C4; assignments of the spectrum of fig.15 are as follows:$\delta$12.09(A,4 x dmgH $\underline{Me}$), 29.25 (B, Co-$\underline{C}H_2$, broad due to coupling

Figure 13. Kinetic Data for the Rearrangement of Cyclopropylmethyl- to But-3-enyl(pyridine)cobaloxime in $CD_2Cl_2$ at 298K

| Time | %cp | Log %cp | Time | %cp | Log %cp |
|---|---|---|---|---|---|
| 4.3 | 70.0 | 1.940 | 242.0 | 68.0 | 1.672 |
| 20.5 | 65.5 | 1.928 | 266.5 | 64.6 | 1.642 |
| 32.75 | 62.0 | 1.920 | 299.5 | 58.3 | 1.602 |
| 45.75 | 59.3 | 1.898- | 329.0 | 53.0 | 1.561 |
| 60.25 | 57.5 | 1.870 | 360.0 | 46.5 | 1.536 |
| 75.5 | 55.75 | 1.853 | 392.0 | 45.5 | 1.497 |
| 93.25 | 99.5 | 1.846 | 421.5 | 40.3 | 1.466 |
| 120.5 | 87.0 | 1.819 | 479.5 | 36.3 | 1.391 |
| 183.5 | 73.5 | 1.768 | 513.5 | 30.75 | 1.317 |
| 211.5 | 69.0 | 1.710 | | | |

Time = mins.

cp = Area under integral spectra associated with the cyclopropylmethyl-cobaloxime.



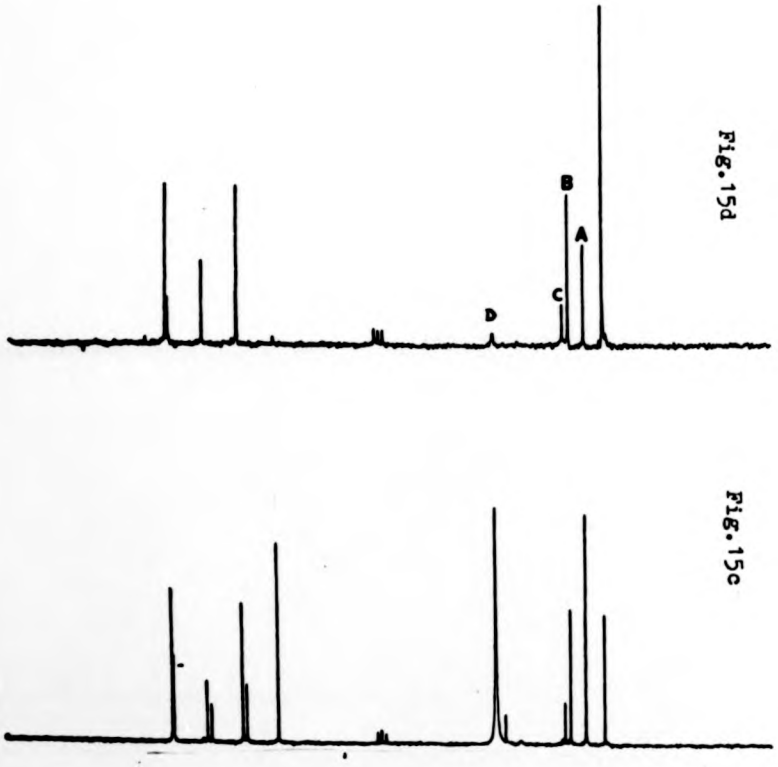



Fig.15 $^{13}C$ n.m.r. Spectra of Partially Rearranged Cyclopropylmethylcobaloxime

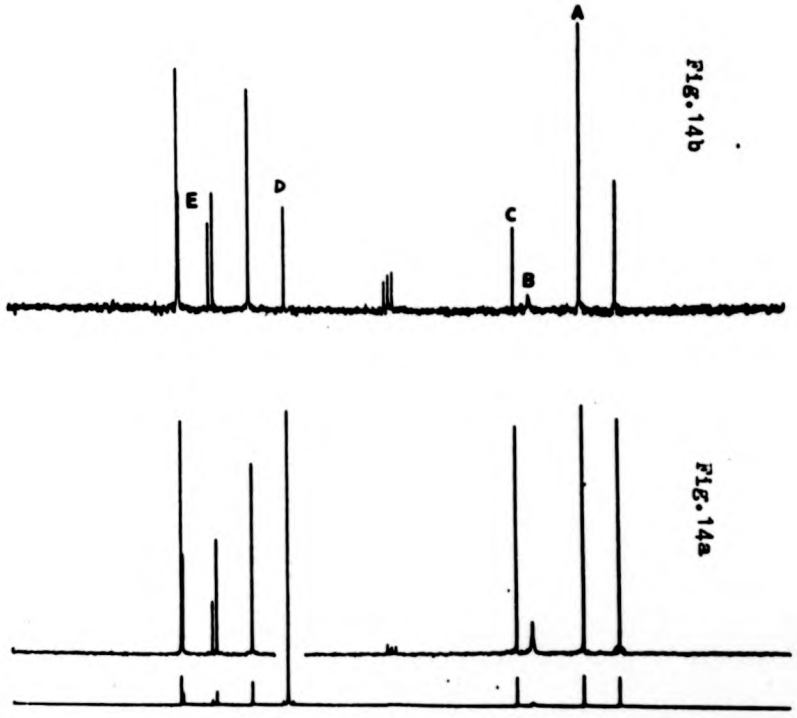



Fig.14 $^{13}C$ n.m.r. Spectra of But-3-enylcobaloxime

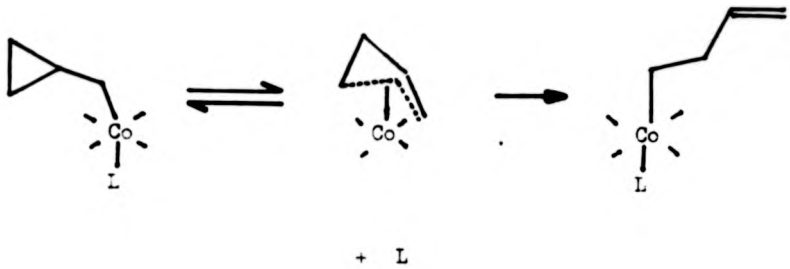
to $^{59}Co$,I=7/2), 34.51 (C,C2), 112.90 (D,C4), 139.09 (E,C3) and 125.25, 137.53,149.30, and 149.82 p.p.m. due to pyridine carbon atoms and 4 x C=N of dmgH).

The spectra demonstrate the C1 of the cyclopropylmethylcobaloxime become C4 of the but-3-enylcobaloxime. No other resonance of the product but-3-enylcobaloxime is enhanced in intensity. This indicates that the $^{13}C$ label is located exclusively in one position (i.e. at C4 of the but-3-enylcobaloxime) and thereby rules out mechanisms involving hydride shifts of cyclobutyl intermediates.

These results are consistent with a rearrangement which proceeds *via* a cobalt-homoallyl intermediate (Scheme 11). To form a homoallyl-cobalt species and to preserve an 18 electron configuration requires loss of a formally 2 electron donor. The possible donor atoms which could be removed from the first coordination sphere are one of the four nitrogens of the dimethylglyoximato ligands or the nitrogen of the axial pyridine. The observation that addition of free pyridine to cyclopropylmethylcobaloxime arrests or retards the rearrangement (no observed rearrangement when cyclopropylmethylcobaloxime was treated with one mole equivalent of pyridine and heated at 60° for two days) strongly suggests that it is coordinated pyridine which is lost during formation of a 5-coordinate intermediate. Also addition of excess dimethylglyoxime to cyclopropylmethylcobaloxime has no noticeable effect on the rate of rearrangement.

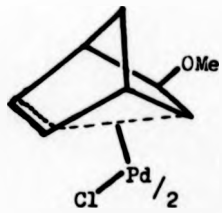
There is scanty evidence in the literature to support the homoallyl metal structure. Green and Hancock[79] found that the $\sigma$-$\eta$-norbornenyl-palladium complex (fig.16) possessed spectroscopic properties in accord with a delocalised homoallylic structure. The reaction of e.g.cyclopentadienyl

Scheme 11. Unimolecular Mechanism via a Homoallylic Intermediate for the Conversion of Cyclopropylmethyl- to But-3-enylcobaloxime




L== Lewis base e.g. pyridine

Figure 16. The $\sigma$- $\eta$-Norbornenylpalladium Complex



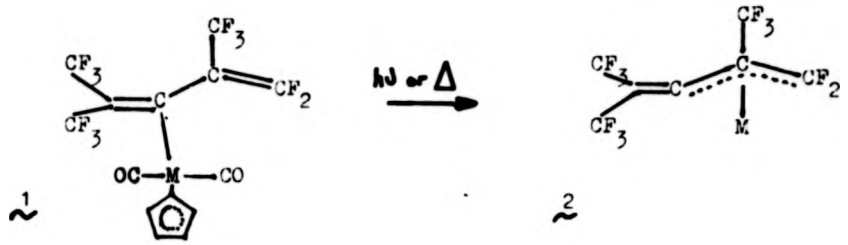
$Fe(CO)_2$, $Mn(CO)_4$-, cyclopentadienyl ($W(CO)_3$ with tetrakis(trifluoromethyl)-allene(Scheme 12), yields initially the complex 1, which on photolysis loses CO to yield the $\pi$ allyl[80] 2.

There are a variety of ways in which at $C_4H_7$ unit (from a structural standpoint) can bind to a transition metal, these are outlined in fig.17.

One attempt to prepare homoallylic complexes of nickel was undertaken by J.M.Brown[81] who studied reactions of alkyl-$\pi$-cyclopentadienyltriphenyl-phosphinenickel complexes, which are known to readily expel their triphenylphosphine ligand[82]. Compound 1a in fig.18, was found upon thermolysis to give trans-1,3-$\eta$-but-2-enyl-$\pi$-cyclopentadienylnickel complex 2, as the only major organometallic product. Specifically deuterated butenyl ligands were used to investigate the mechanism of this transformation. Analysis of the deuterium distribution in the butenyl ligand, in the product 2 from photolysis of 1b,c, produced evidence consistent with the participation of a homoallylic species in this conversion.

Suggestions have been put forward previously[83,84], for the existence of stable pentacoordinate alkylcobaloximes, e.g. in ligand exchange reactions where methyl(pyridine)cobaloxime was irradiated under nitrogen to yield methyl(aquo)cobaloxime, presumably via the pentacoordinate species. Dehydrated complexes have been formed from alkyl(aquo)-cobaloximes e.g. methyl, chloromethyl and difluoromethyl(aquo)cobaloximes by azeotropic distillation from benzene [85] or by heating in vacuo at 80-100°[86]. The dehydrated complexes thus obtained appear to be dimers in the solid state or when dissolved in non-coordinating solvents e.g.

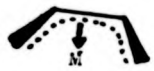
Scheme 12. Reaction of Tetrakis(trifluoromethyl)allene with some Metal Carboxylate Anions




M = Fe, Mn, W.

Figure 17. Bonding Representations for the $-C_4H_7$ Unit to Transition Metals


σ - η -homoallyl



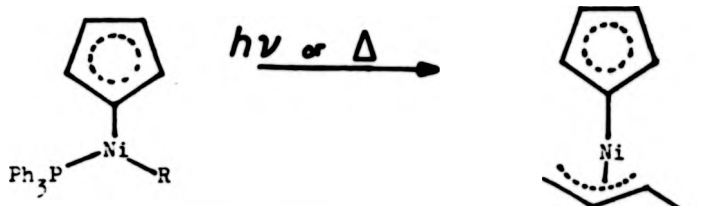

delocalised homoallyl


cyclopropylmethyl


metallobicyclopentane


bicyclobutonium

Figure 18. Reaction of the Alkyl-π-cyclopentadienyltriphenylphosphinenickel Complex




1 a; R = $CH_2CH_2CH{=}CH_2$
b; R = $CH_2CH_2CH{=}CD_2$
c; R = $CD_2CH_2CH{=}CH_2$

2

Scheme 13. The Bimolecular Mechanism for the Conversion of Cyclopropylmethyl- to But-3-enyl(pyridine)cobaloxime


$$Cl_3C\bullet + CH_2{=}CHCH_2C(H)MeCo(dmgH)_2py \longrightarrow$$


$$+ Co^{II}(dmgH)_2py$$

$$Co^{II}(dmgH)_2py + BrCCl_3 \longrightarrow BrCo^{III}(dmgH)_2py + Cl_3C\bullet$$

equation 7

benzene. Evidence for the structure of the dimer comes from a single crystal X-ray diffraction study[87]. Dimers are unlikely to occur at any appreciable concentration in coordinating solvents e.g. methanol, water, because the axial cobalt atom is likely to be solvated by solvent molecules. Evidence has recently been provided for the existence of pentacoordinate species in reactions of alkyl(aquo)cobaloximes with amines which replace their ligated water[88].

An alternative mechanism has been proposed[89] by M.D.Johnson and coworkers for the conversion of cyclopropylmethyl to but-3-enylcobaloxime shown in Scheme 13. This is a chain mechanism and requires the presence of traces of catalytic (pyridine)cobaloxime(II) as carrier. Evidence for the bimolecular mechanism comes from several examples[90] of electrophilic radical attack at the carbon of a butenylcobaloxime to yield a substituted cyclopropane and displacement of cobaloxime(II) according to equation 7. Evidence accumulated against the bimolecular mechanism and in favour of the unimolecular mechanism is listed below.

(a) The rearrangement of cyclopropylmethyl(pyridine)cobaloxime was studied at 38°C in the presence of 2 mole% (bis)aquo(cobaloximeII). The peak resonances in the $^1$H n.m.r. spectrum were sufficiently well defined (i.e. not too broad) at this concentration of (bis)aquo(cobaloximeII) to permit the study of the rearrangement of the cyclopropylmethylcobaloxime by $^1$H n.m.r. spectroscopy. The rate constant for the rearrangement $k_1 = (2.91 \pm 0.04) \times 10^{-4} s^{-1}$ cf. rate constant at 38°C in the absence of (bis) aquo(cobaloximeII), $k_1 = (3.4 \pm 0.04) \times 10^{-4} s^{-1}$. It can therefore be concluded that Co(II) has no catalytic effect at 2 mole% in the rearrangement of cyclopropylmethyl- to but-3-enyl(pyridine)cobaloxime.

(b) The rearrangement of cyclopropylmethylcobaloxime was studied at 38°C under both anaerobic and aerobic conditions. Cobaloxime(II) is very unstable in air being rapidly oxidised to cobalt(III). Therefore, conducting the rearrangement under anaerobic conditions, would increase the stability of cobalt(II) species (suggested in the bimolecular mechanism) and be manifested in an increased rate of rearrangement of cyclopropylmethylcobaloxime if this mechanism were operative. The rate constant calculated for the rearrangement under anaerobic conditions $k_1=(2.61 \pm 0.08) \times 10^{-4}\ s^{-1}$. These results are inconsistent with the bimolecular mechanism.

(c) All alkylcobaloximes described in this study were purified in darkness by column chromatography using an eluting solvent containing pyridine (this procedure should remove cobalt(II) species).

(d) No appreciable broadening of $^1H$ n.m.r. signals was observed during the course of the rearrangement of cyclopropylmethyl- to but-3-enylcobaloxime.

(e) A large positive entropy of activation is associated with the rearrangement of cyclopropylmethyl- to but-3-enylcobaloxime: see section 3: 4(b) below for discussion.

The reversibility of the rearrangement of cyclopropylmethylcobaloxime to but-3-enylcobaloxime was demonstrated by another $^{13}C$-labelling experiment outlined in Scheme 14. Here, a but-3-enylcobaloxime was specifically labelled at C1 with 20.2 atom $^{13}C$ [91], and its rearrangement ($CDCl_3$, 55°C

Scheme 14. Equilibration of a $^{13}C$ Labelled But-3-enylcobaloxime

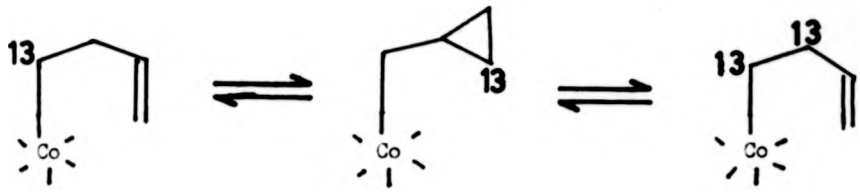



Table 6. Values of $k_1$ for the Rearrangement of Cyclopropylmethyl- to But-3-enylcobaloxime

| Temperature (K) | k $s^{-1}$ |
|---|---|
| 298 | $(4.40 \pm 0.04) \times 10^{-5}$ |
| 305 | $(1.45 \pm 0.03) \times 10^{-4}$ |
| 311 | $(3.41 \pm 0.04) \times 10^{-4}$ |
| 317 | $(6.90 \pm 0.25) \times 10^{-4}$ |

$$k_1 = \frac{kT}{h} e^{-\Delta H^{\neq}/RT} e^{\Delta S^{\neq}/R}$$

equation 8.

where $k_1$ = The calculated rate constant
k = Boltzmann's constant
h = Plank's constant
T = Temperature

for several days with noticeable decomposition of the alkylcobaloxime) was clearly demonstrated in the scrambling of the $^{13}C$ label between carbon atoms C1 and C2 of the but-3-enylcobaloxime as demonstrated by $^{13}C$ n.m.r. spectroscopy.

3:4 (b) Kinetics and Activation Parameters for the Rearrangement of Cyclopropylmethyl(pyridine)cobaloxime.

The data obtained for the temperature dependence of the rate constant for the rearrangement of cyclopropylmethyl- to but-3-enylcobaloxime in $CDCl_3$ solvent is shown in fig.19. The calculated rate constants are given in Table 6. The activation parameters $\Delta H^{+}$ and $\Delta S^{+}$ for the rearrangement were calculated using the Eyring equation (equ.8). The calculation was performed using a computer program ACTPAR. This produces a plot (lnK/T)(1/T) (see fig.20) from the data given in Table 6. The activation parameters thus obtained are:

$$\Delta H^{+} = 117.4 \pm 2.7 \text{ kJ mol}^{-1}.$$
$$\Delta S^{+} = 65.7 \pm 9.0 \text{ J mol}^{-1}\text{K}^{-1}.$$
$$k^{298} = 4.45 \times 10^{-5} \text{ s}^{-1}$$

The demonstration that the rate of the rearrangement is first order w.r.t. [cobaloxime] is consistent with the proposed mechanism involving dissociation of pyridine.

The activation parameters provide a useful piece of information regarding the mechanism of the rearrangement of cyclopropylmethylcobaloxime. The physical meaning of entropy of activation is an area subject to both interpretation and overinterpretation. In terms of transition state diagrams which describe the energy profile of a reaction, it is considered

FIG. 19. : FIRST ORDER REARRANGEMENT OF CYCLOPROPYLMETHYL- TO BUT-3-ENYL(PYRIDINE)COBALOXIME

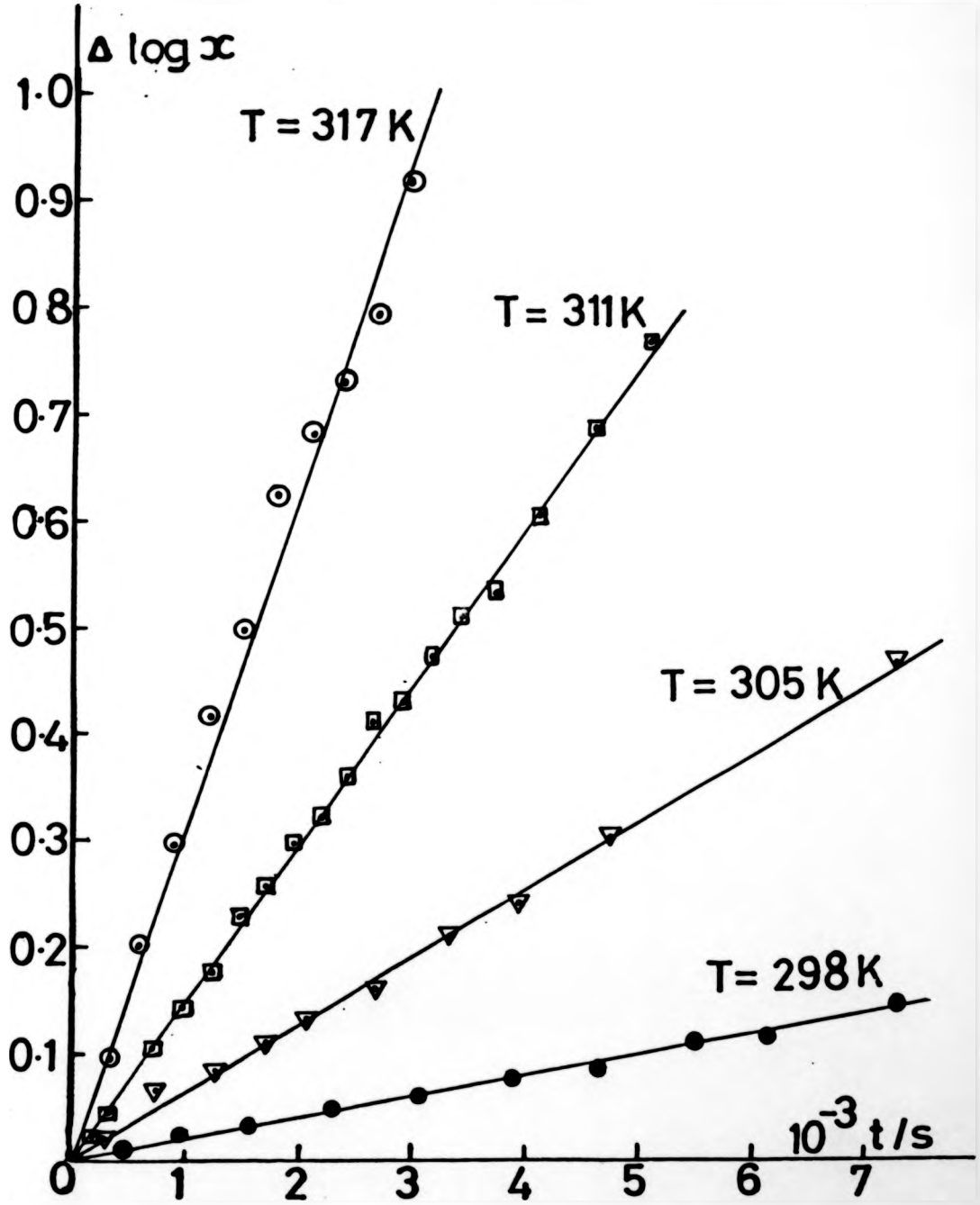
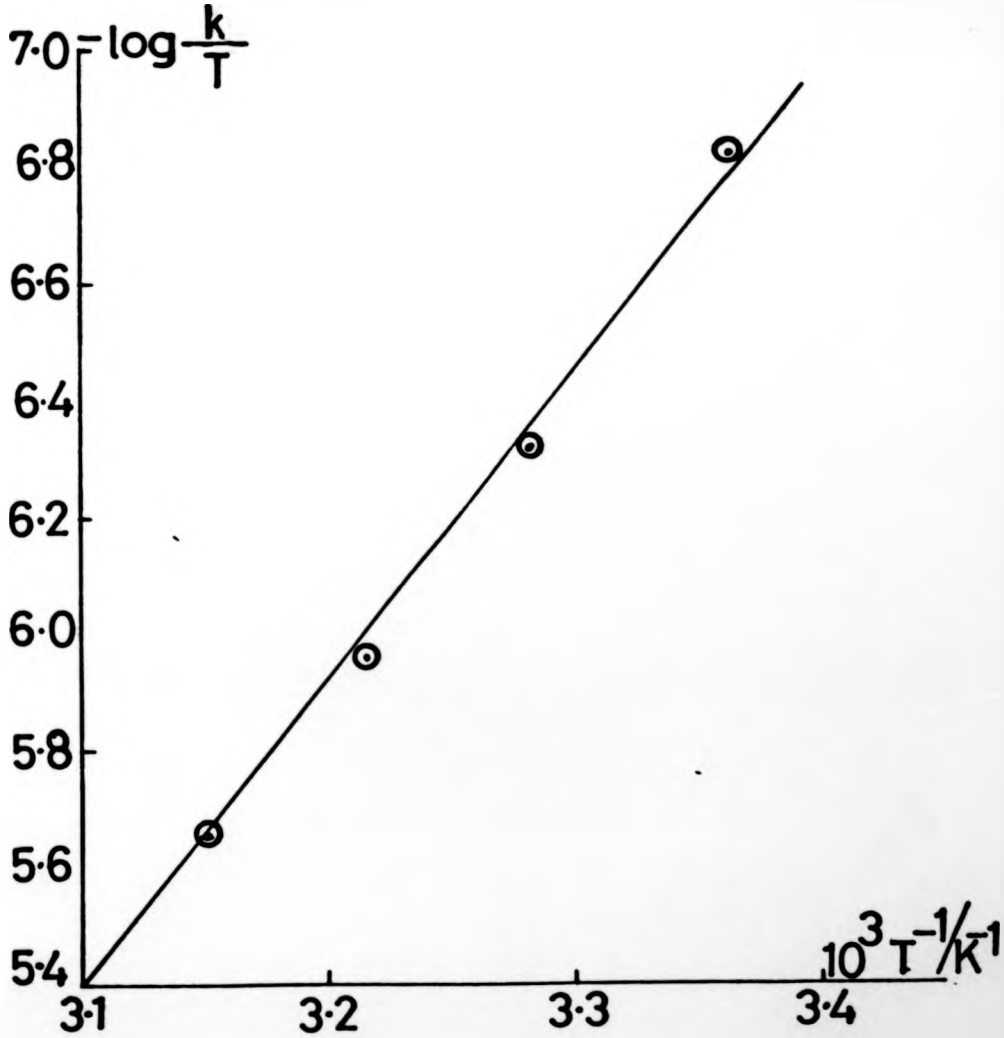


FIG 20 : EYRING PLOT FOR THE REARRANGEMENT OF CYCLOPROPYL-METHYL- TO BUT-3-ENYL(PYRIDINE) COBALOXIME



purely in terms of the change of number of molecules involved in the production of the transition state, which can be either positive or negative, in the activated complex. In practice however, it can be defined more simply; the enthalpy of activation is a measure of the energy barrier which must be overcome by reacting molecules and the entropy of activation can be considered as a measure of the change in order (or disorder) in achieving the transition state, which reflects a change in the number of molecules, development of charge in the transition state, ordering of the solvent, steric and orientation requirements, concentration effects etc..

Unimolecular reactions generally have entropies of activation near zero or positive because no concentration or orientation requirements usually exist for such reactions. Bimolecular reactions however, tend to have negative entropies of activation simply as a result of the entropy requirement for bringing together two molecules to a single activated complex, and are likely to have still more negative entropies from steric and orientation requirements, including losses of translational and rotational degrees of freedom in the transition state.

The positive nature of the entropy of activation $\Delta S^{+}$, calculated for this rearrangement provides a powerful piece of evidence in support of the unimolecular pathway for the rearrangement of cyclopropylmethylcobaloxime Scheme 11, and against the bimolecular pathway suggested Scheme 13. The large positive value of $\Delta S^{+}$ is indicative of a dissociation mechanism, i.e. formation of a pentacoordinate species. There are two possibilities to be considered as to which is the rate determining step in the rearrangement i.e. is it dissociation of pyridine to give the pentacoordinate species or is it the formation of the homoallyl intermediate from the

pentacoordinate cyclopropylmethylcobaloxime? These two processes could well be concerted with each other.

The fact that the value of $\Delta S^{+}$ is very large (65 $Jmol^{-1}K^{-1}$) is indicative that dissociation of pyridine occurs before the activated complex has been formed (fig.21), the activated complex probably consisting of a homoallyl type intermediate with the pyridine fully dissociated from the complex.

For comparative purposes, the value for the activation energy of the gas phase conversion of cyclopropane to propene[92] at 550K is $\Delta H^{+}$ =248 kJ $mol^{-1}$ and the entropy associated with the process[93] of $\Delta S^{+}$ = +9 $Jmol^{-1}K^{-1}$. This value is probably a good indication as to the gain in entropy of the system derived from strain energy accompanying the ring opening.

3:4(c) Solvent and Axial Base Dependence of the Rearrangement of Cyclopropylmethyl- to But-3-enyl(pyridine)cobaloxime.

The rearrangement was followed by $^{1}H$ n.m.r. spectroscopy in a variety of solvents of differing polarity e.g. $C_6D_6$, $CD_3OD$, $CD_2Cl_2$ and $CDCl_3$, under identical conditions at 298K. The results of the study are shown in Table 7.

There is no marked effect on the rate of rearrangement with changes in solvent polarity in passing from the least polar $C_6D_6 < CDCl_3 < CD_2Cl_2 < CD_3OD$. This result is consistent with the proposal that the rearrangement of cyclopropylmethylcobaloxime taking place in the different solvent systems does so by an essentially similar pathway, and this pathway is unlikely to involve species with ionic/charged character. The rate of

Figure 21. Suggested Energy Profile for Intermediates in the Rearrangement of Cyclopropylmethyl(pyridine)cobaloxime

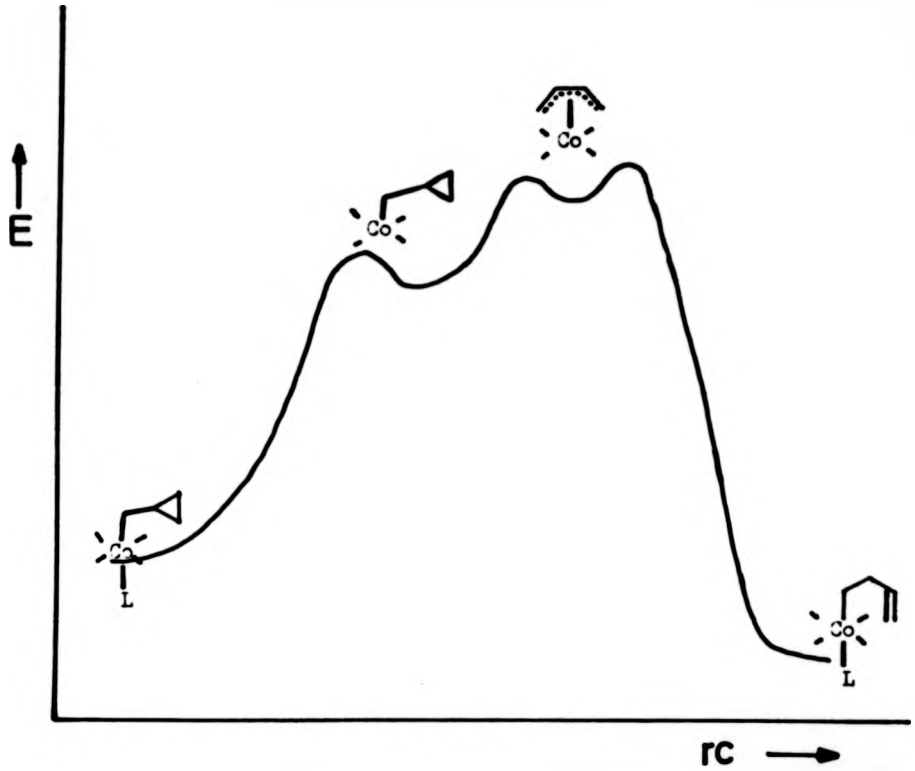
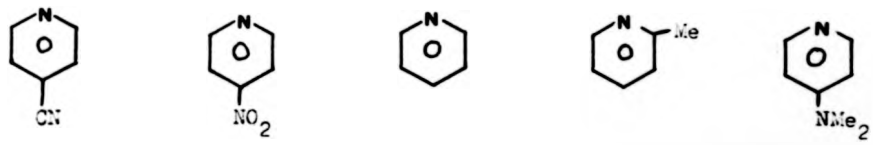



Table 7. Rate Constants for the Rearrangement of Cyclopropylmethyl-(pyridine)cobaloxime in Various Solvents

| SOLVENT | POLARITY INDEX | RATE CONSTANT ($s^{-1}$) |
|---|---|---|
| $C_6D_6$ | 34.5 | $(1.95 \pm 0.05) \times 10^{-5}$ |
| $CDCl_3$ | 39.0 | $(4.43 \pm 0.04) \times 10^{-5}$ |
| $CD_2Cl_2$ | 41.0 | $(4.54 \pm 0.07) \times 10^{-5}$ |
| $CD_3OD$ | 55.5 | $(1.02 \pm 0.03) \times 10^{-5}$ |

the rearrangement is slowest in methanol. A likely reason for this behavior is that methanol can coordinate to cobalt after pyridine has been lost from the coordination sphere of the cobaloxime, thus reducing the concentration of the active pentacoordinate species and retarding the rearrangement.

Cyclopropylmethylcobaloxime with axial ligands other than pyridine were prepared with the aim of investigating potential electronic effects associated with the rearrangement. The series of substituted pyridines used possess either electron-withdrawing side-chains (e.g. cyano) or electron-donating groups (e.g. methyl). The cyclopropylmethyl(base)-cobaloximes were prepared by a method analogous to that described for the preparation of cyclopropylmethyl(pyridine)cobaloxime from bromo (pyridine)cobaloxime. The axial bases chosen were:




A product of rearrangement i.e. but-3-enylcobaloxime, was only isolated from the reaction mixtures in attempts to prepare cyclopropylmethyl-cobaloximes containing 2-methyl- and 4-dimethylamino- pyridines as axial bases. In these cases it is apparent that dissociation of the substituted pyridine from the cobaloxime occurs readily; an explanation in the case of the 2-methylpyridine could be simply based on a steric argument, the 2-methyl substituent interacting unfavourably with the dimethyl-glyoximato ring system, tending to make the ring system less planar. A yellow product (insoluble in $H_2O$, MeOH, $CHCl_3$, $CD_2Cl_2$) was isolated from the reaction of bromo(4-nitropyridine)cobaloxime with

cyclopropylmethyl bromide in the presence of hydroborate. The nitro group may have been reduced under the conditions used to yield 4-amino pyridine which could then coordinate to cobalt, to yield ultimately a polymeric material.

Cyclopropylmethyl(4-cyanopyridine)cobaloxime was isolated from the reaction of bromo(4-cyanopyridine)cobaloxime with cyclopropylmethyl-bromide in the presence of hydroborate, as the sole alkylcobaloxime product (i.e. no rearrangement to the but-3-enylcobaloxime was observed). This material rearranged to but-3-enyl(4-cyanopyridine)cobaloxime at 25°C in $CDCl_3$ in the usual manner. The reaction was monitored by $^1H$ n.m.r. spectroscopy, with the rate constant for the rearrangement calculated to be $k_1 = (2.01 \pm 0.03) \times 10^{-5} s^{-1}$, cf. cyclopropylmethyl(pyridine)-cobaloxime $k_1 = (4.44 \pm 0.04) \times 10^{-5} s^{-1}$. The observed rate of rearrangement with 4-cyanopyridine as axial base is slower than for pyridine as axial base indicating that dissociation of the 4-cyanopyridine from the cobaloxime is relatively slower than for pyridine.

## 3:5 Stabilities of Cyclopropylmethyl Cations and Radicals

### 3:5(a)Cyclopropylmethyl carbonium ions

When cyclopropylcarbinol or cyclobutanol is dissolved in $SbF_5$-$SO_2ClF$ at -80°, a clear yellow-brown solution is obtained. $^1H$ and $^{13}C$ n.m.r. spectra of this solution are consistent with the production of the cyclopropylmethyl carbonium ion.

In the reaction of cyclopropylmethylamine with 'nitrous acid' which should give the cyclopropylmethyl cation, 48% of cyclopropylcarbinol, 47% of cyclobutanol and 5% of 3-buten-1-ol were obtained[94] as shown

in fig. 22. An identical product distribution was obtained when cyclobutylamine was treated with 'nitrous acid'. Reaction of 1-aminobut-3-ene with 'nitrous acid' yields a different set of products (fig.23). These observations suggest that the intermediate derived from 1-aminobut-3-ene is different from that of the cyclopropyl and cyclobutyl system. Cyclobutylamine labelled either in the α-position with $^{13}C$ or with $^{2}H$ attached to the α-carbon, reacts with 'nitrous acid' to yield products in which the label is scrambled. Deamination of cyclopropylamine labelled at the α-carbon, causes extensive but not complete scrambling of carbon and deuterium[95,96].

Such scrambling may occur via a cyclopropylmethyl-cyclobutyl interconversion but also via a direct interconversion between cyclopropylmethyl carbonium ions as shown in equation 9. The rationale for this transformation has been explained in two ways. Firstly, a direct interaction of the 2,3-bond of the cyclopropyl ring with the cationic centre (path A, fig. 24) would lead to inversion at one of the methylene groups. Secondly, (path B) the backside of one of the orbitals forming the 2,3-bond could interact with the cationic centre, leading to no charge at the methylene group. Path B has been found to be in accord with the stereochemical observations made[97,98]. Molecular orbital calculations[97] suggest involvement of a puckered cyclobutyl cation as an intermediate.

The structure of the intermediate cation linking the cyclopropylmethyl-cyclobutyl systems has been the subject of much discussion (reviewed by Wiberg, Hess and Ashe)[99]. Of the structures proposed, shown in fig.25, rapidly equilibrating unsymmetrical bicyclobutonium ions **1** and the

Figure 22. Reaction of Cyclopropylmethylamine with 'Nitrous Acid'

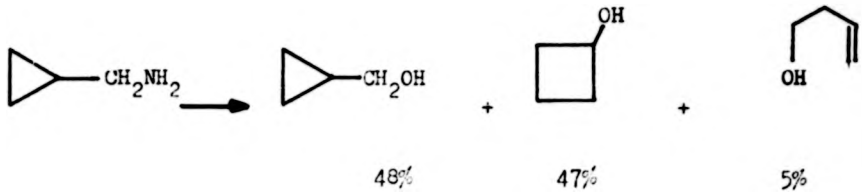
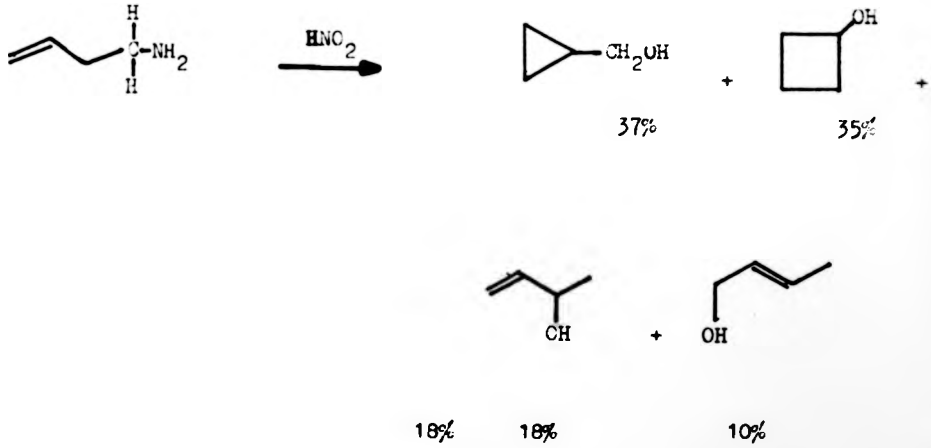


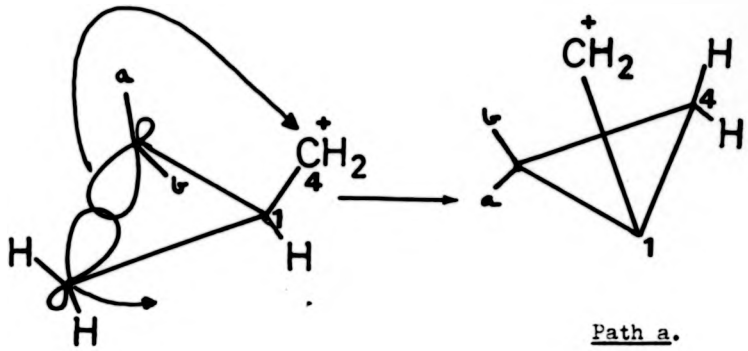

Figure 23. Reaction of 1-Aminobut-3-ene with 'Nitrous Acid'



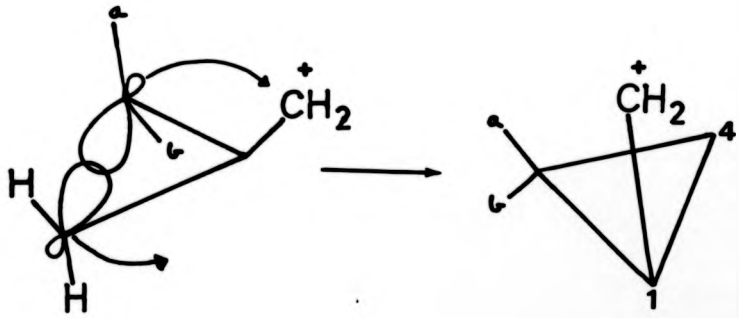


equation 9

Figure 24. Interconversion Between Cyclopropylmethyl Carbonium Ions.

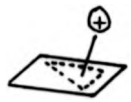



Path a.

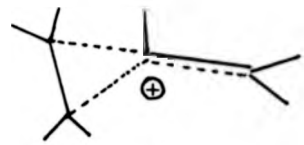



Path b.

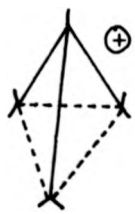
Figure 25. The Intermediate Cation Linking the Cyclopropylmethyl-Cyclobutyl System



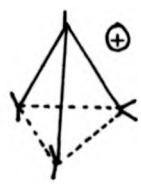
1



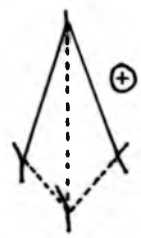
2



3



4



5

"bisected" structure 2 have been most widely accepted. The more symmetrical ($C_{3v}$) tricyclobutonium ions 3 and 4 have been considered, but deemed unlikely on the basis of theoretical studies[100,101]. In the cyclopropylmethyl carbonium ions there is assumed to be interaction of the cyclopropyl ring carbon-carbon bonds with the empty p orbital of the cationic centre, with the cyclopropane ring retaining essentially its original symmetry. The bicyclobutonium ion is non-planar with considerable interaction of the C-3 atom with the cationic centre. The homoallyl ion has overlap between the empty p orbital of C-1 and the nearest p orbital of C-3. The symmetrical homoallyl ion must resemble either the idealised bicyclobutonium ion or the idealised cyclopropylmethyl cation depending on its geometry.

A solution of [$^{13}CH_2OH$] cyclopropylcarbinol in $SbF_5$-$SO_2ClF$-$SO_2F_2$ at -100°C has $^1H$ and $^{13}C$ n.m.r. spectra consistent with the production of O-protonated cyclobutanol[102,103] 2 (fig.26). The relative intensities of resonances observed for C1, C2, C3 and C4 in the $^{13}C$ n.m.r. spectrum of 2 (fig.26) shows that the $^{13}C$ label has become essentially randomly distributed between the two non-equivalent methylene positions, but is not localised at the methine position. Above -70° 2 is converted by acidic media to $C_4H_7^+X^-$. The observed scrambling pattern in the transformation of cyclopropylmethanol to 2 suggests either a transalkylation mechanism, by way of the conjugate acid of cyclobutylcyclopropylmethyl ether 3 fig.27 (which would have scrambled methylene in the cyclobutyl group), or internal return involving $C_4H_7^+X^-$, where X is suggested to be $SbF_5OH$ or $Sb_2F_{10}OH$. The solution containing $C_4H_7^+$ and 2 (fig.26) was warmed to -70°, cooled to -100° and its $^{13}C$ n.m.r. spectrum recorded. This showed $C_4H_7^+$ as the only detectable species and

Figure 26. Reaction of [$^{13}CH_2OH$]cyclopropylmethanol with $SbF_5$-$SO_2ClF$-$SO_2F_2$

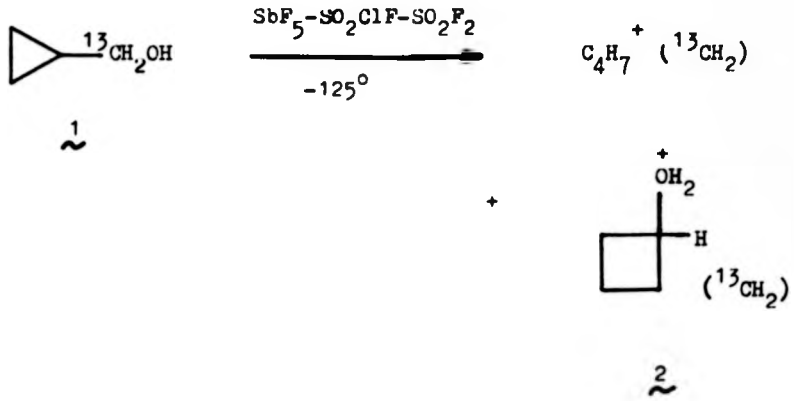
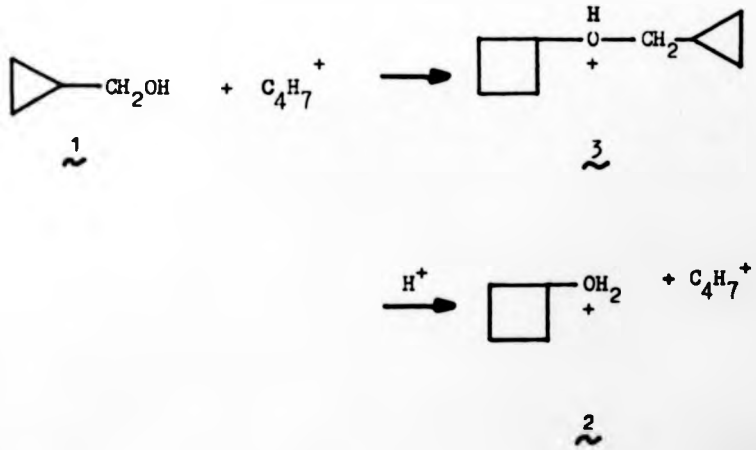



Figure 27. Suggested Transalkylation Mechanism for the Observed Scrambling of the $^{13}C$ label in [$^{13}CH_2OH$]cyclopropylmethanol



demonstrated that the $^{13}C$ label was randomly distributed in both the methylene and methine positions. These observations suggest that hydride migrations from methylene to methine carbons of $C_4H_7^+$ occur under the 'superacid' conditions at -70°C.

The stability of the cyclopropylmethyl carbonium ions have been attributed to significant absorption of the positive charge by the cyclopropyl ring. The stability of these carbonium ions may be due to some extent to the loss of part of the ring strain in the ion precursors, as well as to charge delocalisation. Several descriptions of the charge delocalisation in cyclopropylmethyl carbonium ions have been examined.

The "unsymmetrical homoallylic" ion 1 (fig.28) has been described as a resonance hybrid [95]. Maximum stabilisation energies (delocalisation minus strain energies) of ca 25[104] and 17[101] kJ $mol^{-1}$ have been estimated for this ion. The assumption of molecular orbital calculations employed, considered the overlap of the p orbitals in 4 (fig.28) to be a function of the C2-C3-C4 bond angle[105]. The "symmetrical homoallylic" ion 5 can also be described as a resonance hybrid (fig.29). This ion differs from the "unsymmetrical" analogue in that both C3 and C4 are involved in delocalisation. Representation of the symmetrical homoallylic ion as 9 (fig.29), implies an added contributor to the basis set of resonance canonicals.

In an equivalent representation, the cyclopropylmethyl carbonium ion has been regarded as a $\pi$complex 11, stabilised not only in the manner represented by the short straight arrow in (fig.30), but also by the

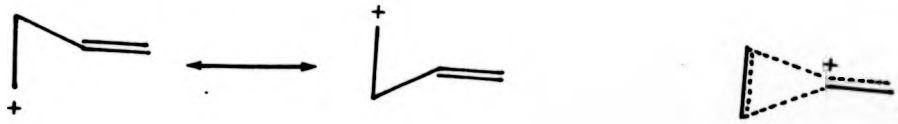
Figure 28. The "Unsymmetrical Homoallylic" Ion.

1 2

3 4

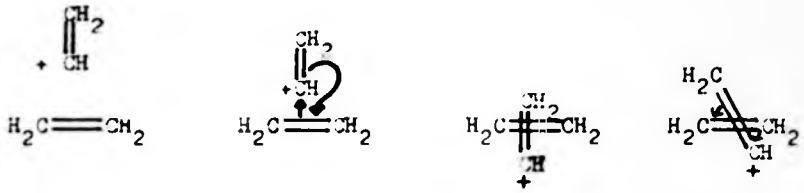
Figure 29. The "Symmetrical Homoallylic" Ion.

5 6



7 8 9

Figure 30. Representation of the Cyclopropylmethyl Carbonium Ion as a π Complex



10 11 12 13

Figure 31. Resonance Canonicals for the Bicyclobutonium Ion

14 15 16 17

18

back donation indicated by the long, curved arrow. It has been proposed[106] that the geometry of the complex is either symmetrical as in 12 or distorted 13.

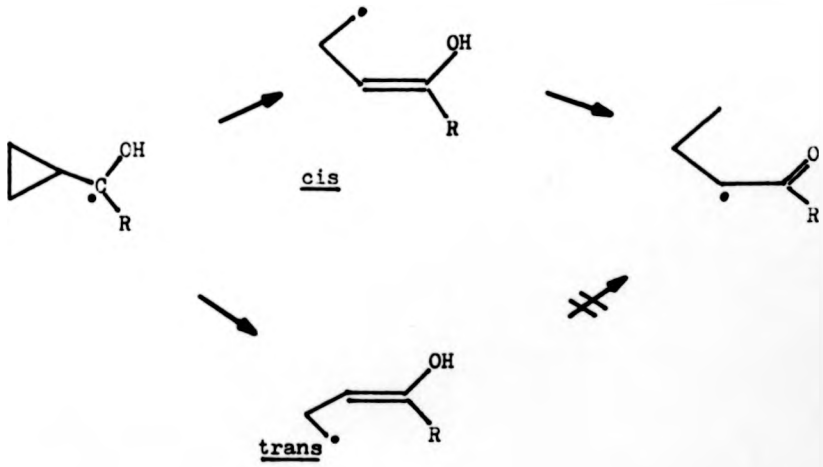
The resonance hybrid description of the "bicyclobutonium" ion is shown in (fig.31). This ion differs from the homoallylic ions in having significant bonding between C1 and C4 and hence significant positive charge at C2. A maximum stabilisation energy of about 44 kJ $mol^{-1}$ has been estimated for this ion on the basis of molecular orbital calculations in which the overlap appearing in 18 (fig.31) is considered as a function of several bond angles[101]. The ion 14 in fig.31 is considered to be in rapid equilibrium with closely related isomers in which C1, C3 and C4 have interchanged positions. The "tricyclobutonium ion" 19 (fig.32) in which C1, C3 and C4 (if unsubstituted) are equivalent, is not a possible description because these carbon atoms, when labelled, are not always equilibrated equally in reactionsthought to proceed through cyclopropylmethyl carbonium ions. Calculations indicate that the tricyclobutonium ion structure is of high energy. The ground state would be orbitally degenerate if the methylene hydrogens were disposed as in cyclopropane (3 H's above and 3 H's below the plane of the methylene carbons) and the energy would be unfavorably high if the six hydrogens lay in one plane[101].

### 3:5(b) Cyclopropylmethyl Radicals

1-Cyclopropyl-1-hydroxymethyl radicals (fig.33) undergo the cyclopropylmethyl-homoallyl rearrangement to the two isomers (cis and trans) of substituted but-3-ene-4-ol radicals as observed by e.s.r. spectroscopy[107]. For temperatures above -50° the α-keto radical fig.(33) is detected.

Figure 32. The Tricyclobutonium Ion


Figure 33. Reactions of 1-Cyclopropyl-1-hydroxycarbinyl Radicals



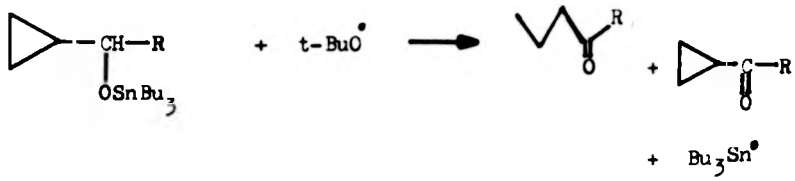

R = -H, -$CH_3$, -Cyclopropane, -Phenyl

This is formed by an intramolecular rearrangement followed by a somewhat unusual 1,5-hydride shift from oxygen to carbon. This rearrangement was observed only for the cis-but-3-ene-4-ol and was not reversible.

Cyclopropylmethyltin alkoxides react with tertiary butoxide radicals to produce substantial amounts of the ring-opened ketone (equation 10)[108]. Kochi et al[109] have carried out extensive studies in this area. Cyclopropylmethyl radicals undergo rapid ring opening even at -100°C. Thus, the secondary cyclopropylmethyl radical shown in fig. 34 generates the primary butene radical.

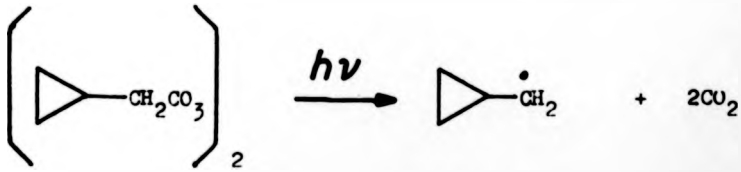
Employing radicals generated from methylcyclopropane and $^{t}$butoxy radical it was shown that at -140° cyclopropylmethyl radicals were formed, but at -100° the allylcarbinyl radical was formed. Radicals with an identical e.s.r. spectrum at the same temperature were obtained by the photolysis of cyclopropylacetyl peroxide (equation 11). These observations indicate that cyclopropylmethyl and allylcarbinyl are discrete radicals, and that the cyclopropylmethyl radical rapidly rearranges to allylcarbinyl radical at temperatures above -120°. No evidence was found for the production of cyclopropylmethyl radicals during the photolysis of allylacetylperoxide. Even at temperatures below -140°, allylcarbinyl radicals were the only observed species.

Essentially similar results were obtained by Krusic et al[110] who studied the radicals derived from various alkylcyclopropanes shown in fig.35. They found that for substituted cyclopropylmethyl radicals, unlike allylcarbinyl radicals, the cis isomer predominates over the trans isomer by a factor at 4 at -48°. The preferred conformation of



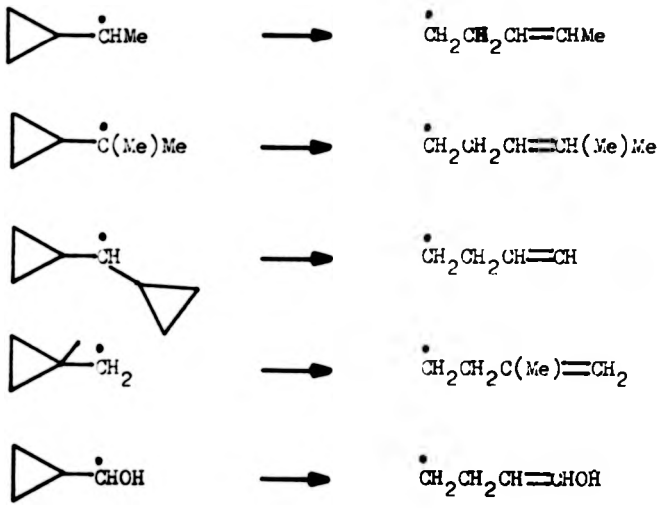

equation 10

Figure 34. Rearrangement of the Secondary Cyclopropylmethyl Radical


equation 11

Figure 35. Radicals Derived from Substituted Cyclopropanes



cyclopropylmethyl radicals is the same as for the analogous cation[111] (section 3:5 (a)).

The chemistry observed with the cyclopropylmethyl carbonium ion is markedly different from that observed in the cobaloxime analogue, in the former a $^{13}C$ label originally at the 1-position of the cyclopropylmethyl group is totally scrambled upon formation of the derived carbonium ion, whereas in the cobaloxime the label is retained essentially located on one carbon atom. This evidence strongly suggests that carbonium ion species are not likely to be involved in the rearrangement of cyclopropylmethyl- to but-3-enyl(pyridine)cobaloxime. It is a general feature of the rearrangement exhibited by cyclopropylmethyl carbonium ions that substantial amounts of cyclobutyl products are formed. No evidence was found for the presence of cyclobutyl species in the conversion of cyclopropylmethyl- to but-3-enyl(pyridine)cobaloxime. Radical intermediates cannot be rigorously excluded at this state, but evidence against their participation is presented fully in chapter 4.

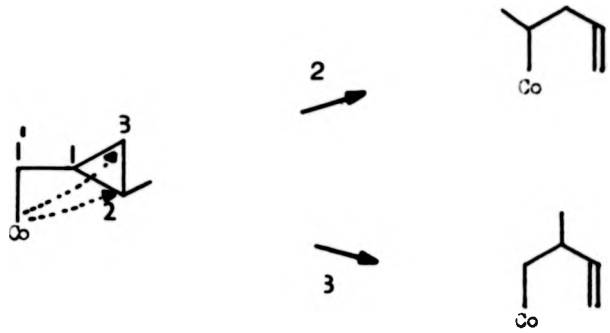
# Chapter 4. Studies of the Rearrangement of 1-Methylbut-3-enyl- to 2-Methylbut-3-enyl(pyridine)cobaloximes

## 4: 1 Introduction

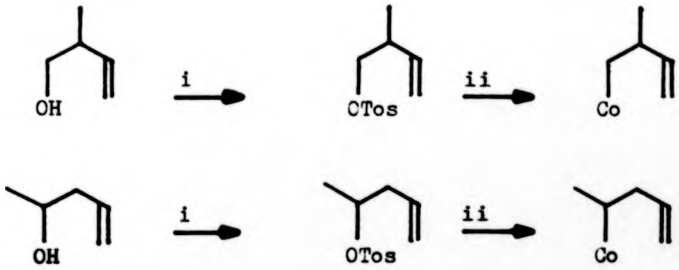
A consequence of the unimolecular and bimolecular mechanisms proposed (see chapter 3) for the rearrangement of cyclopropylmethyl- to but-3-enyl(pyridine)cobaloxime is that if one of the equivalent methylene carbons of the cyclopropane group were labelled in some way e.g. by a methyl substituent, then two products would be expected from its rearrangement (fig.36). Migration of cobalt to the 2 position would give a 1-methylbut-3-enyl product, whereas migration to the 3 position would give a 2-methylbut-3-enylcobaloxime. Furthermore, 1-methylbut-3-enyl- and 2-methylbut-3-enylcobaloximes should be interconvertible via a methylcyclopropylmethylcobaloxime if either mechanism is operating. To study such processes 1-methylbut-3-enyl and 2-methylbut-3-enyl-(pyridine)cobaloximes together with the cis and trans isomers of the postulated intermediates in this interconversion, i.e. 2-methylcyclopropyl-methyl(pyridine)cobaloximes, were synthesised. The preparation of the 1-methylbut-3-enyl and 2-methylbut-3-enylcobaloximes is outlined in Scheme 15. The preparation of cis and trans-2-methylcyclopropylmethyl-(pyridine)cobaloximes is outlined in Scheme 16.

Consideration[90] of the stereochemical consequences of the unimolecular and bimolecular mechanisms suggest that the unimolecular mechanism should proceed via a $\eta^3$-homoallylcobalt species with retention of configuration at C1 of the starting but-3-enyl complex (Scheme 17.). For the bimolecular pathway, inversion at this centre appears to be the most likely stereochemistry. To probe the stereochemistry of the

Figure 36. Expected Rearrangement Products from 2-Methylcyclopropylmethyl(pyridine)cobaloxime



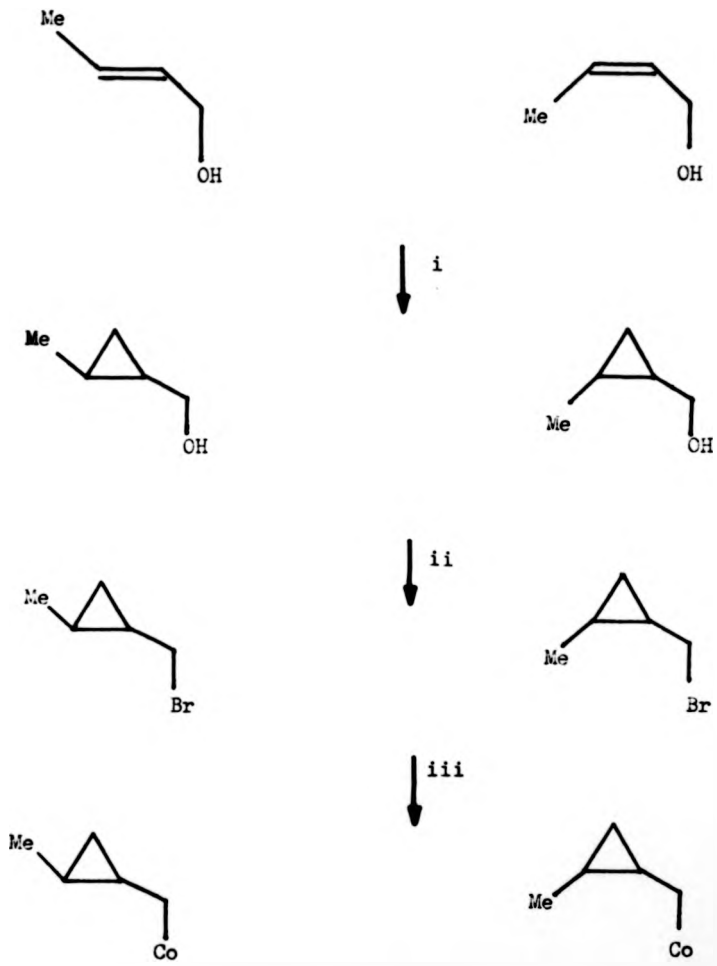

Scheme 15. Synthesis of 1-Methyl- and 2-Methylbut-3-enylcobaloximes




i = Toluene-4-sulphonyl chloride

ii = [Pyridine] cobaloxime[I]

Scheme 16. Synthesis of cis- and trans-2-Methylcyclopropylmethyl-(pyridine)cobaloximes

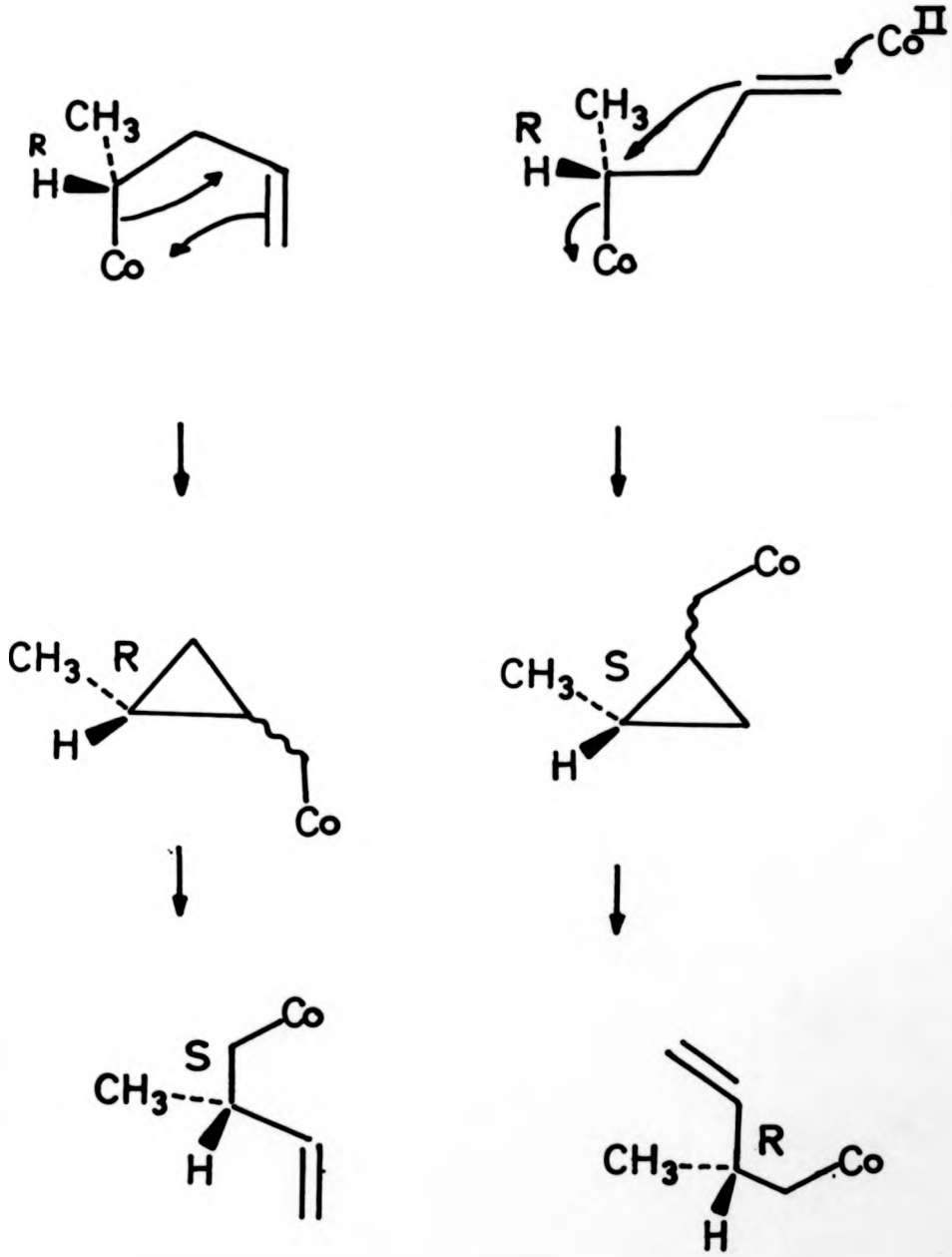



i = Zn/Cu couple (type II), $CH_2I_2$

ii = $PBr_3$/pyridine/ethoxyethane

iii = Bromo(pyridine)cobaloxime/$NaBH_4$/ethanol

Scheme 17. Stereochemical correlations for the Bimolecular and Unimolecular Rearrangements of Methylbutenylcobaloximes



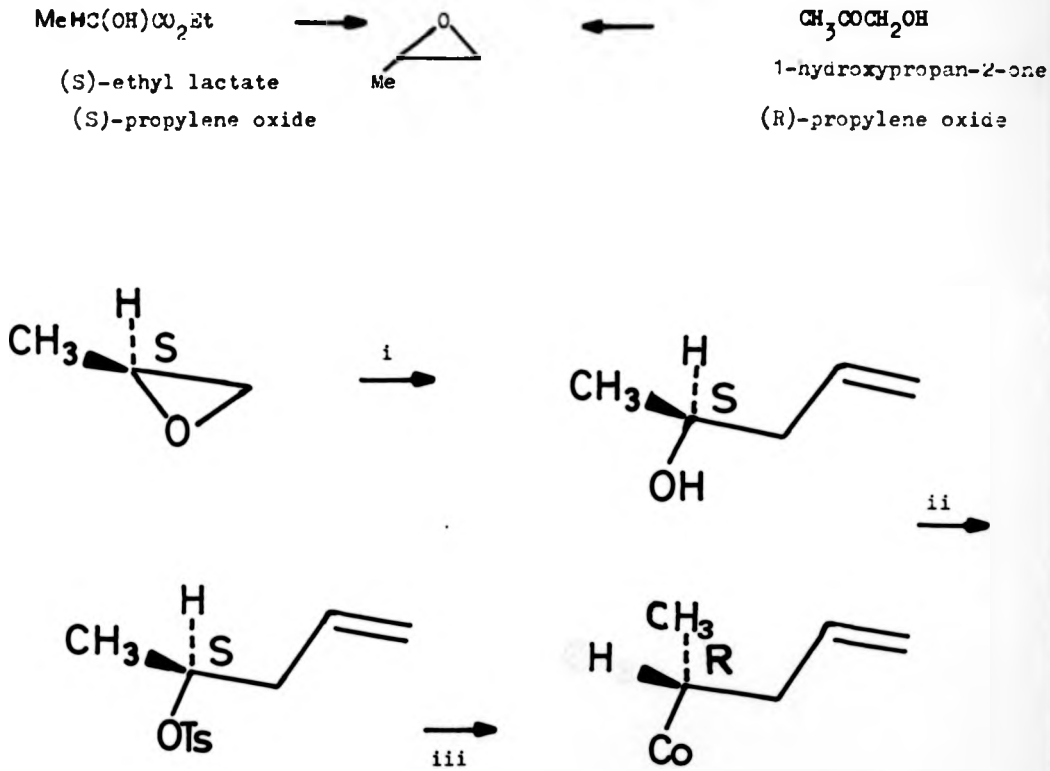
rearrangement of 1-methyl- to 2-methylbut-3-enyl(pyridine)cobaloximes, a series of optically active cobaloximes were prepared. The preparation of (R)- and (S)-1-methylbut-3-enyl(pyridine)cobaloximes is outlined in Scheme 18. The preparation of (S)-2-methylbut-3-enyl(pyridine)-cobaloxime is outlined in Scheme 19.

The rearrangement of 1-methyl- to 2-methylbut-3-enylcobaloxime involves the migration of a vinyl group from C2 to C1 with concomitant migration of Co from C1 to C2 of the butenylcobaloxime. Note that the methyl groups do not migrate but undergo, attached to carbon an interchange process.

The rearrangement of 1-methylbut-3-enyl(pyridine)cobaloxime serves as a model for the AdoCbl-catalysed interconversion of α-methyleneglutarate to methylitaconate discussed in Chapter 1. The parallels between these two processes are shown in fig.37. For the α-methyleneglutarate mutase reaction, the migrating group is an acrylate moiety and the interchanging group is carboxyl, whereas in the conversion of 1-methylbut-3-enyl- to 2-methylbut-3-enylcobaloxime system the migrating group is a vinyl moiety and the interchanging group is methyl. Dowd has postulated a substituted cyclopropylmethylcorrinoid (two stereoisomers possible) in the reaction catalysed by α-methyleneglutarate mustase[114]. For the model rearrangement of 1-methylbut-3-enyl- to 2-methylbut-3-enyl(pyridine)-cobaloxime the analogous intermediate 2-methylcyclopropylmethyl(pyridine)-cobaloximes were prepared and their properties examined.

To explore the scope of the rearrangements discussed above, the preparations of several substituted cyclopropylmethyl(pyridine)cobaloximes were undertaken, namely those derived from 1-methylcyclopropylcarbinol,

Scheme 18. Synthesis of Optically Active 1-Methylbut-3-enyl-(pyridine)cobaloximes.



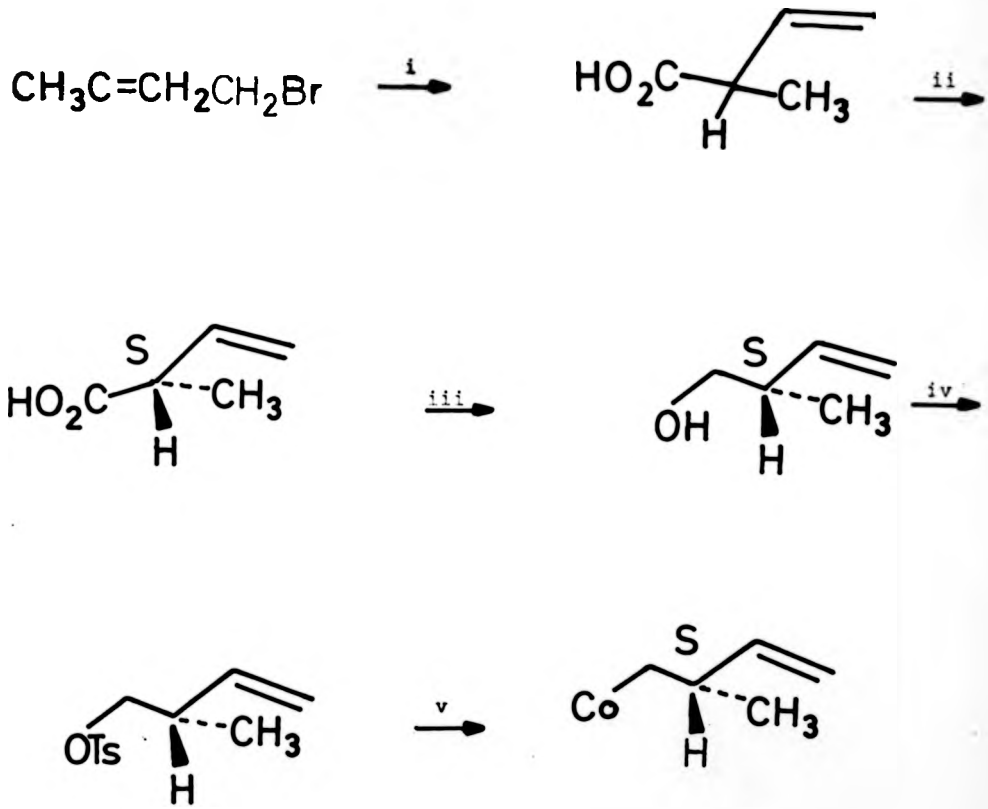

i = $CH_2{=}CHMgBr$/Cu(I) cat./ethoxyethane

ii = Toluene-4-sulphonyl chloride/pyridine

iii = (pyridine)cobaloxime(I)/ethanol

NB. Optically active propylene oxides were prepared according to literature procedures.[112,113]

Scheme 19. Synthesis of (S)-2-Methylbut-3-enyl(pyridine)cobaloxime




i = Mg/ethoxyethane/$CO_2$

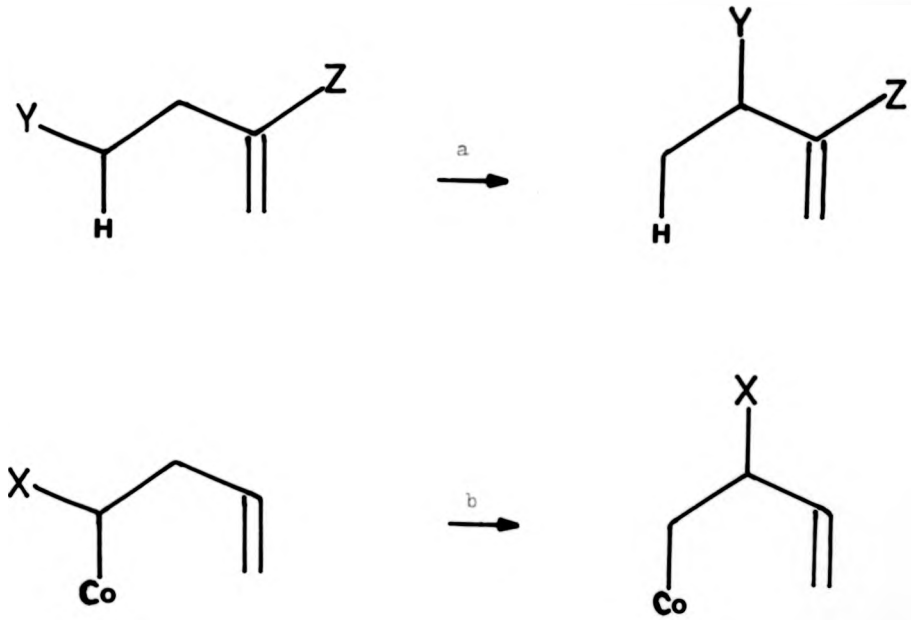
ii = $\alpha$-(+)-methylbenzylamine

iii = $LiALH_4$/ethoxyethane

iv = Toluene-4-sulphonyl chloride/pyridine

v = (pyridine)cobaloxime(I)/ethanol

Figure 57. Parallels between the Conversions of α-Methyleneglutarate to Methylitaconate and 1-Methyl- to 2-Methylbut-3-enyl-(pyridine)cobaloximes




a = **conversion** of α-methyleneglutarate to methylitaconate

b = conversion of 1-methyl- to 2-methylbut-3-enyl(pyridine)cobaloxime

X = $CH_3$
Y = $CO_2H$
Z = $CO_2H$

1-cyclopropylethan-1-ol and 2-phenylcyclopropylcarbinol (cf. Schemes 20, 21 and 22 respectively) and their properties investigated. cis-Hex-3-enyl(pyridine)cobaloxime was prepared according to Scheme 23 and its reactions investigated.

It has been shown[115] that 1,2-dimethylbut-3-enyl(pyridine)cobaloxime spontaneously rearranges to at least two isomers of 2,3-dimethylcyclopropylmethyl(pyridine)cobaloxime upon purification. In an attempt to identify the isomers of the 2,3-dimethylcyclopropylmethylcobaloxime produced in these rearrangements, 1,2-dimethylbut-3-enyl(pyridine)-cobaloximes with known stereochemistry (i.e. via threo and meso intermediates) were synthesised (Scheme 24) and their conversion to respective 2,3-dimethylcyclopropylmethylcobaloximes observed. For comparative purposes a mixture of (cis, trans)-and (trans, trans)-2,3-dimethylcyclopropylcarbinols was synthesised according to Scheme 25.

## 4: 2 Experimental

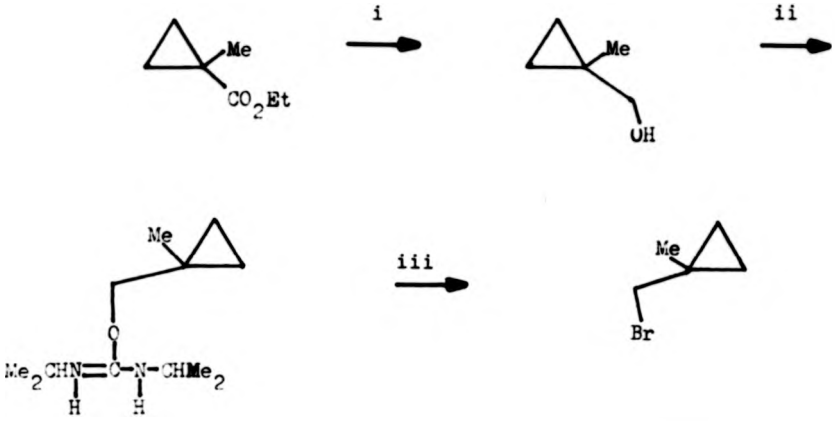
### Section 1 - Preparation of (R)- and (S)-1-methylbut-3-enyl(pyridine)-cobaloxime. (Scheme 18).

#### Preparation of (R)- and (S)-1-methylbut-3-ene-1-ol

N.B. For the preparation of racemic 1-methylbut-3-ene-1-ol racemic propylene oxide was used in place of (R)- or (S)- propylene oxide.

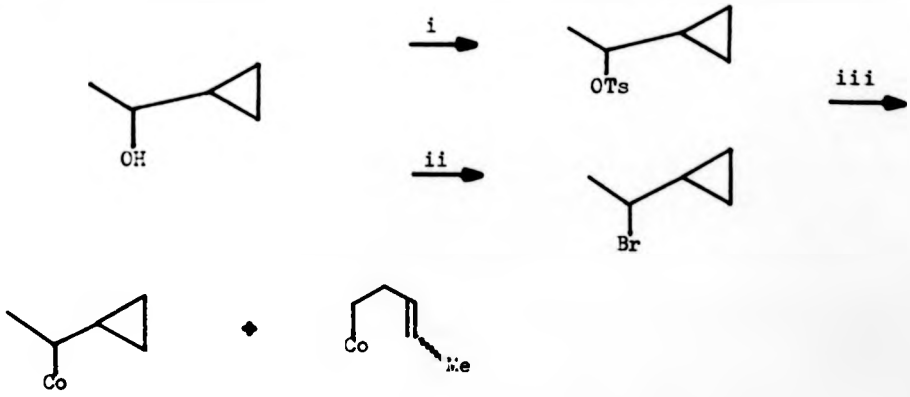
To a 250cm$^3$ three necked round-bottomed flask fitted with reflux condenser, pressure-equalising dropping funnel and a nitrogen inlet system was added magnesium (3.5g; 150 mmol) and tetrahydrofuran (25cm$^3$). Vinyl

Scheme 20. Attempted Synthesis of 1-Methylcyclopropyl(pyridine)-cobaloxime



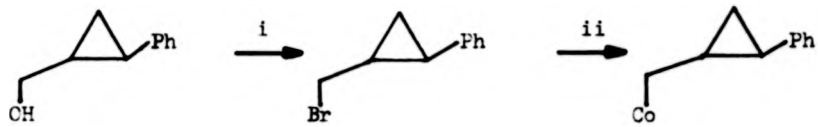

i = $LiAlH_4$/ethoxyethane; ii = diisopropylcarbodiimide/Cu(I) cat.; iii = HBr/$CHCl_3$

Scheme 21. Attempted Synthesis of 1-Cyclopropylethyl(pyridine)cobaloxime




i = Toluene-4-sulphonyl chloride/pyridine; ii = $PBr_3$/pyridine/$Et_2O$; iii = (pyridine)cobaloxime(I)/ethanol.

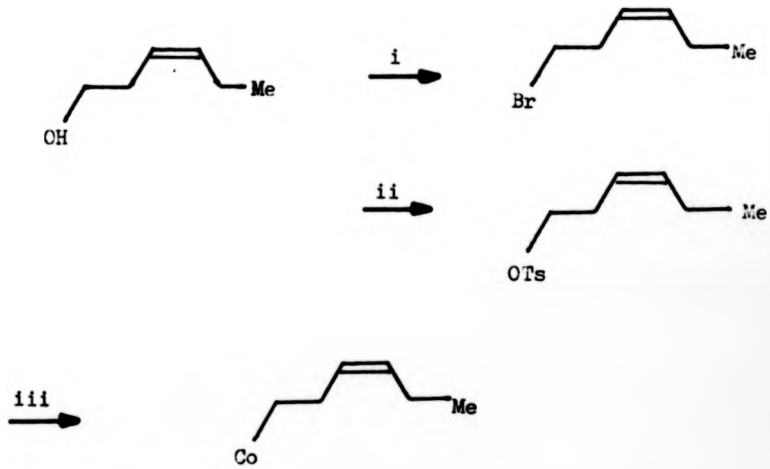
Scheme 22. Attempted Synthesis of trans-2-Phenylcyclopropylmethyl-(pyridine)cobaloxime




i = $PBr_3$/pyridine/ethoxyethane

ii = (pyridine)cobaloxime(I)/ethanol

Scheme 23. Preparation of cis-Hex-3-enyl(pyridine)cobaloxime

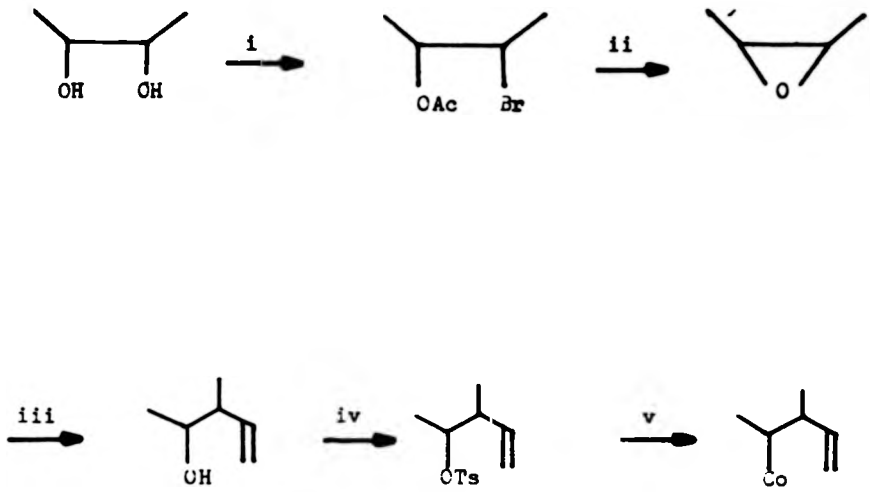



i = $PBr_3$/pyridine/ethoxyethane

ii = Toluene-4-sulphonyl chloride/pyridine

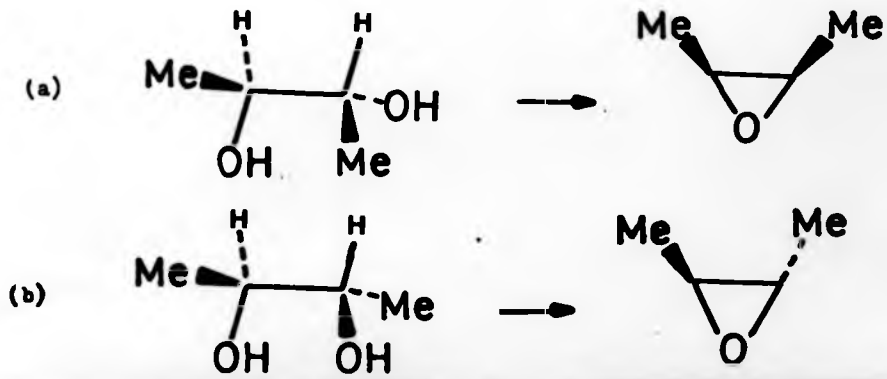
iii = (pyridine)cobaloxime(I)/ethanol

Scheme 24. Synthetic Route to meso- and threo-1,2-Dimethylbut-3-enyl-(pyridine)cobaloximes

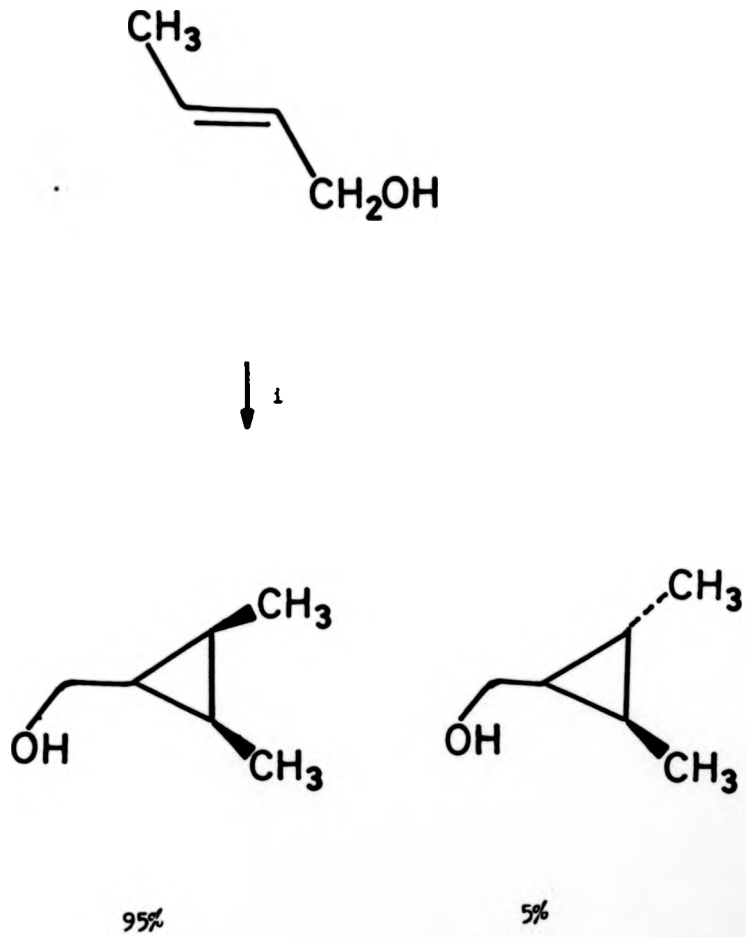



i = 48% w/v HBr/glacial acetic acid; ii = $K^+$Pentylate/pentan-1-ol;
iii = $CH_2{=}CHMgBr$/ethoxyethane; iv = Toluene-4-sulphonyl chloride/pyridine
v = (pyridine)cobaloxime(I)/ethanol

N.B. meso-butane-2,3-diol in the synthetic route gives rise to the cis-2,3-epoxybutane; threo-butane-2,3-diol gives the trans-2,3-epoxybutane, as shown below (a) and (b) respectively.



Scheme 25. Synthesis of cis,trans- and cis,cis-Dimethylcyclopropylcarbinols




i = $(C_2H_5)Zn/CH_3\overset{H}{C}I_2$/dimethoxyethane/toluene

bromide ($0.5cm^3$) and iodoethane (2-6 drops) were added to start the reaction after which dry tetrahydrofuran ($40cm^3$) was added. Vinyl bromide ($11.1cm^3$; 100 mmol) in tetrahydrofuran ($15cm^3$) was then added over a 1h. period maintaining reflux. The reaction was stirred for 30 minutes then cooled in an ice-bath. To the resulting solution was added copper(I)iodide (1.9g; 5 mmol) followed by the slow, dropwise, addition of either (R)- or (S)-epoxypropane (2.9g; 50 mmol) in tetrahydrofuran ($25cm^3$) over a 1.5h. period. After stirring for 2h. at $0^oC$, the solution was poured into saturated aqueous ammonium chloride ($150cm^3$) and was extracted with ethoxyethane ($3 \times 100cm^3$). The combined organic extracts were washed successively with water ($30cm^3$) and saturated aqueous sodium chloride ($30cm^3$). After drying ($MgSO_4$), solvent was evaporated off and the residue was fractionally distilled to yield 2.1g (50%) of pure material (b.p. 114-116$^o$ at 760 mm Hg).
<u>$^1H$ n.m.r.($CCl_4$)</u> $\partial$1.15 (d,3H), 2.15 (t,2H), 3.7 (q,1H), 3.5 (broad, 1H), 5.1 (m,2H), 5.8 (m,1H) p.p.m.

<u>Preparation of (R)- and (S)-1-Methylbut-3-ene-1-ol Tosylate</u>

Toluene-4-sulphonyl chloride (2.44g; 11.4 mmol) in pyridine ($8cm^3$) was added dropwise over 10 minutes to a stirred solution of (R)- or (S)-1-methylbut-3-ene-1-ol (0.9g; 10.4 mmol) in pyridine ($2cm^3$) at $0^oC$. The reaction was stirred at $0^oC$ for 15 minutes and then at room temperature overnight. Ice was added to dissolve the precipitated pyridinium hydrochloride and the mixture was poured into ice-cold 5M hydrochloric acid ($20cm^3$). The aqueous acidic solution was then extracted with dichloromethane ($3 \times 20cm^3$). The combined organic

extracts were washed successively with cold 5M hydrochloric acid ($20cm^3$), cold 10% aqueous sodium carbonate ($20cm^3$), dried ($Na_2CO_3$) and solvent was evaporated off to yield 1.6g. (75%) pure product $[\alpha]_D = -11.9^\circ$ (C,0.049, $CHCl_3$) for (S)-1-methylbut-3-ene-1-ol tosylate.

$^1H$ n.m.r. ($CCl_4$) ∂1.25 (d,3H), 2.3 (m,2H), 2.45 (s,3H), 4.65 (q,1H) 5.0(m,2H), 5.6(m,1H), 7.3(d,2H), 7.8 (d,2H) p.p.m.

Preparation of (R)- and (S)-1-Methylbut-3-enyl(pyridine)cobaloxime

$CoCl_2.6H_2O$ (4.76g; 20 mmol) and dimethylglyoxime (4.64g; 40 mmol) were stirred with methanol (75 $cm^3$) at $0^\circ C$ in a $250cm^3$ three-necked flask under nitrogen for 30 minutes. Pyridine (1.62 $cm^3$; 20 mmol) was added to the reaction mixture followed by 17.3M aqueous sodium hydroxide ($4.65cm^3$; 80 mmol). The dark homogenous solution was stirred at $0^\circ C$ for a further 15 minutes, then a solution of (R)- or (S)-1-methylbut-3-ene-1-ol tosylate (2.28g; 10 mmol) in methanol ($5cm^3$) was added. The mixture was allowed to warm slowly to room temperature (3h) and was then stirred overnight (14h) under nitrogen. The resulting suspension was cooled in ice and 0.5% v/v aqueous acetic acid ($200cm^3$) was added with stirring. The precipitated cobaloxime was filtered with suction, washed with small quantities of ice-water until washings were colourless and the product was finally air-dried to yield 2.1g (46%) of crude material. The solid was purified by silica gel chromatography in the usual manner, to yield after evaporation of solvent (R)- or (S)-1-methylbut-3-enyl(pyridine)cobaloxime (1.9g; 44%).

$^1H$ n.m.r ($CDCl_3$) ∂0.4 (d,3H), 1.75 (m,1H), 2.15 (s,12H), 2.3 (m,2H), 4.8 (t,2H), 5.7 (m,1H), 7.3(m,2H), 7.7 (t,1H), 8.6 (d,2H), p.p.m.

$^{13}C$ n.m.r. ($CDCl_3$) ∂12.25, 21.74, 42.07 (broad due to coupling to $^{59}Co$, nuclear spin 7/2), 43.21, 113.88, 125.26, 137.51, 138.43, 149.54 p.p.m.

(S)-isomer $[\alpha]^{21}_{D} = -58^{\circ}$ (C,0.03 in $CHCl_3$)

(R)-isomer $[\alpha]^{21}_{D} = +60^{\circ}$ (C,0.058 in $CHCl_3$)

Section 2: Preparation of (S)-2-Methylbut-3-enyl(pyridine)cobaloximes (Scheme 19).

Preparation of 2-Methylbut-3-enoic acid

This was prepared according to the literature method of J.F.Lane, J.D. Roberts and W. G. Young, J.Am.Chem.Soc., 1944, 66,543

Resolution of 2-Methylbut-3-enoic acid

This was performed according to the literature procedure of G.T.Pearce et al: J.Org.Chem., 1976, 41, 2927 employing (+) – $\alpha$ -methylbenzylamine as resolving agent.

The (S)-2-methylbut-3-enoic acid had a $[\alpha]_D = +24.0^{\circ}$ (58% optically pure) cf. literative value of $[\alpha]_D = +28.8^{\circ}$ (70% optically pure) ref. R.Rossi, P.Diversi and G.Ingrosso Gazz.Chim.Ital..1968, 98, 1391 $^1H$ n.m.r. ($CCl_4$) $\delta$1.15 (d,3H), 3.0 (m,1H), 5.0 (m,2H), 5.75 (m,1H) p.p.m.

Preparation of (S)-2-Methylbut-3-ene-1-ol

To a stirred suspension of lithium tetrahydroaluminate (0.952g; 25 mmol) in ethoxyethane ($25cm^3$) was added dropwise over 1h, a solution of (S)(+)-2-methylbut-3-enoic acid (2.5g; 25 mmol) in ethoxyethane ($10.5cm^3$). The mixture was heated under reflux for 3h, then cooled in ice.

Ice-cold 10% aqueous sulphuric acid ($36.6cm^3$) was added cautiously, followed by water ($32cm^3$). The ethoxyethane layer was separated and the aqueous layer was extracted with ethoxyethane ($3 \times 20cm^3$). The combined organic extracts were dried ($MgSO_4$) and solvent was evaporated off. The crude product was distilled (b.p. 50-53° at 40 mm Hg) to afford 1.5g (70%) pure material.

$^1H$ n.m.r. ($CDCl_3$) ∂0.9 (d,3H), 2.2 (m,1H), 313 (d,2H), 3.7(s, broad, OH), 5.0 (m,2H), 5.6 (m,1H) p.p.m.

Preparation of (S)-2-Methylbut-3-ene-1-ol Tosylate

To a stirred solution of (S)-2-methylbut-3-ene-1-ol (1.53g; 15.3 mmol) in pyridine ($3cm^3$) at 0°C, was added dropwise over 10 minutes, a solution of toluene-4-sulphonyl chloride (3.73g; 21.8 mmol) in pyridine ($12cm^3$). The reaction was stirred at 0°C for 5 minutes and for 65 minutes at room temperature. Ice was added to dissolve the precipitated pyridinium hydrochloride and the mixture was poured into ice-cold 5M hydrochloric acid ($20cm^3$). The aqueous acidic solution was then extracted with dichloromethane ( $3 \times 20cm^3$). The combined organic extracts were washed successively with cold 5M hydrochloric acid ($20cm^3$), cold 10% aqueous sodium carbonate ($20cm^3$), dried ($Na_2CO_3$) and solvent was evaporated off to yield 3.5g (88%) pure material.

$^1H$ n.m.r. ($CDCl_3$) ∂0.85 (d,3H), 2.0 (m,1H), 2.46 (s,3H), 3.5 (d,2H), 5.1 (m,2H), 5.7(m,1H), 7.2 (d,2H), 7.8 (d, 2H) p.p.m.

$[\alpha]$ = + 9.8° (0.023, hexane)

Preparation of (S)-2-Methylbut-3-enyl(pyridine)cobaloxime

Bromo(pyridine)cobaloxime (2.47g; 5.5 mmol) and absolute ethanol ($50cm^3$) were stirred under nitrogen at ambient temperature in a Schlenk tube for

30 minutes. Sodium tetrahydroborate (0.624g; 5.5 mmol) and (S)-2-methylbut-3-ene-1-ol tosylate (1.5g; 5 mmol) were added and the reaction mixture was stirred overnight (14h) at room temperature. Air was blown through the reaction mixture for 45 minutes and water ($50cm^3$) containing 2% v/v pyridine was added. The precipitated cobaloxime was filtered with suction and was washed successively with $50cm^3$ portions of water, absolute ethanol and carbon tetrachloride to remove occluded tosylate. The product was purified by silica gel chromatography in the usual manner and the material was dried *in vacuo* to yield 0.8g (35%) pure product.

$^1H$ n.m.r. ($CDCl_3$) $\delta$0.85 (d,2H), 1.25 (m,1H), 2.0 (m,2H), 2.1 (d,12H), 4.7 (m,2H), 5.6 (m,1H), 7.35 (m,2H), 7.75 (t,1H), 8.6 (d,2H) p.p.m.

$^{13}C$ n.m.r. ($CDCl_3$) 12.9, 23.8, 37.0, 38.9, 109.8, 125.3, 137.6, 146.6, 149.3, 149.6, 149.8 p.p.m.

$[\alpha]_D = +9.5^\circ$ (C,0.03, $CHCl_3$)

CD (C,2.36 x $10^{-4}$ mol $dm^{-3}$ in $CHCl_3$) maxima at 350 nm (A= 0.03) and 445 nm (A= 0.10).

Preparation of 1-Methyl- and 2-Methylbutyl(pyridine)cobaloxime (fig. 38(a) and (b)).

Preparation of Pentan-2-ol

This was prepared using the standard procedure ("Practical Organic Chemistry", Vogel, third edition, P.279) by reduction of pentan-2-one with sodium borohydride.

Preparation of 2-Bromopentane

This was prepared by the standard procedure (Vogel) by the reaction of pentan-2-ol with 48% HBr solution.

Figure 38(a),(b). Synthetic routes to 1-Methylbutyl- and 2-Methylbutyl(pyridine)cobaloximes

(a) $CH_3CH(OH)CH_2CH_2CH_3 \xrightarrow{i} CH_3CH(Br)CH_2CH_2CH_3$

$\xrightarrow{ii} CH_3CH(Co)CH_2CH_2CH_3$

(b) $OHCH_2CH(CH_3)CH_2CH_3 \xrightarrow{i} BrCH_2CH(CH_3)CH_2CH_3$

$\xrightarrow{ii} CoCH_2CH(CH_3)CH_2CH_3$

i = $HBr/H_2SO_4$

ii = (pyridine)cobaloxime(I)/ethanol

Co = $Co(dmgH)_2$pyridine

Preparation of 1-Methylbutyl(pyridine)cobaloxime

$CoCl_2.6H_2O$ (1.37g; 5 mmol) and dimethylglyoxime (1.16g; 10 mmol) in methanol ($15cm^3$) were stirred under nitrogen in a Schlenk tube for 30 minutes. Aqueous 10M sodium hydroxide ($1cm^3$; 10 mmol) and pyridine ($0.4cm^3$; 5 mmol) were added and the reaction mixture was cooled to $-15^oC$ for 15 minutes. Potassium tetrahydroborate (0.068g; 1.25 mmol) dissolved in 10M aqueous sodium hydroxide ($0.5cm^3$) was added , followed by 1-bromopentane (7.55g; 5 mmol). The mixture was stirred overnight at room temperature under nitrogen. Water ($50cm^3$) was added and the precipitated cobaloxime was washed with water until the washings remained colourless. The solid was dried in vacuo and purified by silica gel chromatography in the usual manner to yield 0.4g (35%) pure material.

$^1H$ n.m.r. ($CDCl_3$) $\delta$ 0.4 (d,3H), 0.75(m,3H), 0.8 (m,1H), 1.1 (m,1H), 1.4 (m,2H), 1.8 (m,1H), 2.15 (s,12H), 7.3 (t,2H), 7.7 (t,1H), 8.6 (d,2H) p.p.m.

Elemental Analysis Found C 49.10, H 6.88, N 15.94%; calculated for $C_{18}H_{30}N_5O_4Co$ C 48.96 H 6.65 N 15.98%.

Preparation of 1-Bromo-2-methylbutane

Prepared by the standard method (Vogel) by reaction of 2-methylbutan-1-ol with 48% HBr.

Preparation of 2-Methylbutyl(pyridine)cobaloxime

This was prepared in an analogous procedure to that used in the preparation of 1-methylbutyl(pyridine)cobaloxime to yield 0.48g (39%) pure material.

$^1H$ n.m.r. ($CDCl_3$) $\delta$ 0.8 (m,6H), 1.1 (m,2H), 1.5 (t,1H), 1.9 (m,2H), 2.2 (s,12H), 7.4 (t,2H), 7.8 (t,1H), 8.6 (d,2H) p.p.m.

Elemental Analysis Found C 48.48, H 6.70, N 15.98% calculated for $C_{18}H_{30}N_5O_4Co$ C 48.96 H 6.65 N15.98%.

Section 3: Preparation of cis- and trans-2-Methylcyclopropylmethyl-(pyridine)cobaloximes (Scheme 16.)

Preparation of the Zinc-Copper Couple (type I)

To a solution of 20% w/v aqueous copper(II)sulphate (0.57cm$^3$) diluted with water (2.86cm$^3$) was added with swirling zinc dust (1.714g; 26 mmol). The precipitate of zinc-copper couple was filtered off with suction in a stream of nitrogen. The still damp couple was added to the reaction mixture immediately.

Preparation of Zinc-Copper Couple (type II)

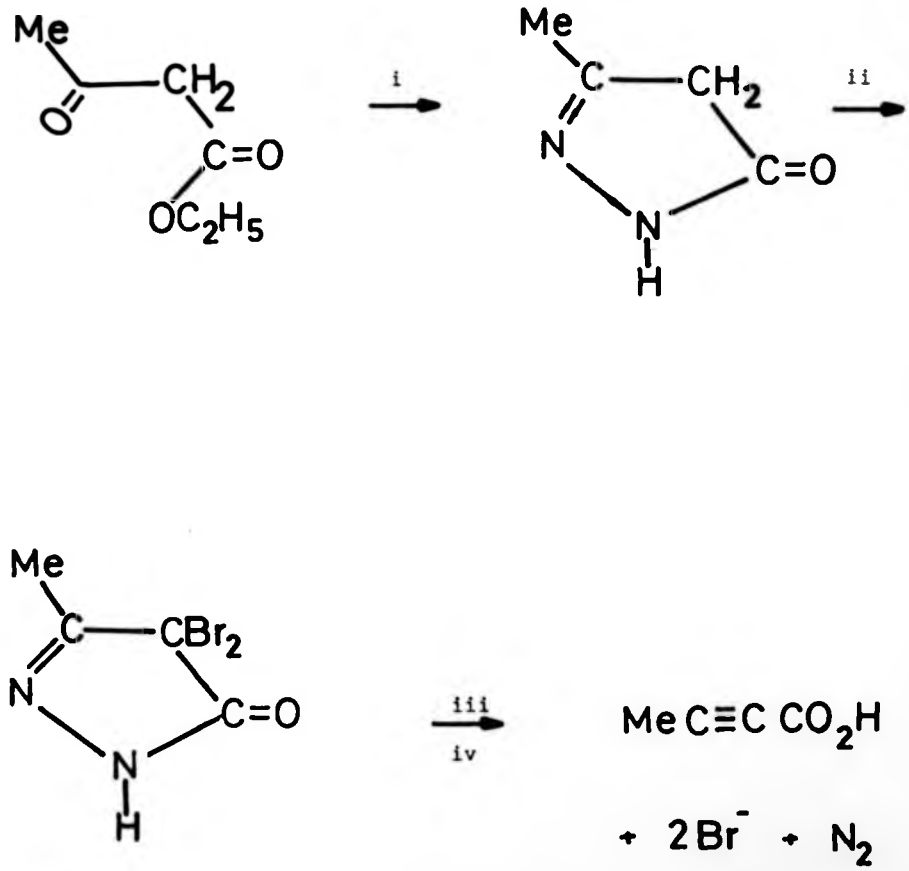
The reaction was conducted under dry nitrogen. To a hot, rapidly stirred solution of copper(II)acetate monohydrate (2g; 10 mmol) in glacial acetic acid (50cm$^3$), was added zinc dust (35g; 540 mmol). Within 30 seconds the reaction was complete, as judged by a colour change of the precipitate from grey to bronze. After 1 minute settling time, as much as possible of the glacial acetic acid was decanted from the fine couple. The dark reddish-bronze couple was then washed with glacial acetic acid (50cm$^3$), followed by ethoxyethane until the washings were neutral to litmus. The couple was then used immediately.

Preparation of But-2-ynoic Acid

This was prepared according to the method described in "Textbook of Practical Organic Chemistry", Vogel, 4th Edition, P.594. The synthesis is outlined in Scheme 26, and involves the hydroxide-induced decomposition of an intermediate 3-methylpyrazol-5-one, liberating molecular nitrogen and but-2-ynoic acid upon work up.

$^1$H n.m.r. ($CDCl_3$) $\delta$1.2 (s,3H), 13.2 (s, broad 1H) p.p.m.

Scheme 26. Synthesis of But-2-ynoic Acid




i = Hydrazine Hydrate

ii = Bromine

iii = Sodium Hydroxide/water

iv = 5M HCl

Preparation of cis-Crotonic Acid

To a stirred suspension of zinc-copper couple (type I) (39.1g; 0.6 mol) in absolute ethanol ($100cm^3$) was added but-2-ynoic acid (30g; 0.38 mol). The mixture was then heated under reflux for 5.5h. The suspension was then cooled in ice and filtered through Celite with suction. Ethoxyethane ($500cm^3$) was added to the filtrate to precipitate inorganic salts. The suspension was then filtered, dried ($MgSO_4$) and solvent was evaporated off to yield cis-crotonic acid (20g; 66%) 95% cis, 5% trans isomer as determined by $^1H$ n.m.r. spectroscopy .

$^1H$ n.m.r. $(CD_3)_2CO$ ∂1.90 (d,3H), 5.83 (d,1H), 7.10 (m,1H), 12.18 (s broad 1H). p.p.m.

Preparation of cis-Crotyl Alcohol

To a stirred suspension of lithium tetrahydroaluminate (8.82g; 0.233 mol) in ethoxyethane ($115cm^3$) was added cautiously cis-crotonic acid (20g; 0.233 mol) in ethoxyethane ($80cm^3$) over 1h. The suspension was heated under reflux for 2h. Water ($8cm^3$) and 15% aqueous sodium hydroxide ($8cm^3$) were added cautiously to the mixture followed by a further aliquot of water ($25cm^3$). The ethoxyethane layer was removed and the granular precipitate was washed with ethoxyethane ( 2 x $40cm^3$). The combined organic layers were dried ($MgSO_4$ ), solvent was evaporated off and the product was distilled (b.p. 121-122° at 760 mm Hg) to yield 14.1g (84%) pure material.

$^1H$ n.m.r. $(CDCl_3)$ ∂1.95 (d,3H), 4.2 (d,2H), 5.3 (m,1H), 5.9 (m,1H) p.p.m.

G.l.c. (20% DEGS, $N_2$ carrier, 100°, showed 95% cis-isomer 5% trans isomer).

Preparation of trans-Crotyl alcohol

To a suspension of lithium tetrahydroaluminate (13g; 0.37 mol) in

ethoxyethane ($300cm^3$) was added, dropwise, over 1.5h, a solution of redistilled crotonaldehyde (77.5g; 1.1 mol) in ethoxyethane ($100cm^3$). The mixture was heated under reflux for 2h. Water ($13cm^3$) and 15% aqueous sodium hydroxide ($13cm^3$) were added (care!) to the mixture, followed by a further aliquot of water ($40cm^3$). The ethoxyethane layer was removed and the granular precipitate was washed with ethoxyethane (2 x 100 $cm^3$). The combined organic layers were dried ($MgSO_4$), solvent was evaporated off and the product was distilled (b.p. 121-122° at 760 mm Hg) to yield 40g (50%) pure material.

$^1H$ n.m.r. ($CDCl_3$) δ1.7 (d,3H), 4.0 (s,2H), 5.6(m,2H) p.p.m.

G.l.c. (DEGS, 100° $N_2$ carrier, showed a single component).

Preparation of cis- and trans-2-Methylcyclopropylcarbinol

To a stirred suspension of zinc-copper couple (type II) (15g; 0.23 mol), diiodomethane (44g; 0.16 mol) and ethoxyethane ($250cm^3$) was added, dropwise, over 1½h, a solution of either cis-or trans-crotyl alcohol (5.5g; 80mmol) in ethoxyethane ($50cm^3$). The progress of the reaction was monitored by g.l.c. (20% DEGS, 100°,) and upon completion of the reaction, aqueous saturated ammonium chloride ($100cm^3$) was added. The organic layer was separated and the aqueous phase was saturated with sodium chloride and re-extracted with ethoxyethane (2 x $50cm^3$). The combined organic layers were washed with saturated aqueous potassium carbonate solution (3 x $20cm^3$), saturated aqueous sodium chloride (2 x $30cm^3$), dried ($Na_2SO_4$), and solvent was evaporated off. The crude material was distilled (spinning-band column) to yield pure material 4.2g; 62%. The cis-2-methylcyclopropylcarbinol has a b.p. 50-51° at 20 mm Hg; the trans-isomer has a b.p. 55-57° at 20 mm Hg.

$^1$H n.m.r. ($CDCl_3$) cis-isomer $\delta$ 0.8-1.6 (m,3H,broad), 1.2 (d,3H), 2.0 (m,1H) 3.6 (m,2H), 3.9 (s,1H broad) p.p.m.

$^1$H n.m.r. ($CDCl_3$) trans-isomer $\delta$ 0.2-0.8 (m,3H, broad), 1.2 (m,3H), 1.4 (m, 1H), 3.5 (d, 2H), 3.8 (s,broad,1H) p.p.m.

Preparation of trans-2-Methylcyclopropylcarbinol Tosylate

Toluene-4-sulphonyl chloride (1.37g; 8 mmol) in pyridine (4.4cm$^3$) was added dropwise over 10 minutes to a stirred solution of trans-2-methylcyclopropylcarbinol (0.56g; 6.5 mmol) in pyridine (0.6cm$^3$) at 0°C. The reaction was stirred for 5 minutes at 0°C, and 90 minutes at room temperature. Ice was added to dissolve the precipitated pyridinium hydrochloride and the mixture was poured into ice-cold 5M hydrochloric acid (10cm$^3$). The aqueous acidic solution was then extracted with dichloromethane (3 x 20cm$^3$). The combined organic extracts were washed successively with cold 5M hydrochloric acid (10cm$^3$), cold 10% aqueous sodium carbonate (10cm$^3$), dried ($Na_2CO_3$) and solvent evaporated to yield 0.82g (60%) pure material.

$^1$H n.m.r. ($CDCl_3$) $\delta$ 0.2-0.8 (m,3H), 1.2(d,3H), 2.5 (s,3H), 4.0 (d,2H), 7.7 (q,4H) p.p.m.

Preparation of cis-or trans-2-Methylcyclopropylmethylbromide

To a stirred solution of either cis- or trans-2-methylcyclopropylcarbinol (2.29g; 26.6 mmol) in pyridine (2.11 cm$^3$) and ethoxyethane (16.8cm$^3$) was added dropwise over a 1h. period a solution of phosphorus(III)tribromide (2.87cm$^3$; 31 mmol) in ethoxyethane (26cm$^3$). The mixture was stirred at -10° for 1h, and was left in a cold room (0-3°C) for 2 days. The excess phosphorus(III)tribromide was destroyed with ice-water (5g.), and the ethoxyethane layer was separated and washed successively with 10cm$^3$

portions of ice-water, 80% orthophosphoric acid, ice-cold saturated aqueous sodium bicarbonate, ice-water and finally dried ($MgSO_4$). The solvent was evaporated off and the residual oil was distilled (b.p. 60-63° at 20 mm Hg) to yield 1.8g (45%) pure material.

$^1H$ n.m.r. ($CCl_4$) trans-isomer $\delta$ 0.2-0.8 (m,4H), 1.1 (d,3H), 3.3 (m,3H) p.p.m.

$^1H$ n.m.r. ($CCl_4$) cis-isomer $\delta$ 0.8-1.4 (m,4H), 1.15 (d,3H), 3.3 (m,2H) p.p.m.

Preparation of cis- and trans-2-Methylcyclopropylmethyl(pyridine) cobaloxime

Bromo(pyridine)cobaloxime (2.25g; 5 mmol) and absolute ethanol (50cm$^3$) was stirred under nitrogen at 0°C in a Schlenk tube for 30 minutes. Sodium tetrahydroborate (0.57g; 5 mmol) and either cis- or trans-2-methylcyclopropylmethyl bromide (0.745g; 4.4 mmol) were added and the reaction mixture was stirred at 0°C for 4h. Water (40cm$^3$) containing 2% v/v pyridine was added and air blown through the reaction mixture for 30 minutes. The precipitated cobaloxime was filtered and was washed successively with 50cm$^3$ portions of water, absolute ethanol and ethoxyethane. The solid was purified by silica gel chromatography in the usual manner and dried in vacuo to yield 1.1g (45%) pure material.

trans-isomer $^1H$ n.m.r. ($CDCl_3$) $\delta$ 0.1 (m,2H), 0.35 (m,2H), 0.9 (d,3H), 1.6 (m,2H), 2.1 (s,12H), 7.3 (m,2H), 7.6 (t,1H), 8.5 (d,2H) p.p.m.

trans-isomer $^{13}C$ n.m.r. ($CDCl_3$) $\delta$ 12.14, 14.40, 15.10, 18.88, 22.82, 38.03, 125.32, 137.56, 49.27, 149.59 p.p.m.

cis-isomer $^1H$ n.m.r. ($CDCl_3$) $\delta$ 0.6 (m,4H), 0.9 (d,3H), 1.6 (m,2H), 2.15 (s,12H), 7.3 (m,2H), 7.5 (t,1H), 8.4 (d,2H) p.p.m.

cis-isomer $^{13}C$ n.m.r. ($CDCl_3$) $\delta$ 10.39, 12.14, 13.51, 18.98, 23.10, 38.05, 126.10, 137.66, 149.30, 149.61 p.p.m.

Elemental Analysis Found C 49.20, H 6.55, N 15.71% : calculated for $C_{18}H_{28}N_5O_4Co$ C49.20, H 6.55, N 15.71%.

Section 4 - Attempted Synthesis of meso- and threo-1,2-Dimethylbut-3-enyl(pyridine)cobaloximes (Scheme 24).

The meso- and threo-butane-2,3-diols used in the following synthetic routes were provided as a gift by Bayer, Leverkusen, FRG.

Preparation of meso- and threo-2,3-Acetoxybromobutanes

These were prepared by a modification of standard procedures[112, 113]. To a 250cm$^3$ round-bottomed three-necked flask fitted with pressure-equalising dropping funnel, drying tube and magnetic follower, was added either meso- or threo-butane-2,3-diol (9.01g; 0.1 mol). The reaction vessel was cooled to 0°C. To the rapidly stirred butane-2,3-diol was added 45% v/v HBr in acetic acid (71g; 0.3 mol) over a 5 minute period. The reaction mixture was left stirring at room temperature for 3h. Water (50cm$^3$) was added and the solution was made neutral by the addition of solid $Na_2CO_3$. The aqueous layer was then extracted with ethoxyethane (3 x 100cm$^3$). The combined organic layers were dried ($MgSO_4$) and solvent was evaporated off. The residual oil was distilled to yield 17g (89%) pure material, (threo-2,3-acetoxybromobutane b.p. 80-84° at 12 mm Hg; meso-2,3-acetoxybromobutane b.p. 74-78° at 12 mm Hg).

$^1$H n.m.r. ($CCl_4$) threo-isomer δ1.3 (d,3H), 1.65 (d,3H), 2.05 (s,3H), 4.15 (m,1H), 4.85 (m,1H) p.p.m.

$^1$H n.m.r. ($CCl_4$) meso-isomer δ1.3 (d,3H), 1.65 (d,3H), 2.05 (s,3H), 4.05 (m,1H), 4.9 (m,1H) p.p.m.

Preparation of meso- and threo-2,3-Epoxybutanes

The reaction was carried out as a modification of the literature procedure of Seeley and McElwee[116].

To a $100cm^3$ round-bottomed flask equipped with a Dufton fractionating column and a magnetic follower, was added either meso- or threo-2,3-acetoxybromobutane (15.13g; 79.5 mmol), sodium hydroxide (6.36g; 159 mmol) and ethane-1,2-diol ($50cm^3$). The mixture was gradually heated to $140^o$ when the epoxybutane distilled over directly from the reaction mixture to yield 3.2g (56%) pure material. cis-2,3-Epoxybutane b.p. $58-60^o$ at 760 mm Hg; trans-2,3-epoxybutane b.p. $53-54^o$ at 760 mm Hg.

$^1H$ n.m.r. ($CCl_4$) cis-isomer $\delta$1.2 (d,6H), 2.85 (m,2H)p.p.m.

$^1H$ n.m.r. ($CCl_4$) threo-isomer $\delta$1.25 (d,6H), 2.50 (m,2H) p.p.m.

Alternative Preparation of cis-2,3-Epoxybutane

This was also prepared by a modification of the literature procedure of Pasto and Cumbo[117]. To a $500cm^3$ three-necked round-bottomed flask fitted with a gas inlet system, magnetic follower and a dry ice-acetone condenser was added anhydrous chlorobenzene ($250cm^3$) and m — chloroperbenzoic acid (32.65g; 163 mmol). After solution had been effected, the flask was cooled to $0^oC$, and cis-but-2-ene (10g; 170 mmol) was added via the gas inlet system. The contents of the flask were stirred for 6h (or until the cis-but-2-ene was no longer observed to be boiling under reflux). The flask was then stoppered and stored at $0^oC$ overnight (15h). The cis-2,3-epoxybutane was isolated by direct distillation from the reaction mixture to yield 5.3g (55%) of cis-2,3-epoxybutane. The material was further purified by fractional distillation.

Preparation of meso- and threo-1,2-Dimethylbut-3-ene-1-ol

Vinylmagnesium bromide was prepared according to the procedure in chapter 4, section 2.

To a 100cm$^3$ three-necked round-bottomed flask fitted with a condenser, pressure-equalising dropping funnel and magnetic follower was added vinylmagnesium bromide prepared from magnesium (2.4g; 10 mmol) and vinyl bromide (7.8cm$^3$; 15 mmol) in tetrahydrofuran (28cm$^3$). The reaction mixture was cooled to 0°C in ice and copper(I)iodide (1.319g; 7 mmol) was added. Either cis- or trans-2-3,epoxybutane (2.5g; 3.5 mmol) in tetrahydrofuran (15cm$^3$) was added dropwise over a 1h period. The reaction mixture was stirred for 4h at 0°C and then allowed to warm to room temperature and stirred overnight. The reaction mixture was worked up in the usual manner (chapter 4, section2) to yield 1.7g (48%) pure material, b.p. 125-126° at 760 mm Hg.

$^1$H n.m.r. ($CCl_4$) threo-isomer $\delta$0.95 (d,3H), 1.05 (d,3H), 2.1 (m,1H), 3.55 (m,1H), 5.0 (d,2H), 4.75 (-OH,broad), 5.8 (m,1H) p.p.m.

$^1$H n.m.r. ($CCl_4$) meso-isomer $\delta$0.95 (d,3H), 1.05 (d,3H), 2.15 (m,1H), 3.55 (m,1H), 4.6 (-OH, broad), 5.0 (m,2H), 5.7 (m,1H) p.p.m.

Preparation of rac-1,2-Dimethylbut-3-ene-1-ol

To a three necked 500cm$^3$ round-bottomed flask fitted with a reflux condenser, pressure-equalising dropping funnel and magnetic follower was added magnesium turnings (13.3g; 0.55 mol). Sufficient ethoxyethane (ca 40cm$^3$) to cover the turnings was then added. To the rapidly stirred suspension, a solution of crotyl bromide (25g; 0.19 mol) in ethoxyethane (80cm$^3$) was added, dropwise, over a 3h. period. The solution was cooled to 0°C, and acetaldehyde (8.8g; 0.2 mol) in ethoxyethane (20cm$^3$) was

added, dropwise, over 1h. The reaction mixture was allowed to reach room temperature, and was then heated under reflux for 4h. Saturated aqueous ammonium chloride ($100cm^3$) was added, and the ethoxyethane layer removed. The aqueous layer was extracted with ethoxyethane ($3 \times 50cm^3$) and the combined organic layers were washed with water, dried ($MgSO_4$) and solvent was evaporated off. The residual oil was fractionally distilled to yield 7.6g, 40%, pure material b.p. 125-.26° at 760 mm Hg.

Preparation of meso- and threo-1,2-Dimethylbut-3-ene-1-ol Tosylate

To a $25cm^3$ three-necked pear-shaped flask fitted with a stirrer, drying tube, and pressure-equalising dropping funnel was added either meso- or threo-1,2-dimethylbut-3-ene-1-ol (2.0g; 19.9 mmol) in pyridine ($4cm^3$) and the reaction mixture was cooled in ice. To the stirred reaction mixture was added toluene-4-sulphonyl chloride (4.19g; 22 mmol) in pyridine ($15cm^3$). The progress of the reaction was monitored by the precipitation of pyridinium hydrochloride and was judged complete after 3.5h. Ice was then added to dissolve the precipitated pyridinium hydrochloride and the reaction mixture was poured into ice-cold 5M aqueous hydrochloric acid ($50cm^3$). The aqueous acid solution was extracted with dichloromethane ($3 \times 20cm^3$) and the combined organic extracts were washed successively with $50cm^3$ portions of ice-cold 5M aqueous hydrochloric acid, 10% aqueous sodium carbonate, water, and dried ($MgSO_4$). Solvent was evaporated off to yield 2.9g (95%) pure material.

$^1H$ n.m.r. ($CCl_4$) threo-isomer $\delta$ 0.9 (d,3H), 1.1 (d,3H), 2.2 (m,1H), 2.35 (s,3H), 4.4 (m,1H), 4.9 (m,2H), 5.4 (m,1H), 7.2 (d,2H), 7.6 (d,2H) p.p.m.

$^1$H n.m.r. ($CCl_4$) meso-isomer δ0.9 (d,3H), 1.1 (d,3H), 2.2 (m,1H) 2.35 (s,3H), 4.4 (m,1H), 4.85 (m,2H), 5.3 (m,1H), 7.2 (d,2H), 7.6 (d,2H) p.p.m.

Attempted Preparation of meso- and threo-1.2-Dimethylbut-3-enyl(pyridine) cobaloxime

$CoCl_2.6H_2O$ (4.76g; 20 mmol) and dimethylglyoxime (4.64g; 40 mmol) were stirred with methanol (75cm$^3$) at 0°C in a 250cm$^3$ three-necked round-bottomed flask and nitrogen was bubbled rapidly through the mixture for 30 minutes. Pyridine (1.62cm$^3$; 20 mmol) was added to the reaction mixture followed by 10.4M aqueous sodium hydroxide (0.78cm$^3$; 80 mmol). The dark homogenous solution was stirred at 0°C for a further 15 minutes, then either meso- or threo-1.2-dimethylbut-3-ene-1-ol tosylate was added. The mixture was allowed to warm to room temperature and stirred overnight (15h) under nitrogen. The resulting suspension was poured into ice-water (100cm$^3$) containing 1% v/v pyridine. The precipitated cobaloxime was filtered under suction and washed with portions of ice-water until the washings were colourless. The solid was purified by silica gel chromatography in the usual manner, to yield, after evaporation of solvent, 3.1g (34%) material which had spontaneously rearranged to the 2,3-dimethylcyclopropylmethyl(pyridine)cobaloxime. The cobaloximes prepared from the meso- and threo-isomers of the tosylate precursor possessed identical $^1$H and $^{13}$C n.m.r. spectra.

$^1$H n.m.r. ($CDCl_3$) δ0.15 (m,1H), 0.4 (m,2H), 0.9 (d,6H, broad), 2.15 (s,12H), 7.35 (t,2H), 7.75 (t,1H), 8.6 (d,2H) p.p.m.

$^{13}$C n.m.r. ($CDCl_3$) δ12.02, 12.67, 19.37, 30.94, 39.26, 125.12, 137.34, 148.91, 149.81 p.p.m.

**Preparation of a mixture of *cis*, *trans*- and *trans*, *trans*-isomers of 2,3-Dimethylcyclopropylcarbinols.**

The mixture was prepared according to a modification of a literature procedure[118]. A 250cm$^3$ three-necked round-bottomed flask was fitted with a thermometer, pressure-equalising dropping funnel, magnetic follower and a rubber septum. The flask was filled with nitrogen and a solution of crotyl alcohol (5.6cm$^3$; 66 mmol) in dimethoxyethane (30cm$^3$) was introduced. The reaction mixture was cooled in ice, and diethyl zinc (50cm$^3$ of a 25% w/v solution in toluene; 0.1 mol) was added cautiously *via* hypodermic syringe. 1,1-Diiodoethane[119] (12.43cm$^3$; 85 mmol) was added *via* the dropping funnel over a 30 minute period to the rapidly stirred solution; the reaction was exothermic. The mixture was stirred overnight at room temperature. The suspension was poured into 2M aqueous hydrochloric acid (100cm$^3$) and the organic layer was separated. The organic layer was washed with water (50cm$^3$) and saturated aqueous sodium bicarbonate solution (50cm$^3$), dried ($Na_2SO_4$), and solvent evaporated off. The residual oil was purified by spinning-band distillation (b.p. 78-80$^o$ at 60 mm Hg) to yield 5.6g (85%) pure material (95% *trans*, *trans*-isomer, 5% *cis*, *trans*-isomer by $^1$H n.m.r. spectroscopy; cf. ref.118, 1:1.7 ratio of *cis*, *trans*- to *trans*, *trans* isomers obtained).

$^1$H n.m.r. ($CDCl_3$) *cis*, *trans*-isomer $\delta$ 0.1-0.9 (m,3H), 1.02 (d,3H) 1.12 (d,3H), 1.35 (s,1H), 3.64 (m,2H) p.p.m.

$^1$H n.m.r. ($CDCl_3$) *trans*, *trans*-isomer $\delta$ 0.3-0.9 (m,3H), 1.04 (d,6H) 1.57 (s,1H), 3.45 (d,2H) p.p.m.

**Preparation of a Mixture of *cis*, *trans*- and *trans*, *trans*-2,3-Dimethylcyclopropylmethyl-1-ol Tosylate**

To a three-necked $25cm^3$ round-bottomed flask fitted with magnetic follower, pressure-equalising dropping funnel and silica gel drying tube was added the mixture of cis, trans- and trans, trans-2,3-dimethylcyclopropylcarbinols (2.0g; 19.96 mmol) and pyridine ($4cm^3$). The reaction mixture was stirred at $0^oC$ for 10 minutes. Toluene-4-sulphonyl chloride (4.19; 22 mmol) in pyridine ($15cm^3$) was added dropwise over 15 minutes. The reaction was monitored by the precipitation of pyridinium hydrochloride and was judged complete after 15 minutes at $0^oC$. The tosylate however, decomposed upon working up in the standard manner.

Preparation of a Mixture of cis, trans- and trans, trans-2,3-Dimethylcyclopropylmethylbromides.

To a $100cm^3$ three-necked round-bottomed flask fitted with magnetic follower, pressure-equalising dropping funnel and drying tube was added the mixture of cis, trans- and trans, trans-2,3-dimethylcyclopropylcarbinols (3.0g; 30 mmol) in ethoxyethane ($25cm^3$) and pyridine ($10cm^3$). The reaction mixture was stirred at $-25^oC$ for 15 minutes and a solution of phosphorus(III)bromide ($4.7cm^3$; 30 mmol) in ethoxyethane ($30cm^3$) was added dropwise, over a 1h period. The solution was stirred at $-10^o$ for 1h and at $0^oC$ for 2 days (cold room). The excess phosphorus(III)bromide was destroyed with ice-water (10g) and the ethoxyethane layer was separated and was washed successively with $20cm^3$ portions of ice-water, 80% orthophosphoric acid, ice-cold saturated aqueous sodium bicarbonate, ice-water and finally dried ($MgSO_4$). The solvent was evaporated off to yield a dark brown oil which became viscous and underwent decomposition upon attempted distillation.

Section 5. Other Substituted Cyclopropanes and their Derived Cobaloximes

The attempted synthesis of some substituted cyclopropanes and of their corresponding cyclopropyl(pyridine)cobaloximes are outlined in Schemes 20, 21 and 22.

1-Cyclopropylmethylcarbinol, ethyl 1-methylcyclopropanecarboxylate, trans-2-phenylcyclopropylcarbinol and cis-hex-3-ene-1-ol were commercially available (Aldrich).

Preparation of 1-Methylcyclopropylcarbinol (Scheme 19).

To a 250cm$^3$ round-bottomed three-necked flask fitted with reflux condenser, drying tube, magnetic follower and pressure-equalising dropping funnel was added lithium tetrahydroaluminate (3.5g; 100 mmol) and ethoxyethane (100cm$^3$). To the rapidly stirred suspension was added, dropwise, ethyl cyclopropylmethylcarboxylate (10g; 87.6 mmol) in ethoxyethane (20cm$^3$) over a 30 minute period. The suspension was heated under reflux for 2h. Water (9cm$^3$) was added cautiously, followed by 15% aqueous sodium hydroxide (9cm$^3$) and water (27cm$^3$). The ethoxyethane layer was removed, and the granular precipitate was washed with ethoxyethane (2 x 50cm$^3$). The combined organic layers were washed with water (50cm$^3$), dried ($MgSO_4$), and solvent evaporated off. The residual oil was distilled to yield 7.2g (93%) pure material, b.p. 126-127$^o$ at 760 mm Hg.

$^1$H n.m.r. ($CDCl_3$) $\delta$ 0.3 (s,2H), 0.4 (s,2H), 1.15 (S,3H), 2.45 (-OH broad), 3.35 (s,2H) p.p.m.

Preparation of N,N'-diisopropyl-O-1-methylcyclopropylmethylisourea.

To a 50cm$^3$ round-bottomed flask fitted with silica gel drying tube and magnetic follower, were added diisopropylcarbodiimide (10.27g; 81.4 mmol),

copper(I)chloride (0.016g; 2.5 mmol) and 1-methylcyclopropylcarbinol (7.1g; 81.4 mmol). The mixture was stirred at room temperature for 96h. and petroleum ether 60-80 (20cm$^3$) was added. The precipitated N,N'-diisopropylurea was removed by filtration and the filtrate was passed down a column of neutral alumina (10g; 20 x 2cm). The column was eluted with a further 50cm$^3$ portion of petroleum ether 60-80. The petroleum ether was evaporated off and the crude product distilled b.p. 96-100$^\circ$ at 12 mm Hg to yield 16.0g. (92%) pure material.

$^1$H n.m.r. ($CCl_4$) $\delta$ 0.43 (m,2H), 0.55 (m,2H), 1.05 (d,3H), 1.10 (d,6H), 1,20 (d,6H), 4.03 (m,1H), 4.45 (m,1H), 6.93 (s, broad, 2H) p.p.m.

Attempted Preparation of 1-Methylcyclopropylmethylbromide

N,N'-diisopropyl-O-1-methylcyclopropylmethylisourea (4.24g; 20 mmol) was placed in a stoppered 100cm$^3$ round-bottomed flask and cooled in ice-water. A solution of 0.693M HBr in $CHCl_3$ (40cm$^3$; 27.7 mmol) was added in portions over a period of 10 minutes with gentle swirling. The clear mixture was stirred at room temperature for 3h. The mixture was cooled to 0$^\circ$C when some N,N'-diisopropylurea crystallised. The liquid was removed and fractionally distilled to yield 3.2g (75%) of a colourless liquid, b.p. 126-130$^\circ$ at 760 mm Hg. $^1$H n.m.r. spectroscopy showed that this material was 1-bromo-3-methylbut-3-ene.

$^1$H n.m.r. ($CDCl_3$) $\delta$ 1.86 (d,3H), 2.50 (m,2H), 3.35 (m,2H), 5.45 (m,2H) p.p.m.

N.B. distillation at reduced pressure may well prevent the thermal decomposition of the 1-methylcyclopropylmethylbromide.

Preparation of cis-1-Bromohex-3-ene

This material was obtained from cis-hex-3-ene-1-ol. The procedure used was analogous to that used for the bromination of trans-2-phenylcyclopropyl

carbinol. The product was purified by distillation b.p. 60-63° at 25 mm Hg to yield 4.2g. (22.5%) pure material.

$^1$H n.m.r. ($CCl_4$) $\delta$ 0.95 (t,3H), 2.0 (m,2H), 2.35 (m,2H), 3.90 (t,2H), 5.23 (m,1H), 5.40 (m,1H) p.p.m.

Preparation of trans-2-Phenylcyclopropylmethylbromide

To a 100cm$^3$ three-necked round-bottomed flask equipped with magnetic follower, drying tube and pressure-equalising dropping funnel was added trans-2-phenylcyclopropylcarbinol (5.0g; 33.7 mmol) in pyridine (5.6cm$^3$) and ethoxyethane (22cm$^3$). The solution was stirred at -25°C for 10 minutes. Phosphorus(III)bromide (3.7cm$^3$; 39 mmol) in ethoxyethane (32cm$^3$) was added dropwise over 40 minutes. The reaction was warmed to -10°C for 1h. and stirred for 48h at 0° (cold room). Ice (10g) was added. The ethoxyethane layer was removed and washed successively with 20cm$^3$ portions of ice-water, cold 80% orthophosphoric acid, 10% aqueous sodium bicarbonate solution. After drying ($MgSO_4$) the solvent was evaporated off, and the residual oil was distilled to yield 3.6g (51%) product (containing ca 5% 1-bromo-4-phenylbut-3-ene detected by $^1$H n.m.r. spectroscopy).

$^1$H n.m.r. ($CCl_4$) $\delta$ 0.95 (m,1H), 1.15 (m,1H), 1.5 (m,1H), 1.85 (m,1H), 3.4 (m,2H), 7.1 (m,5H) p.p.m.

Attempts to Prepare trans-2-Phenylcyclopropylmethyl(pyridine)cobaloxime

Method 1. To a stirred suspension of bromo(pyridine)cobaloxime (2.49g; 5 mmol) in absolute ethanol (35cm$^3$) in a Schlenk tube at 0°C, under nitrogen was added sodium tetrahydroborate (0.19g; 5 mmol) followed by trans-2-phenylcyclopropylmethylbromide (1.16g; 5 mmol). The mixture was stirred for a further 4h. under nitrogen, then water (50cm$^3$) containing 2% v/v pyridine was added. A solid was isolated by suction filtration.

Method 2. $CoCl_2.6H_2O$ (2.38g; 10 mmol) and dimethylglyoxime (2.32g; 20 mmol) were stirred with methanol ($75cm^3$) at $0^oC$ in a $100cm^3$ round-bottomed three necked flask under nitrogen for 30 minutes. Pyridine ($0.81cm^3$; 10 mmol) was added to the reaction mixture followed by 10.65M aqueous sodium hydroxide ($2.33cm^3$; 40 mmol). The solution was stirred at $0^oC$ for 15 minutes, then trans-2-phenylcyclopropyl-methylbromide (1.16g; 5 mmol) was added and the reaction mixture stirred at $0^oC$ for 6h. Water ($50cm^3$) containing 2% v/v pyridine was added and the precipitate removed by suction filtration. The solid was washed with water until the washings were colourless, and the solid dried in vacuo.

T.l.c. (silica gel, solvent:chloroform, methanol, pyridine, 180:10:1) showed that material isolated from both methods was a complex mixture. Each had at least 6 components. P.l.c. of both samples yielded a small band ($Rf \simeq 0.6$) which appeared to be associated with an alkyl(pyridine)-cobaloxime. Removal of this band, followed by separation of the material from absorbent yielded an orange solid. $^1H$ n.m.r. spectroscopy of both samples showed that these materials did not contain a dimethylglyoxime chelate.

Attempted Preparation of 1-Cyclopropylethanol Tosylate

An attempt to prepare this tosylate from the corresponding alcohol by a procedure analogous to that described for the preparation of 2,3-dimethyl-cyclopropylmethanol tosylate, gave a brown oil (3.4g). $^1H$ n.m.r. spectroscopy of this product showed it to be devoid of tosyl group.

Preparation of 1-Cyclopropylethylbromide

This was prepared from 1-cyclopropylethanol in a manner analogous to that described for the trans-2-phenylcyclopropylcarbinol. The bromide was isolated in 50% yield and was found to be a 1:1 mixture (determined by $^1$H n.m.r. spectroscopy) of the cyclopropyl and ring-opened product (1-bromo-4-methylbut-3-ene), b.p. 90-95$^\circ$ at 60 mm Hg.

Attempted Synthesis of 1-Cyclopropylethyl(pyridine)cobaloxime

The cobaloxime was prepared by two methods analogous to the procedures described for the preparation of trans-2-phenylcyclopropylmethyl(pyridine)-cobaloxime. The product was purified by silica gel chromatography in the usual manner and the material isolated was the ring-opened product 4-methylbut-3-enyl(pyridine)cobaloxime (as identified by $^1$H n.m.r. spectroscopy - and as predominantly the trans isomer).

$^1$H n.m.r. ($CDCl_3$) $\delta$ 0.20 (m,1H), 0.30 (m,1H), 0.50 (d,2H), 0.90 (m,1H), 1.30 (d,3H), 2.30 (-OH, broad), 3.10 (m,2H) p.p.m.

Preparation of cis-Hex-3-ene-1-ol Tosylate

This was prepared using a procedure analogous to that employed for the preparation of 2,3-dimethylcyclopropylmethanol tosylate. Yield: 2.1g (90%) of pure material.

$^1$H n.m.r. ($CCl_4$) $\delta$ 0.95 (t,3H), 2.0 (m,2H), 2.35 (m,2H), 2.45 (s,3H), 3.90 (t,2H), 5.20 (m,1H), 5.40 (m,1H), 7.30 (d,2H), 7.7 (d,2H) p.p.m.

Preparation of cis-Hex-3-enyl(pyridine)cobaloxime

Bromo(pyridine)cobaloxime (2.47g; 5.48 mmol) and methanol (45cm$^3$) were stirred under nitrogen in a Schlenk tube for 45 minutes. Sodium tetrahydroborate (0.625g; 5.5 mmol) was added in portions over 5 minutes,

followed by cis-hex-3-ene-1-ol tosylate (1.31g; 5.48 mmol). The mixture was stirred overnight (16h) under nitrogen. Air was bubbled through the reaction mixture for 1h. and water ($50cm^3$) containing 1% v/v pyridine was added. The precipitate was filtered with suction and washed with several portions of water until the washings were colourless. The solid was dissolved in the minimum amount of dichloromethane and pentane was then added until the mixture became faintly cloudy. The solution was left to crystallise in a refrigerator at $0^oC$. The crystals were collected by filtration and washed with pentane to yield 0.8g (30%) pure material.

$^1H$ n.m.r. ($CDCl_3$) $\delta$ 0.80 (t,3H), 1.47 (m,4H), 1.80 (m,2H), 2.05 (s,12H), 5.15 (m,2H), 7.23 (t,2H), 7.63 (t,1H), 8.50 (d,2H) p.p.m.

## 4: 3 Instrumental Techniques

$^1H$ n.m.r. spectroscopy was used exclusively to monitor the rearrangement of cis- and trans-2-methylcyclopropylmethyl- to mixtures of 1-methylbut-3-enyl- and 2-methylbut-3-enyl(pyridine)cobaloximes. The kinetic data was processed in a manner essentially similar to that used for the rearrangement of cyclopropylmethyl- to but-3-enyl(pyridine)cobaloxime.

The rearrangement of cis- and trans-2-methylcyclopropylmethyl(pyridine)-cobaloxime to 1-methylbut-3-enyl- and 2-methylbut-3-enyl(pyridine)-cobaloxime was qualitatively followed by $^{13}C$ n.m.r. spectroscopy. A sample containing an approximately equimolar mixture of cis- and trans-2-methylcyclopropylmethyl(pyridine)cobaloximes was dissolved in $CDCl_3$ (at $-33^oC$) and the $^{13}C$ n.m.r. spectrum was recorded. The solution was incubated at $35^oC$ for 30 minutes, the solution was cooled to $-33^oC$ and

the $^{13}C$ n.m.r. spectrum was again recorded. This operation was repeated until the rearrangment was judged complete.

The rearrangement of 1-methylbut-3-enyl- to 2-methylbut-3-enyl(pyridine)-cobaloxime was effectively monitored by $^{1}H$ n.m.r. spectroscopy; their respective $^{1}H$ n.m.r. spectra are markedly different, thus permitting an easy estimation of the proportion of the 1-methylbut-3-enyl- to 2-methylbut-3-enyl product present in a mixture e.g., the methyl groups in the 1-methylbut-3-enyl- and 2-methylbut-3-enyl groups resonate as doublets at $\delta$0.40 and 0.85 p.p.m. respectively.

The rate of rearrangement of (R)- and (S)-1-methylbut-3-enyl(pyridine)-cobaloximes was also estimated from the observed change in optical rotation at 589nm during conversion to (R)- and (S)-2-methylbut-3-enyl-(pyridine)cobaloximes. A Bendix NPL 143D ORD spectrometer was coupled to a chart recorder and the change in optical rotation was thus followed at ambient temperature (20$^{o}$C).

Circular dichroism spectra were recorded by Dr. P. M. Scopes at Westfield College for all samples of (R)- and (S)-1-methylbut-3-enyl-(pyridine)cobaloximes and their respective (S)- and (R)- rearrangement products.

## 4:4 Results and Discussion

### 4:4(a) Rearrangement of (rac)-1-Methylbut-3-enyl- to 2-Methylbut-3-enyl-(pyridine)cobaloximes

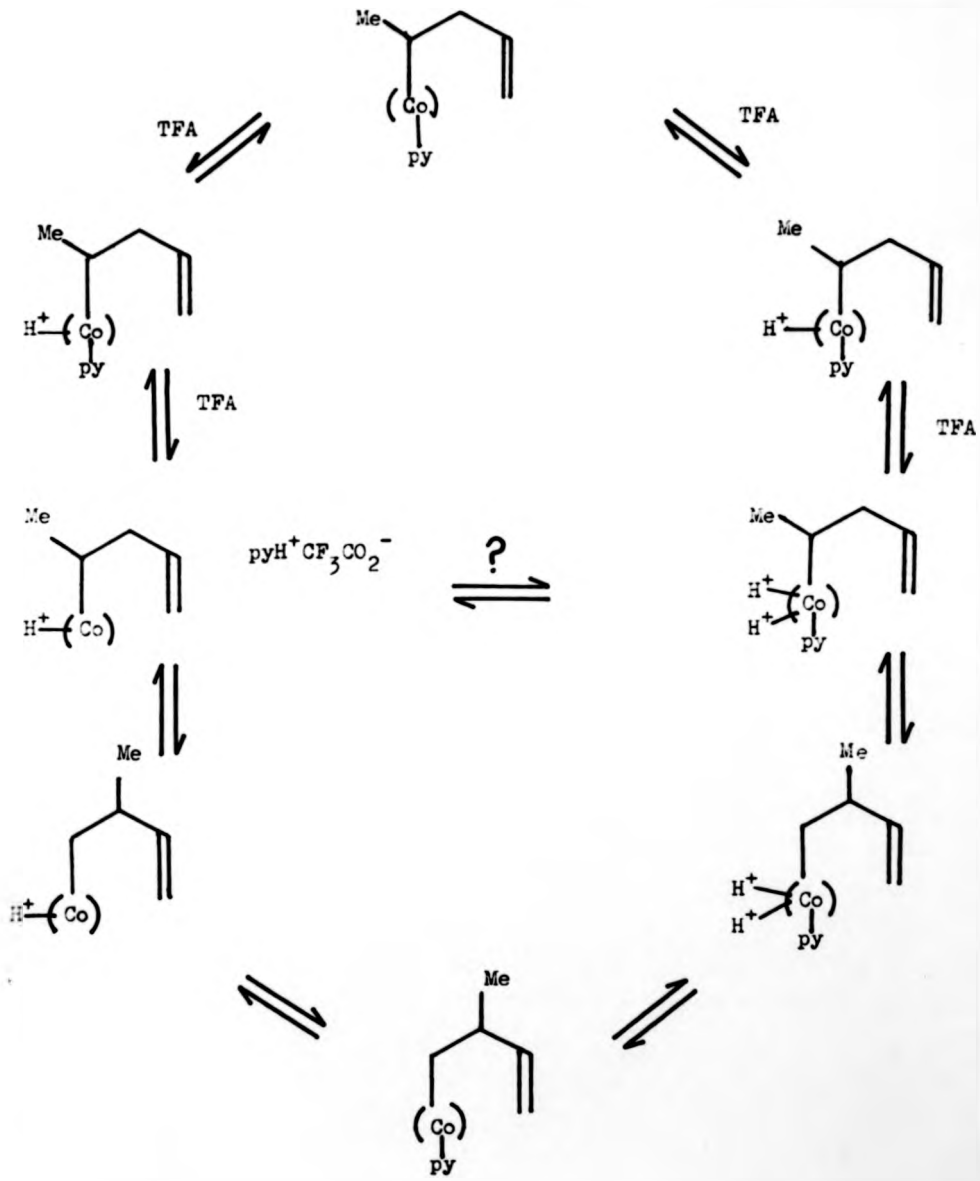
Differences in rate constants $k_1$, for rearrangements calculated from $^{1}H$ n.m.r. spectroscopic data, were not judged as "significant" unless

they differed by a factor of ca 10 (under identical conditions). The rearrangement of 1-methylbut-3-enyl(pyridine)cobaloxime is catalysed by addition of trifluoroacetic acid[120] e.g. [1-methylbut-3-enyl(pyridine)cobaloxime] = 0.39 mol $dm^{3}$, $k_1 = 4.6 \pm 0.2 \times 10^{-4}\ s^{-1}$ at 310K, [TFA] = 0.78M; $k_1 = 2.1 \pm 0.1 \times 10^{-5}\ s^{-1}$, [TFA] = 0.52M. Kinetic studies of the rearrangement of 1-methylbut-3-enyl(pyridine)-cobaloxime to 2-methylbut-3-enyl(pyridine)cobaloxime indicate a first order dependence on the concentration of cobaloxime and an approximately second order dependence on the concentration of trifluoroacetic acid. For the rearrangement catalysed by $CF_3CO_2D$, no incorporation of deuterium into either methylbut-3-enyl group was observed.

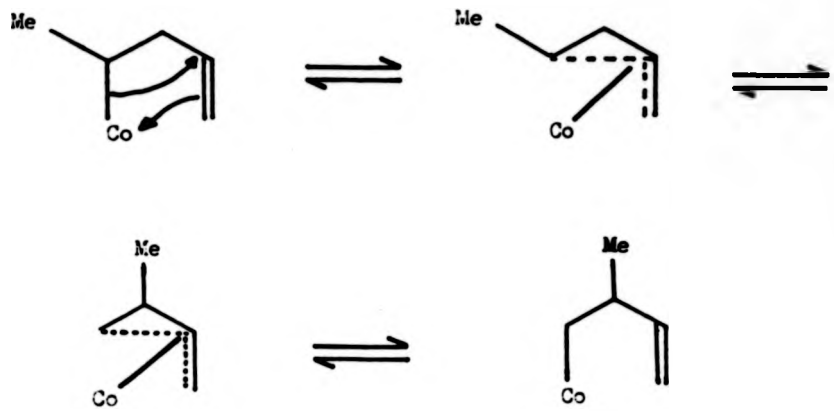
These results are consistent with a rearrangement which proceeds either via a diprotonated alkyl(pyridine)cobaloxime (6-coordinate) or a monoprotonated alkylcobaloxime (5-coordinate) as shown in Scheme 27. For either pathway, the consequence of protonation of the dimethylglyoximato chelate could be to render the cobalt more electrophilic and therefore more susceptible to attack e.g. by a butenyl double bond (cf. Scheme 28). The bimolecular mechanism (Scheme 29) is considered later.

The thermal rearrangement of 1-methylbut-3-enyl(pyridine)cobaloxime to 2-methylbut-3-enyl(pyridine)cobaloxime in $CDCl_3$ at 55°C leads to substantial decomposition of the alkylcobaloxime and considerable broadening of peak resonances observed by $^1H$ n.m.r. spectroscopy suggesting formation of some cobalt(II) species under these conditions. The addition of pyridine decreases the rate of rearrangement of 1-methylbut-3-enyl- to 2-methylbut-3-enyl(pyridine)cobaloxime.

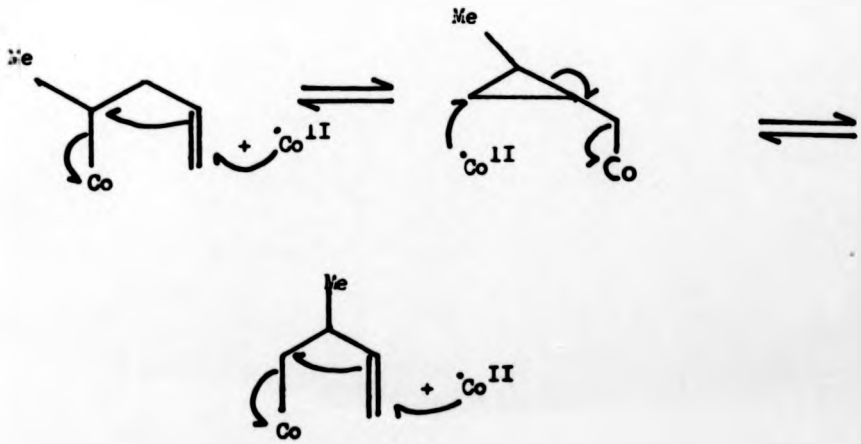
Scheme 27. Possible Pathways for the TFA Catalysed Interconversion of 1-Methyl- to 2-Methylbut-3-enyl(pyridine)cobaloxime



Scheme 28. Unimolecular Mechanism for the Interconversion of 1-Methyl- to 2-Methylbut-3-enyl(pyridine)cobaloxime




Scheme 29. Bimolecular Mechanism for the Interconversion of 1-Methyl- to 2-Methylbut-3-enyl(pyridine)cobaloxime



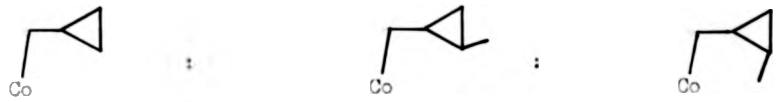
Under comparable conditions (concentrations of cobaloxime, TFA, and temperature) no rearrangement was observed with the 1-methylbutyl- and 2-methylbutyl(pyridine)cobaloximes.

The equilibrium between 1-methylbut-3-enyl- and 2-methylbut-3-enyl-(pyridine)cobaloxime under thermodynamically controlled conditions favours the primary alkylcobaloxime i.e. the 2-methylbut-3-enylcobaloxime. It is expected that such a primary cobaloxime should have enhanced stability compared to a structurally closely related secondary alkylcobaloxime. Evidence from single crystal X-ray diffraction data shows that the Co-C bond length of secondary alkylcobaloximes is considerably longer than that for primary alkylcobaloximes[121]. E.g. Co-C = 2.085 Å for isopropyl(pyridine)cobaloxime; Co-C = 1.997 Å for methyl(pyridine)-cobaloxime. If the electron density in the Co-C bond in both cobaloximes is similar, then the secondary alkylcobaloxime will possess a weaker bond (i.e. of lower bond energy) than the primary alkylcobaloxime. The difference in free energy of formation of the primary and secondary alkylcobaloximes may reasonably be related to a small difference in their respective Co-C bond energies. Thus, for K = [primary] / [secondary] = 7 which is the case for the 1-methylbut-3-enyl- to 2-methylbut-3-enyl-(pyridine)cobaloxime equilibrium, this would correspond to a difference in free energies of formation of 1-methylbut-3-enylcobaloxime and 2-methylbut-3-enylcobaloxime of ca.5 kJ $mol^{-1}$. The Co-C bond energy has been estimated[122] for Co-([14]tetraene$N_4$)$(OH_2)CH_3^{2+}$ and Co([14]ane-$N_4$)$(OH_2)CH_3^{2+}$ at 217 kJ $mol^{-1}$.

4:4(b) cis- and trans-2-Methylcyclopropylmethyl(pyridine)cobaloximes as Possible Intermediates in the Conversion of 1-Methylbut-3-enyl- to

2-Methylbut-3-enyl(pyridine)cobaloximes

The cis- and trans-2-methylcyclopropylmethyl(pyridine)cobaloximes are labile species thermally and rearrange at room temperature to mixtures of 1-methylbut-3-enyl- and 2-methylbut-3-enyl(pyridine)cobaloximes. The cis-methylcyclopropyl isomer gives rise to an initial mixture containing 5% of the 1-methylbut-3-enyl isomer whereas the trans-methylcyclopropyl isomer gives rise to an initial mixture containing ca 10% of the 1-methylbut-3-enyl isomer. Comparison of the rate data for mixtures of cyclopropylmethyl-, cis-2-methylcyclopropylmethyl- and trans-2-methylcyclopropylmethyl(pyridine)cobaloximes indicate the following order of reactivity:




1 : 1.4 : 5

The rates of rearrangement (aerobically, anaerobically and in the presence of 2 mole% aquocobaloxime(II)) of cis- and trans-2-methylcyclopropylmethyl-(pyridine)cobaloximes were monitored by $^1$H n.m.r. spectroscopy. The calculated rate constants are given in Table 8.

The rate of rearrangement of cis- and trans-2-methylcyclopropylmethyl-(pyridine)cobaloximes is increased by the addition of trifluoroacetic acid and decreased by the addition of pyridine. Trifluoroacetic acid serves to remove pyridine from the coordination sphere of cobalt thus increasing the concentration of the 5-coordinate alkylcobaloxime - the

Table 9. Rearrangements of Methylcyclopropylmethylcobaloximes in the Presence of Co(II).

cis-2-Methylcyclopropylmethylcobaloxime :

| Conditions | $k_1$ $s^{-1}$ |
|---|---|
| Cobaloxime under aerobic conditions | $(4.11 \pm 0.04) \times 10^{-3}$ |
| 2 mole% Co(II) added (aerobic) | $(4.60 \pm 0.07) \times 10^{-3}$ |
| 2 mole% Co(II) added (anaerobic) | $(5.20 \pm 0.10) \times 10^{-3}$ |
| trans-2-Methylcyclopropylmethylcobaloxime : | |
| Cobaloxime under aerobic conditions | $(1.02 \pm 0.03) \times 10^{-3}$ |
| 2 mole% Co(II) added (aerobic) | $(1.55 \pm 0.03) \times 10^{-3}$ |
| 2 mole% Co(II) added (anaerobic) | $(2.03 \pm 0.05) \times 10^{-3}$ |

Temperature = 303K

[Cobaloxime] = 0.153M

precurser to the homoallyl intermediate. The rate of rearrangement is therefore likely to be enhanced. Pyridine addition decreases the rate of rearrangement because the equilibrium concentration of the 5-coordinate alkylcobaloxime is reduced relative to the 6-coordinate alkyl(pyridine)-cobaloxime.

The data of Table 8 indicates that the cis-2-methylcyclopropylmethyl-(pyridine)cobaloxime rearranges ca 3-4 fold more rapidly than trans-2-methylcyclopropylmethyl(pyridine)cobaloxime. This small difference in rate indicates merely a subtle difference in the intermediate in the two pathways for the cis- and trans-methylcyclopropyl isomers. The presumed reacting conformations of both isomers have their Co-C1' bond eclipsed with C1-C2 (or C1-C3) bond and as a consequence a severe steric interaction between the methyl group on the cyclopropane ring and the bis(dimethylglyoximato) ring system occurs only in the case of the cis-methyl isomer. This steric interaction could account for the increase in the 2-methylbut-3-enyl isomer in the initial mixture for the cis-2-methylcyclopropylmethyl(pyridine)cobaloxime over the corresponding trans-isomer because ring-opening via a cobalt 1,3-shift would favour attack at the 3-carbon atom of the cyclopropane ring of the cis-2-methyl-cyclopropylmethyl(pyridine)cobaloxime instead of the sterically less accessible 2-position.

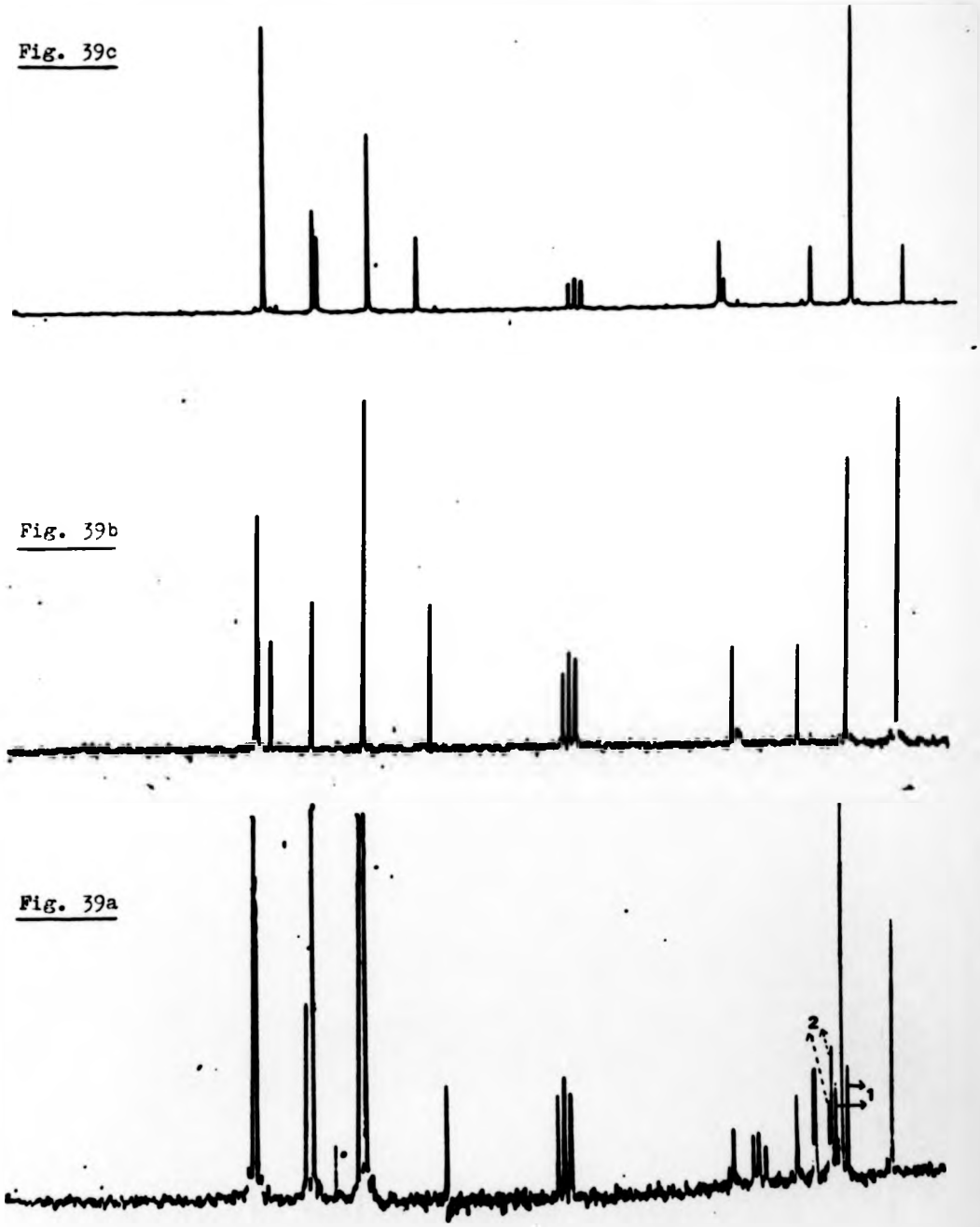
For the bimolecular mechanism, the presumed reacting conformation has the Co-C1' bond trans (antiparallel) to the C1-C2 (or C1-C3) bond axis, and hence the cis-isomer may react faster than the trans-isomer because of relief of ground state steric strain.

Evidence against a substantial contribution from the bimolecular mechanism is that addition of 2 mole% cobaloxime(II) shows no appreciable rate enhancement for the rearrangement of cis-2-methyl or trans-2-methylcyclopropylmethyl(pyridine)cobaloximes. Also for rearrangements under aerobic and anaerobic conditions, no marked difference in rates was observed between the two sets of experiments peformed. Cobaloxime(II) is more stable in anaerobic conditions and thus a rate enhancement would be expected for the anaerobic study, if the bimolecular mechanism were operative.

Under comparable conditions (concentrations of alkylcobaloxime, concentration of TFA and temperature) the rate constant for the acid-catalysed rearrangement of trans-2-methylcyclopropylmethyl(pyridine)-cobaloxime ( $9 \pm 1 \times 10^{-3}\ s^{-1}$, [cobaloxime] = 0.52 mol $dm^{3}$ at 298K, [TFA] = 0.21M) is ≈25 times larger than that for the acid catalysed equilibration of 1-methylbut-3-enyl- to 2-methylbut-3-enyl(pyridine)-cobaloximes. Therefore, cis- and trans-2-methylcyclopropylmethyl-(pyridine)cobaloximes are kinetically competent intermediates in the interconversion of 1-methylbut-3-enyl- to 2-methylbut-3-enyl(pyridine)-cobaloximes.

The $^{13}C$ n.m.r. spectra of an approximately equimolar mixture of cis- and trans-2-methylcyclopropylmethyl(pyridine)cobaloximes, and of products from their rearrangement, 1-methylbut-3-enyl- and 2-methylbut-3-enyl-(pyridine)cobaloximes, are shown in fig. 39 (a), (b) and (c) respectively. The arrows 1 and 2 in fig. 39 (a) represent the resonances due to the cis- and trans-methylcyclopropylmethyl(pyridine)cobaloximes respectively. The resonances due to the cyclopropanes are replaced exclusively by the resonances due to 1-methylbut-3-enyl- and 2-methylbut-3-enyl(pyridine)-

Figure 39. $^{13}C$ NMR Spectra of Methyl Substituted Cyclopropylmethyl- and But-3-enyl(pyridine)cobaloximes.



cobaloximes.

4:4(c) Stabilities of cis- and trans-2-Methylcyclopropylmethyl Radicals

The radicals derived from cis- and trans-2-methylcyclopropylmethyl alcohols or ketones have been the subject of much study[123,124]. cis- and trans-2-Methylcyclopropylmethylstannyloxy and -hydroxymethyl radicals have been generated by treating either the corresponding tin alkoxides or alcohols with t-butoxy radicals, or the corresponding ketones with tributylstannyl radicals shown in figs.40 and 41.

It was observed that the cis-methylcyclopropylmethyl isomer radical undergoes rapid ring-opening to the secondary alkyl radical, and the trans-methylcyclopropylmethyl isomer radical gives rise predominantly to the thermodynamically less stable primary alkyl radical shown in equation 12. The product ratios of primary to secondary radicals derived from reactions of cis- and trans-2-methylcyclopropylmethyl radicals are shown in Scheme 30.

It can therefore be concluded that in the reactions of cis- and trans-2-methylcyclopropylmethyl(pyridine)cobaloximes, radical intermediates are unlikely in the transformation to 1-methylbut-3-enyl- and 2-methylbut-3-enyl(pyridine)cobaloximes. If radicals play a major role, the trans-isomer is expected to give predominantly the 2-methylbut-3-enyl product whereas the cis-isomer would be expected to generate the secondary 1-methylbut-3-enyl product. This difference in product ratio is not observed in the cobaloxime analogues.

4:4(d) Study of the Rearrangement of 1-Methylbut-3-enyl- to 2-methylbut-

Figure 40. Formation of cis-2-Methylcyclopropylmethylstannyloxy Radicals

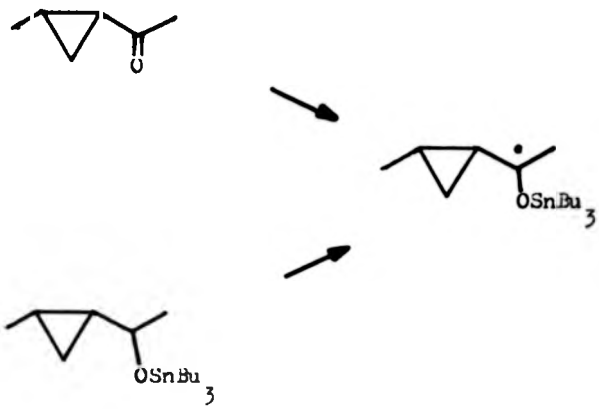
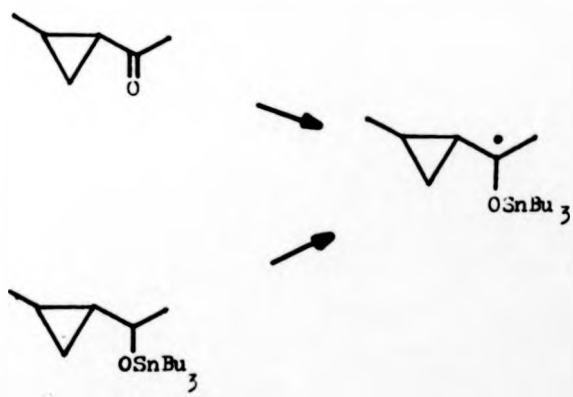
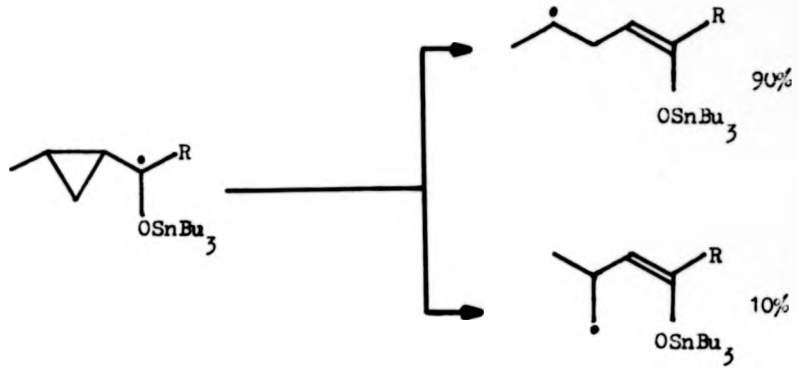
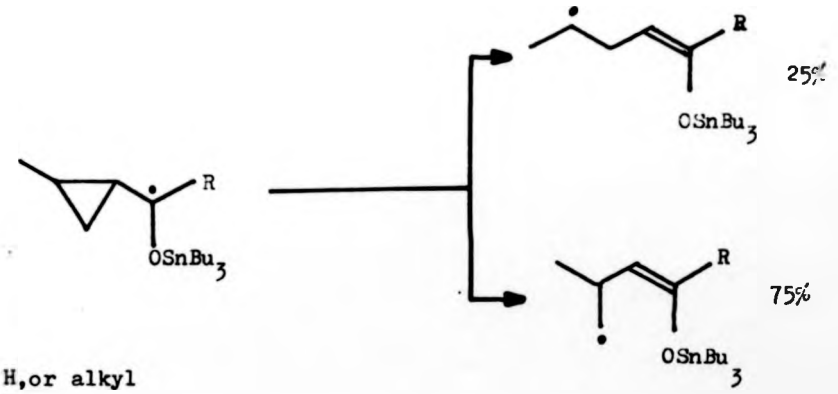



Figure 41. Formation of trans-2-Methylcyclopropylmethylstannyloxy Radicals

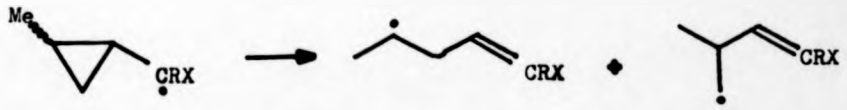


Scheme 30. Products Derived from cis- and trans-2-Methyl-substituted cyclopropanes




R = H,or alkyl




where R = H or alkyl; X = H,OH,or $OSnBu_3$ equation 12

3-enyl(pyridine)cobaloximes Employing Optically Active Compounds

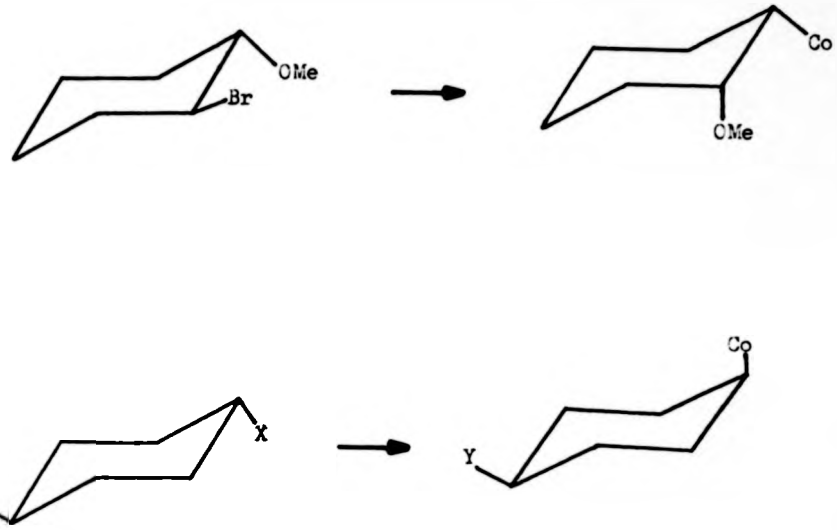
In an effort to exclude dissociative mechanisms involving homolysis or heterolysis of the alkyl-Co bond, optically active 1-methylbut-3-enyl and 2-methylbut-3-enyl(pyridine)cobaloximes were synthesised and their thermal and acid catalysed interconversions studied in detail by polarimetry, c.d., $^{1}H$ n.m.r. and $^{13}C$ n.m.r. spectroscopy.

The stereochemical correlations in the synthetic route to (R)- and (S)-1-methylbut-3-enyl(pyridine)cobaloximes are shown in Scheme 18. Starting from the (S)—propylene oxide, the product is (S)-1-methylbut-3-ene-1-ol and subsequently (S)-1-methylbut-3-ene-1-ol tosylate. The tosylate reacts by an $S_N2$ mechanism (inversion at the chiral centre) with (pyridine)cobaloxime(I) to give (R)-1-methylbut-3-enyl(pyridine)cobaloxime.

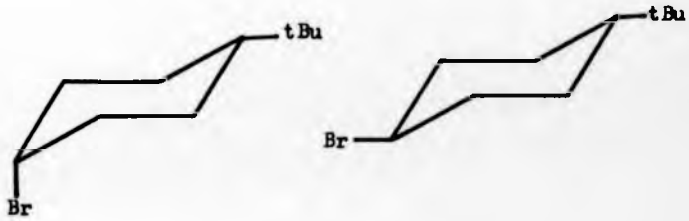
Tosylates and some bromides are known to react with inversion of configuration in displacement reactions involving cobaloxime(I)[125]. Thus both 1,2- and 1,4-disubstituted cyclohexanes containing a displaceable bromide or tosylate group were reacted with (pyridine)cobaloxime(I) under nitrogen (Scheme 31) to give substituted cyclohexylcobaloximes. The sterochemistry was unambiguously established as inversion by use of $^{1}H$ n.m.r. spectroscopy i.e. comparison of the $^{1}H$ n.m.r. spectra of the cobaloxime derivative with $^{1}H$ n.m.r. spectra of cis- and trans-4-t-butylcyclohexyl bromides (equation 13). Especially useful was the H-C-Br resonance, which gives rise to a broad triplet in the cis-1,4-disubstituted molecules, but a broad multiplet in the case of the trans-1,4-disubstituted molecules.

More recent evidence[126] suggests that tosylates react by a purely $S_N2$ process

Scheme 31. Displacement Reactions of 1,2- and 1,4-Disubstituted Cyclohexanes with Cobaloxime(I)




Y = OMe; X = Br, I.




equation 13

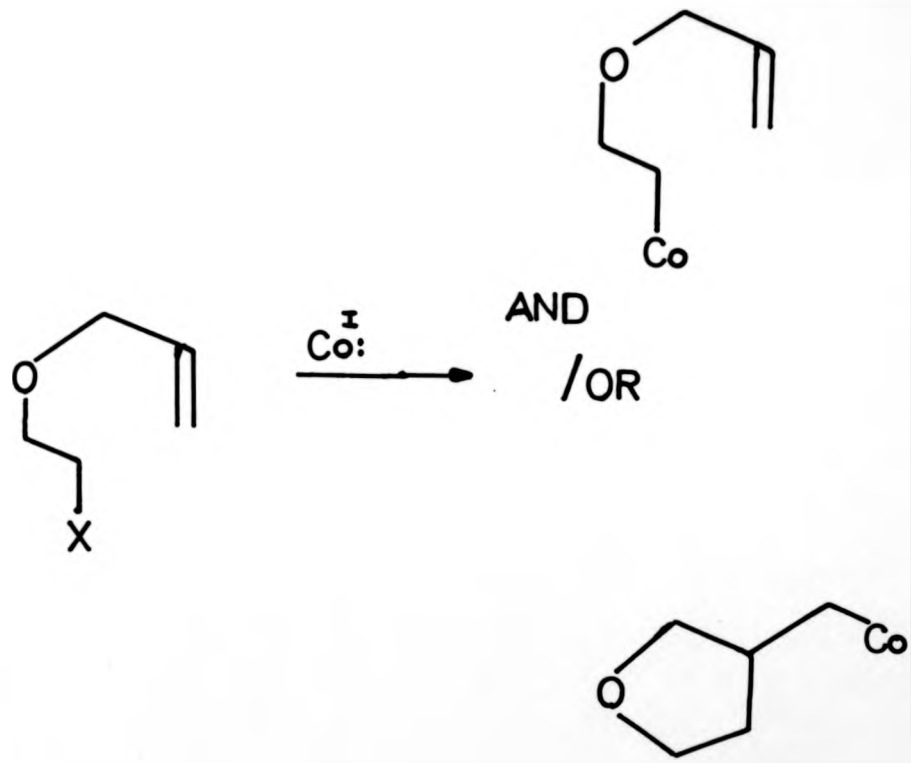
in displacement reactions with (pyridine)cobaloxime(I), whereas bromides and iodides do not necessarily react entirely by an $S_N2$ manner. For these substrates an alternative electron transfer mechanism exists (fig. 42). Cyclisation of 2-allyloxyethyl radicals (to 3-tetrahydrofuranylmethyl radicals) was used as a probe for a radical intermediate arising by separation of halide ion $X^-$ from the radical anion $R\dot{X}^-$, formed as indicated in equation 14:

$$Co^{I} + RX \longrightarrow Co^{II} + R\dot{X}^- \longrightarrow$$
$$Co^{II} + R^{\bullet} + X^- \longrightarrow (Co^{III})R + X^- \qquad \text{equation 14}$$

2-Allyloxyethyltosylate gave the direct substitution product, 2-allyloxyethyl(pyridine)cobaloxime upon reaction with (pyridine)cobaloxime(I), but 2-allyloxyethylbromide and iodide gave rise to mixtures of substitution and cyclised products 2-allyloxyethyl(pyridine)cobaloxime and 3-tetrahydrofuranylmethyl(pyridine)cobaloxime respectively, indicating that electron transfer pathways participate in the latter two reactions.

By employing c.d. spectroscopy the acid-catalysed rearrangement of (R)- and (S)-1-methylbut-3-enyl(pyridine)cobaloxime was shown to be intramolecular and stereospecific resulting in the formation of (S)- and (R)-2-methylbut-3-enyl(pyridine)cobaloxime, respectively. The c.d. spectra of (S)- and (R)-1-methylbut-3-enyl(pyridine)cobaloximes are shown in fig.43. The c.d. spectra of the (S)- and (R)-2-methylbut-3-enyl(pyridine)cobaloximes (A and B) derived from (R)- and (S)-1-methylbut-3-enyl(pyridine)cobaloximes, respectively, and of a sample of

Figure 42. Reaction of (Pyridine)cobaloxime(I) with 2-Allyloxy-Halides and Tosylates



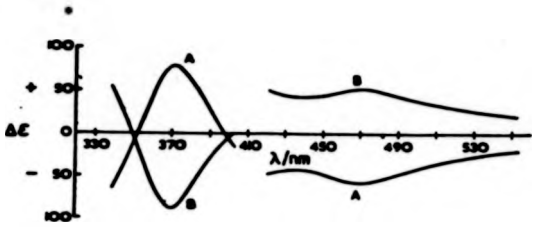

X = OTs, Br, I

(S)-2-methylbut-3-enyl(pyridine)cobaloxime (C) derived from (S)-2-methylbut-3-enoic acid (57.7% enantiomeric excess) are shown in fig.44. The concentration, c, of cobaloxime was estimated from the known extinction coefficients ( $\xi = 4.53 \times 10^2$ and $1.14 \times 10^3$ $mol^{-1}$ $dm^3$ respectively) for 1-methylbut-3-enyl- and 2-methylbut-3-enyl(pyridine)cobaloximes. Thus, the samples of cobaloximes used for recording the c.d. spectra were subsequently analysed spectrophotometrically.

The $\Delta\xi_{450}$ values for (R)- and (S)-1-methylbut-3-enyl(pyridine)cobaloximes and for (R)- and (S)-2-methylbut-3-enylcobaloximes thus derived, and the (S)-2-methylbut-3-enyl(pyridine)cobaloxime obtained *via* reaction from 2-methylbut-3-enoic acid (57.7% enantiomeric excess) are summarised in Table 9. The rearrangement of (S)- and (R)-1-methylbut-3-enyl(pyridine)-cobaloximes to (R)- and (S)-2-methylbut-3-enyl(pyridine)cobaloxime is stereospecific within the error limits (*ca* 15%) of detection. Similar conclusions were drawn using polarimetry by following the change in optical rotation for the respective cobaloximes e.g. (R)-1-methylbut-3-enyl-(pyridine)cobaloxime has a $[\alpha]_D^{21}$ of $+60.5^\circ$ ( [cobaloxime] = 0.13 M in $CHCl_3$), which changes to $-8^\circ$ corresponding to the (S)-2-methylbut-3-enyl-(pyridine)cobaloxime.

The c.d. spectra were also recorded for the thermal rearrangement of (R)-1-methylbut-3-enylcobaloxime and for the acid catalysed rearrangement of (R)- and (S)-1-methylbut-3-enylcobaloximes in the presence of up to 10 mole% aquocobaloxime(II). These $\Delta\xi$ values are also recorded in Table 9. It can be seen that the addition of Co(II) does not affect the stereochemical purity of the rearrangement of 1-methylbut-3-enyl- to 2-methylbut-3-enyl(pyridine)cobaloximes. The thermally induced rearrangement, however, is accompanied by marked decomposition (in $CHCl_3$ solution) of the

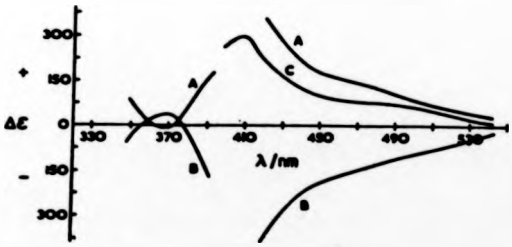
Figure 43. Circular Dichroism Spectra of (R)- and (S)-1-Methylbut-3-enyl(pyridine)cobaloximes.




A = (S)-1-Methylbut-3-enylcobaloxime.

B = (R)-1-Methylbut-3-enylcobaloxime.

Figure 44. Circular Dichroism Spectra of Optically Active 2-Methylbut-3-enyl(pyridine)cobaloximes.




A = (S)-2-Methylbut-3-enylcobaloxime from (R)-1-Methylbutenylcobaloxime

B = (R)-2-Methylbut-3-enylcobaloxime from (S)-1-Methylbutenylcobaloxime

C = (S)-2-Methylbut-3-enylcobaloxime via (S)-2-Methylbut-3-enoic acid (57.7% enantiomeric excess)

Table 9. Values of $\Delta\xi$ for Experiments Performed on the Optically Active 1-Methyl- and 2-Methylbut-3-enyl(pyridine)cobaloximes

| Compound | $\Delta\xi$(calc.) | conc.(M) | A | $\lambda_{nm}$ |
|---|---|---|---|---|
| (R)-1-Me | + 14.4 | $7.65 \times 10^{-4}$ | 0.0055 | 450 |
| (R)-2-Me (via (S)-1-Me) | - 60.56 | $2.36 \times 10^{-4}$ | 0.0075 | 455 |
| (S)-1-Me | - 15.6 | $8.09 \times 10^{-4}$ | 0.0063 | 450 |
| (S)-2-Me (via (R)-1-Me) | + 50.6 | $2.89 \times 10^{-4}$ | 0.0073 | 455 |
| (S)-2-Me (synthetic)* | + 48.0 | $2.45 \times 10^{-4}$ | 0.0045 | 455 |
| (R)-2-Me (via (S)-1-Me + 2 mole% $Co^{II}$). | - 59.8 | $1.66 \times 10^{-4}$ | 0.0069 | 455 |
| (R)-2-Me (via(S)-1-Me + 10 mole% $Co^{II}$). | - 68.8 | $2.34 \times 10^{-4}$ | 0.0073 | 455 |
| (S)-2-Me (via (R)-1-Me via thermolysis) | + 24.7 | $2.56 \times 10^{-4}$ | 0.0071 | 455 |

* This sample was obtained via 2-methylbut-3-enoic acid (57.7% enantiomeric excess) and the value of $\Delta\xi$ is corrected for this.

1-Me = 1-Methylbut-3-enyl(pyridine)cobaloxime
2-Me = 2-Methylbut-3-enyl(pyridine)cobaloxime

alkylcobaloxime and the resulting 2-methylbut-3-enyl(pyridine)cobaloxime (free from decomposition product) is only ca 45% optically pure.

The reaction of (R)-1-methylbut-3-enyl(pyridine)cobaloxime with 10 mole% aquocobaloxime(II) at 40°C, was followed by $^1$H n.m.r. spectroscopy with [TFA]/[cobaloxime] value of 1.56. The peak resonances in the initial spectrum were too broad for analysis but after a few minutes the peaks sharpened up. The rate constant for this rearrangement is $k_1 = 3.27 \pm 0.05 \times 10^{-3}$ $s^{-1}$ at 40°C, c.f. rate constant without aquocobaloxime(II) $k_1 = 8.99 \pm 0.04 \times 10^{-4}$ $s^{-1}$ at 37°C.

The rearrangement of (R)-1-methylbut-3-enyl(pyridine)cobaloxime to (S)-2-methylbut-3-enyl(pyridine)cobaloxime was followed by both $^1$H n.m.r. spectroscopy and polarimetry and the rate constants $k_1$ estimated. For the reaction monitored by $^1$H n.m.r. spectroscopy, $k_1 = 8.48 \pm 0.02 \times 10^{-6}$ $s^{-1}$ and for that by polarimetry $k_1 = 4.92 \pm 0.03 \times 10^{-6}$ $s^{-1}$, [cobaloxime] = 0.132M, [TFA] = 0.104M at 21°C.

All the results discussed so far serve to exclude the bimolecular mechanism from any appreciable participation in the acid-catalysed interconversion between 1-methylbut-3-enyl- and 2-methylbut-3-enyl-(pyridine)cobaloximes. All mechanisms involving homolysis or heterolysis of the alkyl-Co bond are excluded because the results with optically active (R)- and (S)-1-methylbut-3-enyl(pyridine)cobaloximes show a stereospecific equilibration to the corresponding (S)- and (R)-2-methylbut-3-enyl(pyridine)cobaloximes, respectively.

Summarising the results, a unimolecular mechanism consistent with these

is shown in Scheme 32, in which 1-methylbut-3-enylcobaloxime is connected *via* four distinct $\eta^3$-homoallylcobalt intermediates or transition states to 2-methylbut-3-enylcobaloxime.

The formation of the $\eta^3$-homoallylcobalt complex requires removal of pyridine assisted either thermally or by trifluoroacetic acid. Studies of the reaction of alkyl(pyridine)cobaloximes (see chapter 5) with trifluoroacetic acid suggest a general trend in these reactions. Trifluoroacetic acid first protonates a dioximato ligand and a subsequent molecule of trifluoroacetic acid removes pyridine as pyridinium trifluoroacetate. Kinetic studies[127] of the TFA catalysed interconversion of 1-methylbut-3-enyl- to 2-methylbut-3-enyl(pyridine)-cobaloxime are also compatible with this conclusion. The likely reactive intermediate in these conversions is a protonated 5-coordinate alkylcobaloxime.

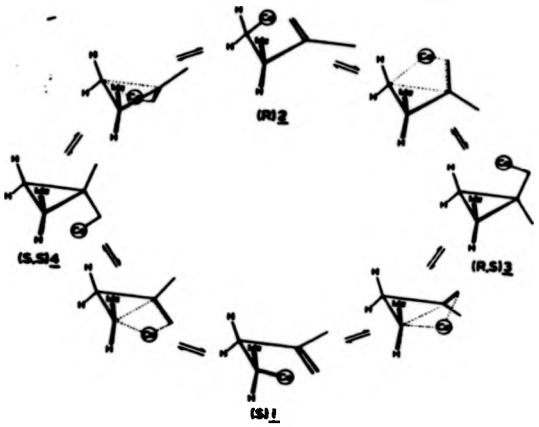
4:4(e) Studies Using Substituted Cyclopropylmethyl(pyridine)cobaloximes

The attempted synthesis of 1-methylcyclopropylmethyl(pyridine)-cobaloxime effectively was stopped at the bromide stage when only the ring-opened 1-bromo-3-methylbut-3-ene was formed. The synthesis of the bromide was attempted using a variety of brominating agents, none of which were successful. All materials isolated were the open-chain isomer.

The synthesis of 1-cyclopropylethyl(pyridine)cobaloxime resulted in the isolation of only the ring-opened 4-methylbut-3-enyl(pyridine)cobaloxime.

The attempted synthesis of 2-phenylcyclopropylmethyl(pyridine)cobaloxime

Scheme 32. $^{3}\eta$-Homoallylcobalt Intermediates Postulated in the Conversion of 1-Methylbut-3-enyl- to 2-Methylbut-3-enyl(pyridine)cobaloximes.




1 = 1-Methylbut-3-enyl(pyridine)cobaloxime.

2 = 2-Methylbut-3-enyl(pyridine)cobaloxime.

3 = cis-2-Methylcyclopropylmethyl(pyridine)cobaloxime.

4. = trans-2-Methylcyclopropylmethyl(pyridine)cobaloxime.

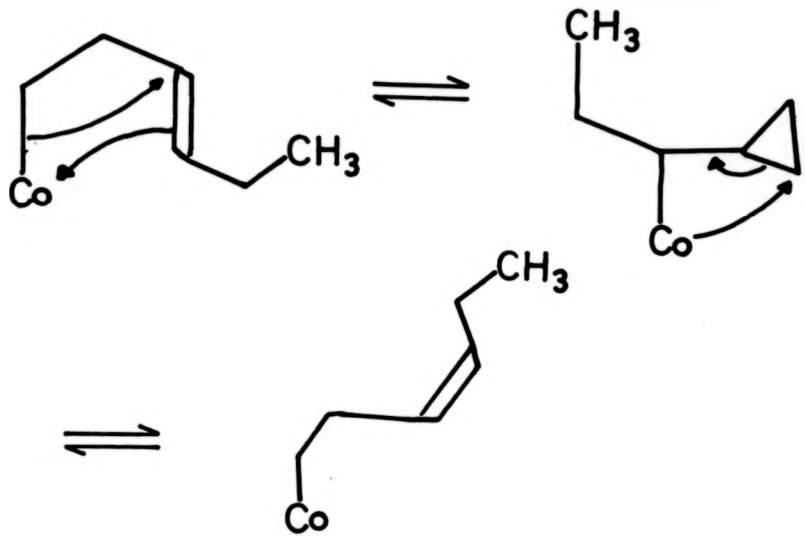
by both the bromo(pyridine)cobaloxime and disproportionation methods yielded a complex mixture of products with at least 4 major components. A minor component with an Rf value indicative of an alkylcobaloxime was observed, but p.l.c. failed to yield an isolable alkyl(pyridine)-cobaloxime; the $^{1}H$ n.m.r. spectrum was inconsistent with such a species being present.

cis-Hex-3-enyl(pyridine)cobaloxime was isolated in good yield. Treatment of this cobaloxime with TFA gave no product with a $^{1}H$ n.m.r. spectrum consistent with the more stable trans-isomer, the $^{1}H$ n.m.r. remained identical to the starting cis-hex-3-enyl(pyridine)cobaloxime. Presumably the expected secondary cyclopropylcobaloxime (shown in fig.45) has too high an energy to be formed.

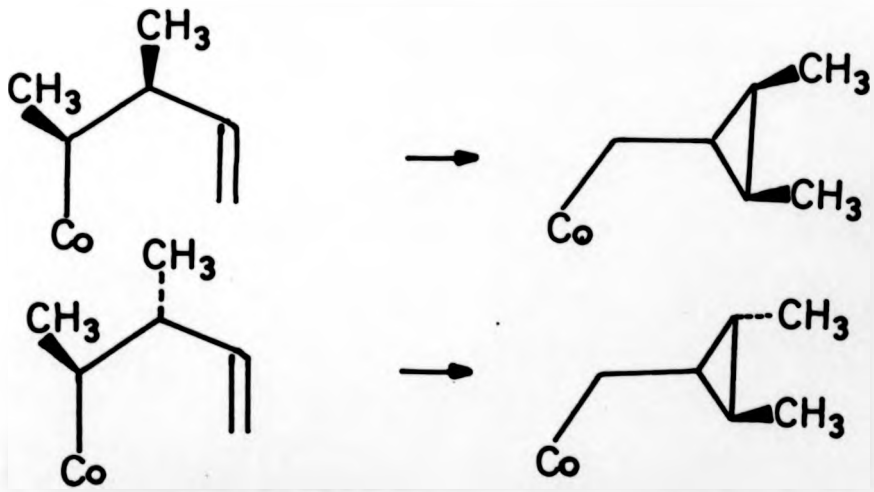
4:4(f) The Cyclisation of 1,2-Dimethylbut-3-enyl(pyridine)cobaloxime to the 2,3-Dimethylcyclopropylmethyl(pyridine)cobaloximes

An interesting feature is exhibited by a dimethylbut-3-enyl(pyridine)-cobaloxime. If another methyl substituent is placed on the 2-position of the 1-methylbutenylcobaloxime, the resultant 1,2-dimethylbut-3-enyl-(pyridine)cobaloxime spontaneously rearranges to the 2,3-dimethylcyclo-propylmethyl(pyridine)cobaloxime. From the known chemistry of the rearrangements of but-3-enyl- and cyclopropylmethylcobaloximes, and of their stereospecific nature, particular isomers of the precursor 1,2-dimethylbut-3-enylcobaloximes should give rise to corresponding isomers of 2,3-dimethylcyclopropylmethylcobaloximes. The sterochemistry expected in the synthetic routes to cis, trans- and trans, trans-2,3-dimethylcyclopropylmethylcobaloximes is shown in Scheme 33. Hence, meso-1,2-dimethylbut-3-enyl(pyridine)cobaloxime should give rise to the trans, trans-2,3-dimethylbut-3-enyl(pyridine)cobaloxime and threo -1,2-

Figure 45. Postulated Mechanism for the Possible Isomerization of cis- and trans-Hex-3-enyl(pyridine)cobaloximes




Scheme 33. Formation of 2,3-Dimethylcyclopropylmethylcobaloximes From the 1,2-Dimethylbut-3-enylcobaloximes



dimethylbut-3-enylcobaloxime should give rise to the cis,trans -2,3-dimethylcyclopropylmethylcobaloxime.

The isolated cobaloximes appeared to be predominantly a mixture of trans, trans and cis, trans-2,3-dimethylcyclopropylmethylcobaloximes as shown by their identical $^{1}H$ and $^{13}C$ n.m.r. spectra. In order to prove that a mixture of isomers of the dimethylcyclopropylmethylcobaloximes had formed, the synthesis of trans, trans- and cis, trans-dimethylcyclopropylmethylcobaloximes was attempted. The trial route to these compounds was unsuccessful. The tosylate was found to be unstable and the bromide decomposed on distillation. It was evident from the 2,3-dimethylcyclopropylcarbinol produced en route, that differences observed in the $^{1}H$ n.m.r. spectra of the two isomers were unlikely to be significant, and so permit easy identification of the respective isomers, e.g. the two methyl peaks of the respective isomers exist as overlapping doublets in the alcohol.

Recent work,[128] suggests that the intermediate 1,2-dimethylbut-3-enyl-(pyridine)cobaloximes can be isolated and their spectral characteristics recorded satisfactorily.

## 4:5 Summary

The results presented in chapters 3 and 4 clearly define the mechanism of interconversion between but-3-enyl- and cyclopropylmethylcobaloximes. The first demonstration of the stereospecific and intramolecular character of a reaction of a but-3-enyl group attached to a metal has been shown in the stereospecific interconversion of optically active 1-methylbut-3-enyl- to 2-methylbut-3-enyl(pyridine)cobaloxime).

The character of the interconversion of but-3-enylcobaloximes as a C1-C2 interchange was confirmed by observations[91] that [1-$^{13}$C]- and [1,1-$^{2}H_2$]-but-3-enyl(pyridine)cobaloximes equilibrate with [2-$^{13}$C]- and [2,2-$^{2}H_2$]-but-3-enyl(pyridine)cobaloximes respectively without any scrambling of the label between the 3- and 4- positions of the but-3-enyl group apparent.

Cyclopropanes were shown to be kinetically competent intermediates in the conversions of 1-methyl- to 2-methylbut-3-enyl(pyridine)cobaloximes although no evidence was obtained for their production *in situ*.

The nature of the rearrangements was defined as a cobalt 1,3-shift by the $^{13}$C labelling study on the [$^{13}CH_2Co$]- cyclopropylmethyl(pyridine)-cobaloxime giving rise to exclusively [$^{13}CH_2$=C]-but-3-enyl(pyridine)-cobaloxime *via* a $\eta^3$-homoallylic intermediate.

The homoallyl intermediate is supported by evidence for the formation of a 5-coordinate cobaloxime precursor. All the rearrangements studied are arrested by addition of pyridine and accelerated by addition of trifluoroacetic acid. The acid serves to remove pyridine from the coordination sphere of cobalt leading to a 5-coordinate cobaloxime which is the precursor to the homoallylic intermediate.

In conclusion therefore, rearrangements of cyclopropylmethyl(pyridine)-cobaloximes or interconversions between but-3-enyl(pyridine)cobaloximes are intramolecular, and proceed *via* the formation of an intermediate 5-coordinate species. This permits the formation of a homoallyl type

intermediate which can rearrange to yield either starting material or rearranged product.

## Chapter 5 - Studies of the Reactions Between Alkyl(pyridine)cobaloximes and Trifluoroacetic Acid

### 5: 1 Introduction

The reaction between acids and alkylcobaloximes may take various courses depending upon the type of alkyl group and the axial base of the cobaloxime (e.g. pyridine, water, triphenylphosphine). If the alkyl group is acid labile e.g. in 1-[3'-σ-(pyridine)cobaloxime]propyl-4-methyl-2,6,7-trioxabicyclo[2.2.2.]octane reaction takes place entirely at the alkyl group leaving the remaining functionalities of the cobaloxime intact. Thus 1-[3'- σ -(pyridine) cobaloxime]propyl-4-methyl-2,6,7-trioxabicyclo[2.2.2.]octane undergoes ready hydrolysis in 0.05M hydrochloric acid to yield 7,7-di(hydroxymethyl)-5-oxa-4-oxo-octyl-(pyridine)cobaloxime in virtually quantitative yield.

If the alkyl group is stable to acidic conditions, then acid may react at another site of the cobaloxime.

The rearrangements of substituted cyclopropylcarbinyl and but-3-enyl-(pyridine)cobaloximes in chloroform solution are catalysed by trifluoroacetic acid (c.f. chapters 3 and 4). A likely role for the trifluoroacetic acid is to remove coordinated pyridine from the cobaloxime, generating a formally 5-coordinate des-pyridinato cobaloxime. It is this intermediate which is considered the possible precursor for the homoallyl-cobalt transition state proposed for the interconversions of but-3-enyl and cyclopropylcarbinylcobaloximes.

The reaction of trifluoroacetic acid with several alkyl(pyridine)-cobaloximes (containing a diversity of alkyl groups) was investigated. The object of this study was to probe possible competition between

protonation of the bis(dimethylglyoximato) system and removal of coordinated pyridine (as pyridinium cation) in the alkyl(pyridine)-cobaloximes. All reactions were monitored by $^1H$ n.m.r. spectroscopy.

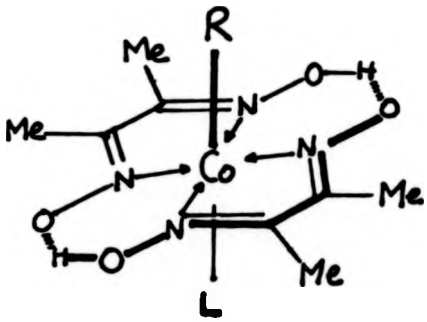
## 5: 2 Experimental Procedure and Instrumentation

A solution of trifluoroacetic acid in deuteriochloroform was prepared from trifluoroacetic acid ($1cm^3$) by diluting to $5cm^3$. The concentration of trifluoroacetic acid in this solution was determined by titration with standard aqueous sodium hydroxide using phenolphthalein, and ethanol as co-solvent. Samples for n.m.r. measurements were prepared by dissolving a fixed weight of the cobaloxime (30, 45 or 60mg), in deuteriochloroform, adding a known volume of the standardised trifluoroacetic acid solution and diluting with deuteriochloroform to a total volume of $0.600cm^3$ in an n.m.r. tube. All solutions were dispensed using an all-glass 'Agla' micrometer syringe. The n.m.r. probe was thermostated at 298K for recording of the $^1H$ n.m.r. spectra associated with the calculation of protonation constants. Single crystal X-ray diffraction measurements were collected with a Syntex $P2_1$ four-circle diffractometer and the data refined by Dr. N.W.Alcock and Dr. E. H. Curzon.

## 5: 3 Results and Discussion

For all the alkyl(pyridine)cobaloximes used (fig. 46), changes in the $^1H$ n.m.r. spectra, consequent of addition of increasing aliquots of trifluoroacetic acid, exhibit a general trend. To illustrate this fact, $^1H$ n.m.r. spectra obtained from the reactions of but-3-enyl(pyridine)-cobaloxime with trifluoroacetic acid are shown in figs. 47 (a)-(d).

Figure 4o. Alkylcobaloximes Used in the Protonation Studies.




R = Me, $CH_2Cl$, $CHCl_2$, Et, i-Pr, Bu, $CH_2{=}CHCH_2CH_2$,
$CH_2{=}CHCHMeCH_2$, $CH{=}C{=}CMe$, $CH_2CH_2CN$, CH(Me)CN.

Figure 47. Incremental Additions of TFA to But-3-enylcobaloxime

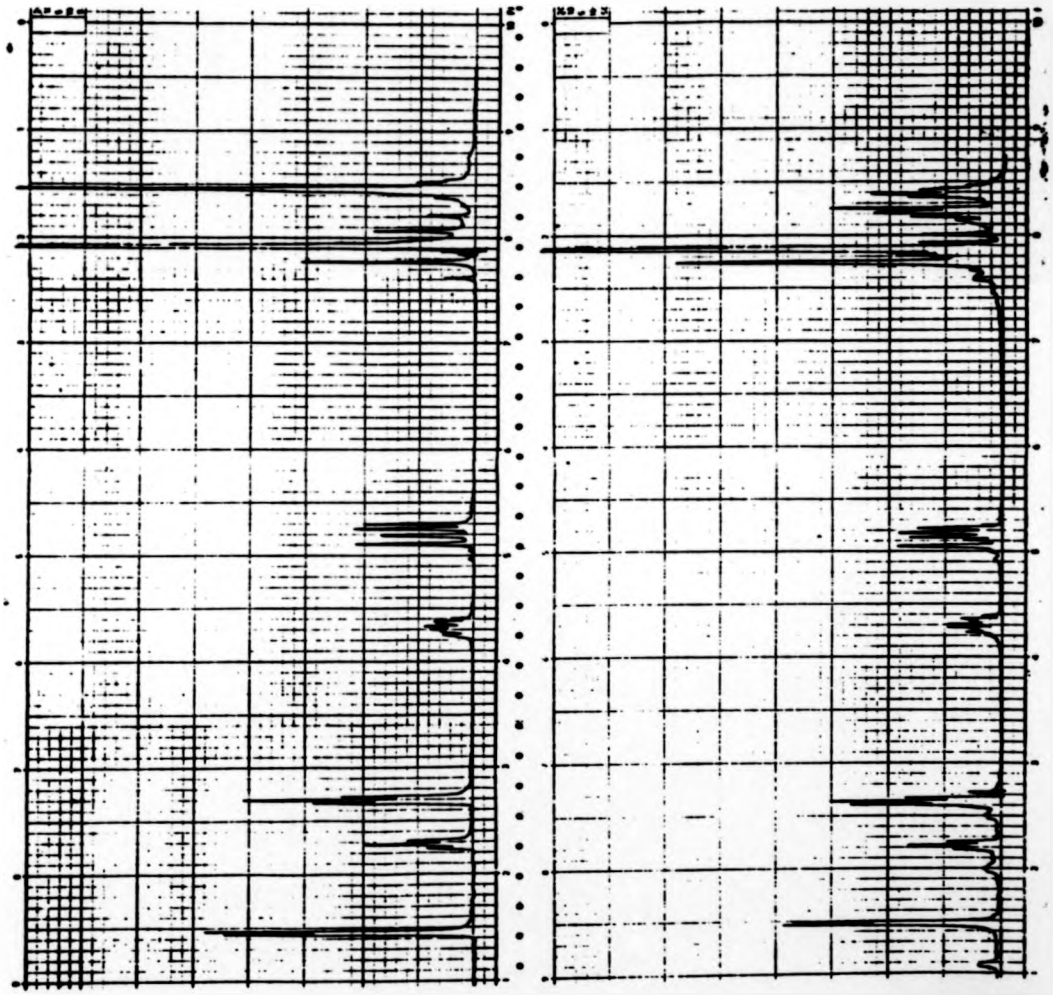


Fig.47a Neutral Complex

Fig.47b 1.5M equ.TFA added.

Figure 47. Incremental Additions of TFA to But-3-enylcobaloxime

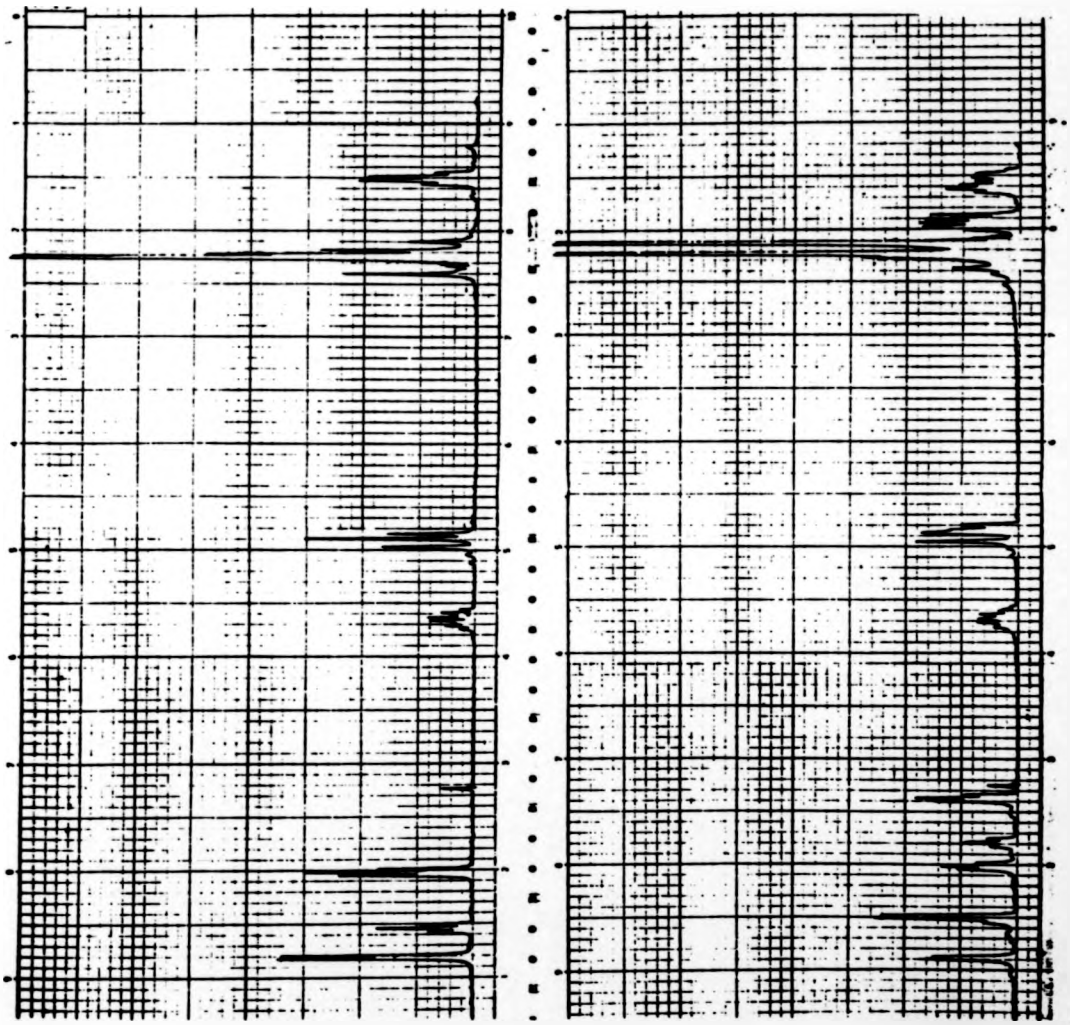


Fig.47d 1 1M equ TFA added

Fig.47c 2.5M equ.TFA added

The spectral features of note during this series of reactions are as follows:

For fixed total cobalt concentration and $0 < [\text{trifluoroacetic acid}] / [\text{total cobalt}] < 10$, new resonances appear at $\delta$ 9.05, $\delta$ 8.55 and $\delta$ 8.80 (due to pyridinium trifluoroacetate). The resonances are unambiguously assigned by comparison with the known spectrum of pyridinium trifluoroacetate and by their increase in intensity of addition of pyridinium trifluoroacetate. As the relative concentration of trifluoroacetic acid is increased, the resonances at $\delta$ 8.05, $\delta$ 8.55 and $\delta$ 8.80 increase in intensity, whilst those at $\delta$ 7.30, $\delta$ 7.72 and $\delta$ 8.55 (originally present in the neutral cobaloxime) decrease in intensity. The total integrated intensity of all the pyridine-derived resonances is constant throughout the incremental additions of trifluoroacetic acid. For $[\text{trifluoroacetic acid}] / [\text{total cobalt}] > 11$, no detectable pyridine resonances due to alkyl(pyridine)-cobaloxime were observed. Thus, at this stage, all the pyridine originally present in the alkyl(pyridine)cobaloxime is now in the form of pyridinium trifluoroacetate.

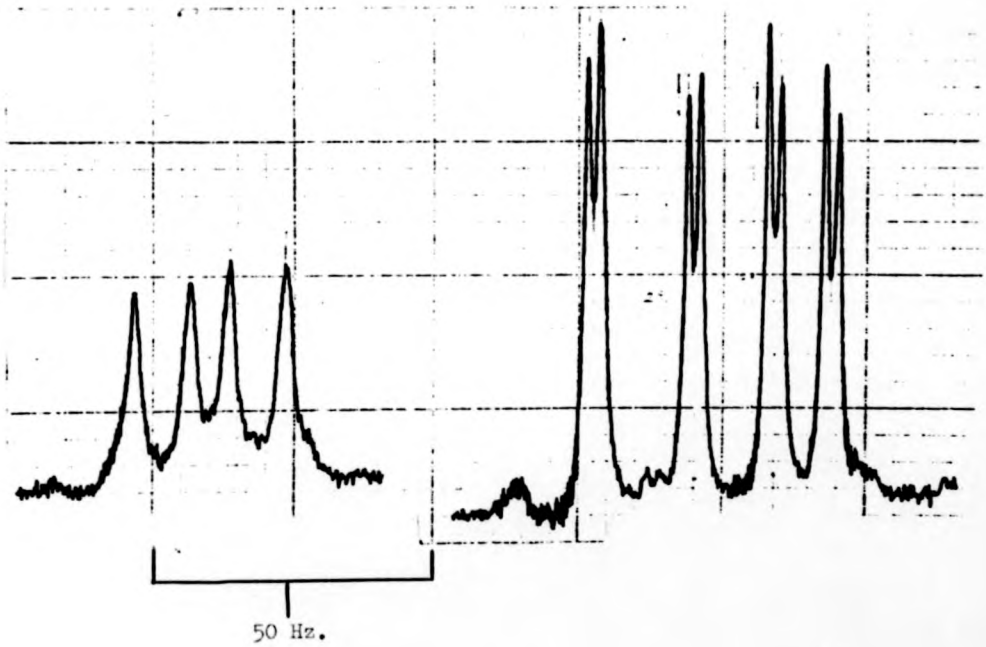
But-3-enyl(pyridine)cobaloxime has a sharp resonance at $\delta$ 2.12 due to the magnetically and chemically equivalent methyl groups of the dimethylglyoximato ligands. Addition of trifluoroacetic acid, causes a new single resonance at $\delta$ 2.30 to appear. As the relative concentration of trifluoroacetic acid is increased, this resonance also increases in intensity with concomitant loss of intensity of the resonance at $\delta$ 2.12 from neutral but-3-enyl(pyridine)cobaloxime. For $[\text{trifluoroacetic acid}] / [\text{total cobalt}] > 11$, the resonance at $\delta$ 2.12 of the alkyl(pyridine)-cobaloxime is not detectable; only a single resonance at $\delta$ 2.30 (12H) remains. The observed increase in intensity of the resonance at $\delta$ 2.30

qualitatively parallels the increase in intensities of the pyridinium trifluoroacetate resonances. No quantitative comparison was possible because of the unreliability of the integrals in the δ 2.1 - 2.3 region caused by overlapping of the intense dimethylglyoximato resonances.

The changes in resonances of those protons of the alkyl side chain are rather more complicated to describe. There are variations both in resonance position and multiplicity of all the peaks. For R = - $CH_2$-$CH_2CH$ : $CH_2$ the resonance at δ 1.55, due to the 2 x $CH_2$ protons (i.e. an overlapping and unresolved multiplet), gradually divides into two distinct multiplets δ 1.60 and δ 1.76 upon incremental addition of trifluoroacetic acid i.e. the peaks are shifted in relative position and multiplicity. The olefinic $C\underline{H}_2$ resonance, centred at δ 4.86, changes from a 4-component multiplet in the neutral cobaloxime to a 3-component multiplet on addition of trifluoracetic acid. Only very minor changes in the multiplicity of the olefinic $C\underline{H}$ resonance were observed.

To investigate more fully the identify of resonances due to species in the mixture, a series of spin decoupling experiments were performed on solutions of but-3-enyl(pyridine)cobaloxime containing trifluoroacetic acid. Irradiation of the saturated methylene proton multiplet ( δ 1.55) causes the olefinic resonances at δ 4.8 and δ 5.7 to collapse to the classical ABX pattern of 12 lines (fig.48). Here $|J_{AB}| = 2.2Hz$ and $|J_{AB} + J_{BX}| = 26.9$ Hz with $|J_{AX}| = 9.9Hz$ and $|J_{BX}| = 17.1$ Hz. For a solution of but-3-enyl(pyridine)cobaloxime containing trifluoroacetic acid in which [trifluoroacetic acid]/[total cobalt] = 8, assignment of the individual resonances of the aliphatic $CH_2$ groups is possible. Thus, the multiplet centred at δ 1.52 collapses to a triplet

Figure 48. The ABX Splitting Pattern Observed for the Olefinic Proton Resonances of But-3-enylcobaloxime in an Off-Resonance Decoupling Experiment.



($J = 8.5$Hz) when the olefinic methine proton is irradiated and is substantially unaltered (i.e. remaining as an apparent quartet) on irradiation of the olefinic methylene protons. This indicates that the resonance at $\delta 1.52$ is due to the methylene group $\beta$- to cobalt. Irradiation of the olefinic methine proton, caused no change in multiplicity of the other methylene group resonance centred at $\delta 2.16$. This multiplet is assigned to the methylene group directly bonded to cobalt. The assignments of the $\alpha$ and $\beta$ methylene groups in this acidified sample of but-3-enyl(pyridine)cobaloxime parallel those for other alkyl(pyridine)cobaloximes e.g. for ethyl(pyridine)cobaloxime, the methyl resonance occurs at higher field ($\delta 0.33$) than the methylene resonance ($\delta 1.70$).

Irradiation of the methylene protons $\beta$- to cobalt, causes the olefinic methine resonance to collapse to a four component multiplet (i.e. the X resonance of an ABX system) with $|J_{AX}| \simeq 9.8$ Hz and $|J_{BX}| \simeq 17.1$ Hz. (This confirms the identification of the multiplet at $\delta 1.52$ as that due to a methylene group $\beta$- to cobalt). These values are similar to those found for the neutral but-3-enyl(pyridine)cobaloxime and correspond to <u>cis</u>-coupling ($J_{AX}$) and <u>trans</u>-coupling ($J_{BX}$) with the olefinic methylene protons.

The observation that addition of trifluoroacetic acid causes shifts of the original resonances of the cobaloxime as well as the appearance of new resonances can be rationalised in terms of stepwise equilibria between the cobaloxime and acid. A minimum of two such processes is indicated. At least one, rapid on the $^1$H n.m.r. time scale, is associated with shifts in resonances and at least one other, slow on the $^1$H n.m.r.

time scale, accounts for the appearance of new peaks.

To explain, semi-quantitatively, the shifts observed in the resonance positions of the alkyl and pyridine groups in the $^1H$ n.m.r. spectrum, an empirical model was set up, illustrated in Scheme 34. Two equilibria are pre-supposed. The first is a reversible monoprotonation of the alkyl(pyridine)cobaloxime; it is this equilibrium which is considered to be rapid on the $^1H$ n.m.r. time scale. It has already been demonstrated that such equilibria do occur for aqueous solutions of alkylcobaloximes and aqueous acids[129]. The particular site of protonation is left undetermined, although it is assumed that protonation occurs at some site on the bis-dimethylglyoximato ligands. The second step in the model, slow on the $^1H$ n.m.r. time scale, is considered to be removal of pyridine from the cobaloxime as pyridinium trifluoroacetate and its replacement by a coordinated trifluoroacetate ligand, thus preserving the single overall charge on the complex.

Transient intermediates such as a protonated 5-coordinate des-pyridinato cobaloxime may be involved in equilibria en route to 3 Scheme 34. but have never been isolated or observed spectroscopically.

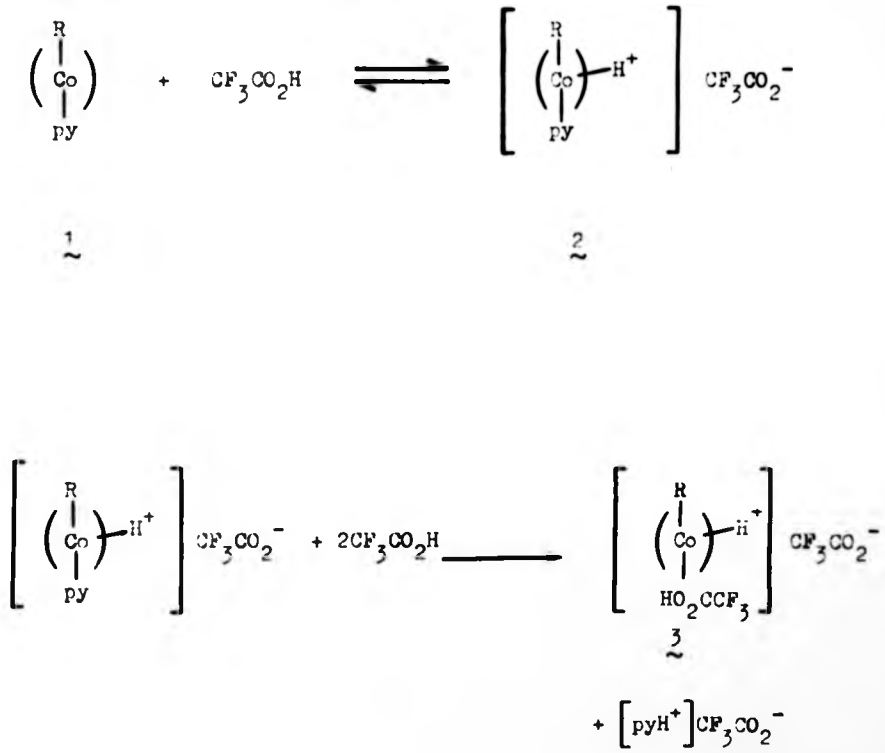
The quantitative description of these series of equilibria is as follows. For the equilibrium,

$$A + B \rightleftharpoons AB$$

the first protonation constant $K_1$ is defined as

$$K_1 = \frac{[AB]}{[A] \times [B]} \quad dm^3 mol^{-1}$$

Scheme II. Suggested Pathway for the Reaction of Trifluoroacetic Acid with Alkyl(pyridine)cobaloximes.




R = alkyl

Co = $Co(dmgH)_2$

For brevity, the symbols A, B, and AB are taken to denote the neutral alkyl(pyridine)cobaloxime, trifluoroacetic acid and the monoprotonated cobaloxime respectively. The brackets denote analytical concentrations of the respective species at equilibrium and activity coefficients are assumed, throughout, to be unity.

For a system in rapid exchange on the n.m.r. time scale, the averaged observed resonance positions, $\delta$ obs, is given by

$$\delta \text{ obs} = \frac{[A]\ \delta A}{[A] + [AB]} + \frac{[AB]\ \delta AB}{[A] + [AB]}$$

$\delta$ A, $\delta$ AB are the limiting resonances of the species A and AB respectively. These are obtained from the $^1H$ n.m.r. spectra of neutral alkylcobaloxime ($\delta$ A) and that of acidified material, when no further shift is observed ($\delta$ AB). The mass balance in total cobalt containing species, $A_T$, is

$$A_T = \left\{ [A] + [AB] \right\}_{rapid} + A_{slow}$$

where $A_{slow}$ represents that contribution to $A_T$ of species in slow equilibrium with A and AB. Hence,

$$\left( A_T - A_{slow} \right)\left( \frac{\text{obs} - A}{AB - A} \right) = [AB]$$

The mass balance in total trifluoroacetic acid $B_T$ is

$$B_T = [B] + [AB] + B_{slow}$$

where $B_{slow}$ represents theconcentrations of pyridinium trifluoroacetate

and the postulated alkylcobaloxime I (Scheme 34). The stoichiometry of this slow reaction requires that the concentration of pyridinium trifluoroacetate and I (Scheme 34) be equal (i.e. $A_{slow}$). The actual value of the concentration of pyridinium trifluoroacetate is determined experimentally from the integral of the resonances at δ 8.05, δ 8.55 and δ 8.80 p.p.m.

The shifts δ A, δ AB, δ obs were measured from that of $CH_2Cl_2$ which was assumed to be invariant under the conditions of the experiment.

$K_1$ was estimated for dichloromethyl(pyridine)cobaloxime at three different concentrations of total cobalt. Values of $K_1$ thus obtained are given in Table 10.

The individually calculated values of $K_1$ are reasonably constant within the limitations of experimental error. The average value for $K_1$, $dm^3\ mol^{-1}$, is similar to that found for the monoprotonation of methyl-(aquo)cobaloxime[130] i.e. 3.1 $dm^3\ mol^{-1}$. An analogous calculation based upon a model with a rapid diprotonation step in which $\beta_2 \gg K_1$, yielded a random set of values for $\beta_2$ all less than 0 $dm^6\ mol^{-2}$. Thus, significant diprotonation is considered unlikely in this system.

For the pointwise calculation of $K_1$, a trend is observed. This trend is attributed to the model used and the experimental errors encountered in the $^1H$ n.m.r. data i.e uncertainties in integral spectra and chemical shift measurement. The design of the experiment is such that only a small number of stepwise equilibria may be considered because the number of experimental observables is strictly limited. Thus, only a single

Table 10. Values of $K_1$ for Dichloromethyl(pyridine)cobaloxime.

| 60mg sample | $B_T$ (M) | $A_T$ (M) | $K_1$ |
|---|---|---|---|
| 1. | 0.050 | 0.230 | 2.57 |
| 2. | 0.090 | 0.220 | 2.65 |
| 3. | 0.132 | 0.212 | 3.24 |
| 4. | 0.168 | 0.198 | 3.68 |
| 5. | 0.199 | 0.179 | 4.26 |
| 6. | 0.231 | 0.161 | 5.01 |
| 45mg sample | | | |
| 1. | 0.038 | 0.173 | 1.86 |
| 2. | 0.074 | 0.170 | 2.55 |
| 3. | 0.107 | 0.165 | 3.47 |
| 4. | 0.138 | 0.159 | 4.60 |
| 5. | 0.168 | 0.155 | 5.38 |
| 30mg sample | | | |
| 1. | 0.024 | 0.112 | 1.45 |
| 2. | 0.048 | 0.110 | 2.94 |
| 3. | 0.070 | 0.110 | 4.47 |
| 4. | 0.092 | 0.106 | 5.87 |

$A_T$ = Total cobalt species other than the des-pyridinato complex.

$B_T$ = Total trifluoroacetic acid species other than pyridinium trifluoroacetate.

rapid equilibrium may be considered because only two limiting shifts, $\delta A$ and $\delta AB$, are known. For the slow step, the estimation of concentrations is limited to proton-containing species with distinct integral measurements. The model employed is thus bound by the strictures of the experiment. No account has been taken, for example, of dimerisation of trifluoroacetic acid in chloroform solution[131], nor has the possibility been considered of the existence of other cobalt-containing species. However, because $K_1$ is indeed, reasonably constant, it is concluded that the equilibria outlined in Scheme 34 play an important and probably dominant role in the reaction between alkyl(pyridine)cobaloximes and trifluoroacetic acid.

Little information concerning the site of protonation on the dimethylglyoximato ring system is available. Protonation could take place on an oxygen site or a nitrogen donor atom. The latter could result in a change of coordination number about cobalt, by causing detachment of one nitrogen atom of a dimethylglyoxime residue.

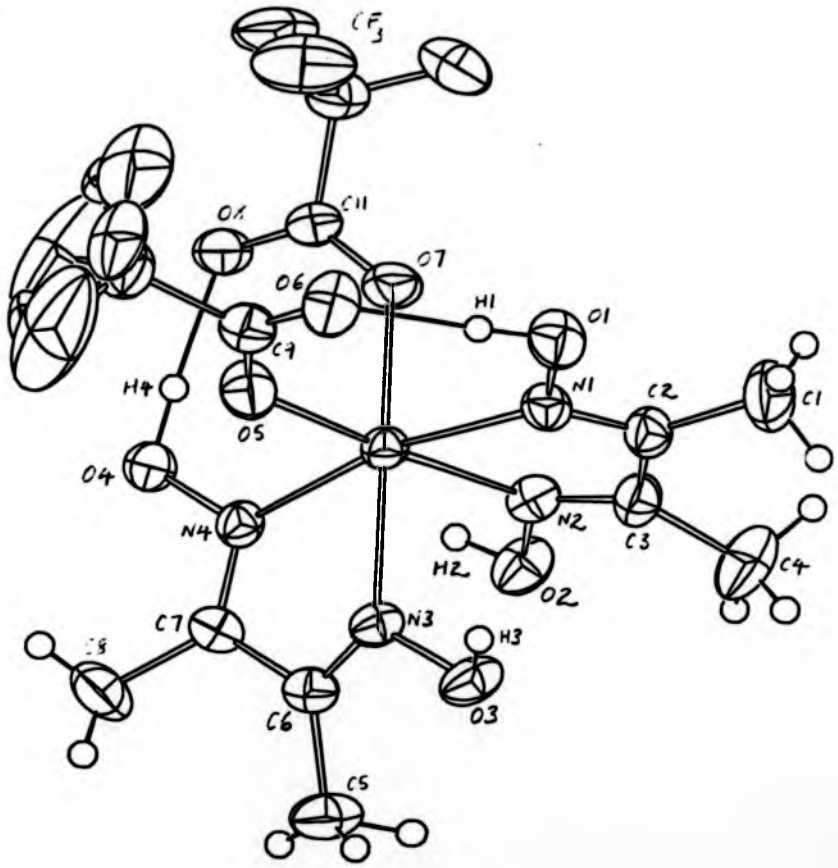
There is evidence from infra red spectroscopy[132] that suggests protonation occurs at the oxygen atom to yield a complex of the type shown in fig.49. Alkyl(aquo)cobaloximes exhibit a broad band in their infra red spectra centred at ca 3120 $cm^{-1}$ assigned to the O-H vibration of free or weakly hydrogen bonded water. The strong intramolecularly bonded O-H stretch of the dimethylglyoximato ligands appears as a broad band at ca 1700 $cm^{-1}$. Comparison with the infra red spectra of the alkyl(aquo)cobaloximes after protonation, shows that the band centred at ca 3120 $cm^{-1}$ in the neutral cobaloxime is split into two components. This has been interpreted as the formation of a new, free or weakly hydrogen-bonded hydroxyl group, suggesting protonation has occurred on an oxime oxygen atom.

A $^{19}F$ study of the reaction of dichloromethyl(pyridine)cobaloxime with TFA was attempted, with the aim of identifying separate resonances due to the various fluorine-containing species suggested. However, at room temperature the system was in rapid exchange on the $^{19}F$ n.m.r. time scale. Only a single very broad resonance which had a small shift in relative position was observed, upon incremental addition of TFA to the alkyl(pyridine)cobaloxime. It was not possible to conclude whether the shift was merely a result of concentration dependence on trifluoroacetic acid, or, alternatively, whether it was a consequence of rapid exchange between several trifluoroacetic acid derived species.

For further additions of TFA to alkyl(pyridine)cobaloximes ( [TFA] / [cobalt] >10) appreciable broadening of the $^{1}H$ n.m.r. spectrum occurs. A red crystalline solid is deposited from chloroform solution over a period of days to several weeks. This crystalline complex has been identified by single crystal X-ray diffraction studies as a mononuclear cis-cobaloxime (fig.50 ).

The crystal structure analysis reveals all the locations of the molecular hydrogen atoms and it is observed that the cis-cobaloxime is entirely different in its arrangement of hydrogen bonding to that observed in the usual trans-cobaloxime structure. Both dimethylglyoxime ligands are neutral in the cis-cobaloxime as opposed to uni-negative in the trans-cobaloxime, and it is evident that for the cis-cobaloxime, the additional protons at the dimethylglyoximato oxygen atoms prohibit the usual trans-geometry of the cobaloxime. In the cis-cobaloxime the dimethylglyoxime moieties form two hydrogen bonds, one intramolecularly and the other intermolecularly between an OH of the glyoximato moiety and a free oxygen

Figure 50. The Mononuclear cis-Cobaloxime.



atom of a coordinated trifluoroacetate ligand. Important bond lengths are shown in Table 11.

The formation of the cis-cobaloxime from 3 (Scheme 34) might occur in the following manner. Geometrical rearrangement from trans to cis geometry of 3 (Scheme 34) could occur either by a dissociation of one arm of a dimethylglyoximato ligand or by a twist mechanism. Loss of alkyl ligand, R, as RH, is followed by coordination of a second molecule of trifluoroacetic acid. The formation of $CH_2Cl_2$ from dichloromethyl-(pyridine)cobaloxime was detected by $^1H$ n.m.r. spectroscopy. The production of propane from isopropyl(pyridine)cobaloxime and trifluoroacetic acid was demonstrated by g.l.c. The exact sequence of loss of R, coordination of a second trifluoroacetic acid ligand and various geometrical rearrangements is not defined. The resulting cis-cobaloxime is formally cobaloxime(II). Magnetic susceptibility measurements give values of $\chi_m = 8350 \times 10^{-6}$ c.g.s. units and $\mu_{eff} = 4.45\ \mu_\beta$ at 297K indicating a high spin cobalt(II) species[133].

Evidence from $^1H$ n.m.r. studies show that the only resonance detectable is a very broad singlet with a shoulder centred at ca $\delta$5.2 and $\delta$5.7 p.p.m. respectively.

Mulls in nujol and hexachlorobut-1,3-diene of the cis-cobaloxime have infra red spectra with broad peaks at ca 3180 $cm^{-1}$ and 2860 $cm^{-1}$ characteristic of strong hydrogen bonding of OH groups, and characteristic C-F stretching bands at 1300 - 1000 $cm^{-1}$. The cis-cobaloxime(II) is a very stable molecule and can be stored in air without significant

Table 11. Important Bond Lengths for Di-trifluoroacetoxy bis-(butane-2,3-dionedioxime)cobalt(II)

| Bond | Length (Å) |
|---|---|
| Co-O(5) | 2.069(2) |
| Co-O(7) | 2.057(2) |
| Co-N(1) | 2.126(3) |
| Co-N(2) | 2.139(3) |
| Co-N(3) | 2.149(3) |
| Co-N(4) | 2.138(2) |
| C(9)-C(10) | 1.559(8) |
| C(10)-F | 1.280(19)avg. |
| C(7)-C(11) | 1.242(6) |
| C(11)-C(12) | 1.538(6) |
| N(1)-O(1) | 1.380(4) |
| C(2)-C(1) | 1.489(9) |
| C(3)-N(2) | 1.276(7) |
| N(2)-O(2) | 1.392(4) |
| N(3)-O(3) | 1.389(4) |
| C(6)-C(7) | 1.478(8) |
| C(5)-H | 0.93(12)avg. |
| O(2)-H(2) | 0.96(10) |
| O(8)-H(4) | 1.69(7) |

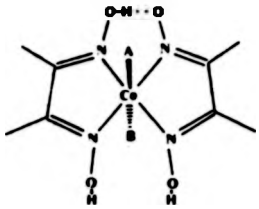
cf.crystal structure fig.50

oxidation to cobalt(III), in contrast to the behavior of diaquocobaloxime (II) which is rapidly oxidised in air[77].

Previous reports of the preparation of cis-cobaloximes have been made. Ablov showed that treatment of trans-hydroxo(aquo)cobaloxime with concentrated aqueous potassium hydroxide produces a cis-cobaloxime which was shown to be a binuclear complex (fig.51) by an X-ray diffraction study[134]. The production of this binuclear species requires strongly basic conditions and its formation probably is preceded by the destruction of the trans-cobaloxime hydrogen bonding system by proton abstraction.

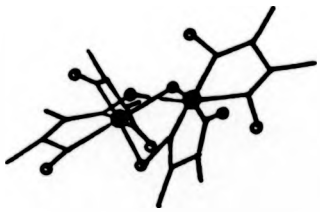
Whilst the behavior described was exhibited by cobaloximes containing R = $-CHCl_2$, but-3-enyl and those shown in fig.46, a number of exceptions to this general trend were noted. For R = $-CH{=}C{=}CMe$, $-CH_2CH_2CN$, -CH(Me)CN, the cis-cobaloxime was not isolated. For these R groups, appreciable broadening of their $^1H$ n.m.r. resonances was observed with subsequent oiling out of the product from chloroform solution. The "oils" obtained were not investigated further.

Figure 49. Postulated Site of Protonation of Cobaloximes




A, and B = axial coordination ligands.

Figure 51. The Binuclear cis-Cobaloxime.



o = O

● = Co

N.B. For clarity, certain hydrogen atoms have been ommited.

## Chapter 6. Carboxysubstituted Cyclopropanes and Models for α-Methyleneglutarate Mutase

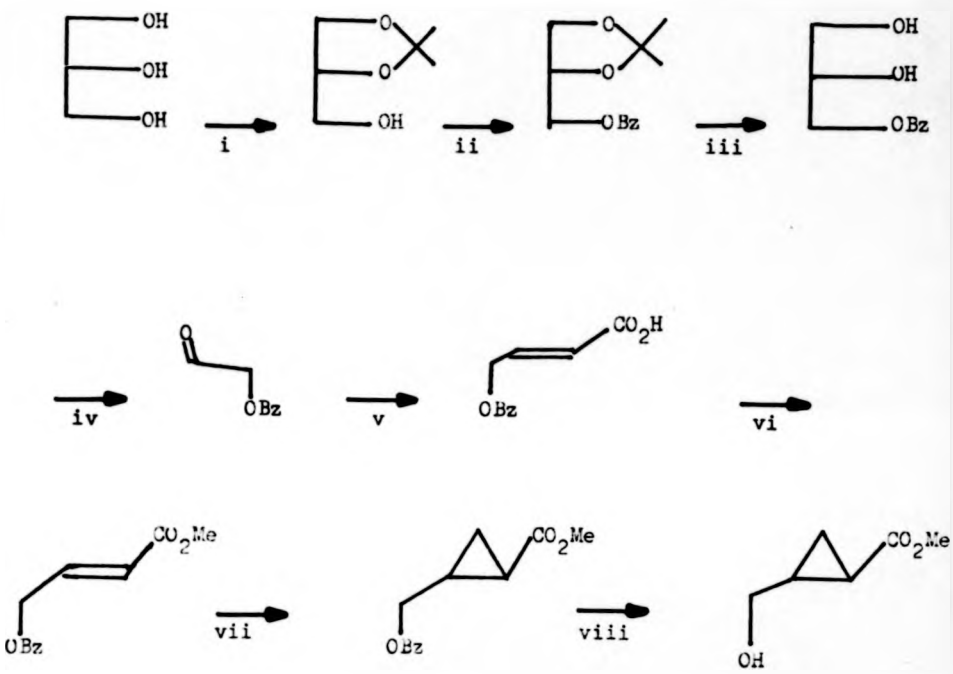
### 6: 1 Introduction

Carboxysubstituted cyclopropanes have been postulated as intermediates for the AdoCbl-catalysed interconversion between α-methyleneglutarate and methylitaconate (see chapter 1). Steps in the interconversion of cyclopropylmethyl- and but-3-enyl(pyridine)cobaloximes have been defined as described (chapters 3, 4 and 5). As a consequence, the synthesis of carboxylsubstituted cyclopropanes was attempted. Such intermediates possess closer similarities to those postulated for the α-methylene-glutarate mutase reaction than do the methylcyclopropylmethyl- and methylbut-3-enyl derivatives discussed earlier.

Attempts to synthesise trans-2-methoxycarbonylcyclopropylmethyl(pyridine)-cobaloxime are outlined in Schemes 35 and 36. Preliminary investigations of a potential route to cis-2-carboxycyclopropylcarbinol are outlined in Scheme 37.

As a masking agent for the carboxy group, the application of a 2,6,7-trioxabicyclo[2.2.2.]octane was investigated[135]. Alkyl(pyridine)-cobaloximes are prepared using a variety of basic conditions (required for the formation of cobaloxime(I)), and a carboxyl protecting group, stable to such conditions was required i.e. to prevent lactonisation of a haloacid under such conditions. 2,6,7-trioxabicyclo[2.2.2.]octane was found to be an excellent protecting group under such conditions and was found to be inert to strong base.

Scheme 35. Synthesis of trans-2-Methoxycarbonylcyclopropylcarbinol




i = Acetone/toluene-4-sulphonic acid cat.

ii = Benzyl bromide/benzyltri-n-butylammonium bromide/NaOH

iii = Dil. $H_2SO_4/100^{\circ}/2.5h$.

iv = $NaIO_4/H_2O$

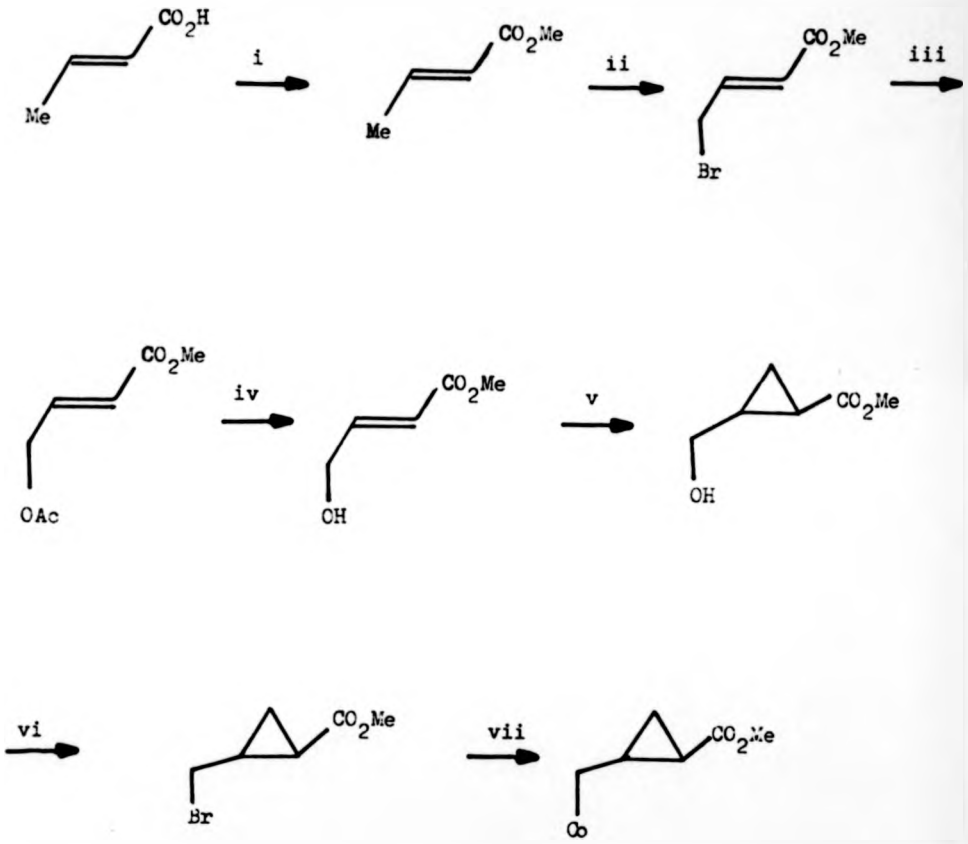
v = Malonic acid/piperidine

vi = N,N-diisopropyl-O-methylisourea/petroleum ether

vii = Zn/Cu (type II)/$CH_2I_2$/ethoxyethane

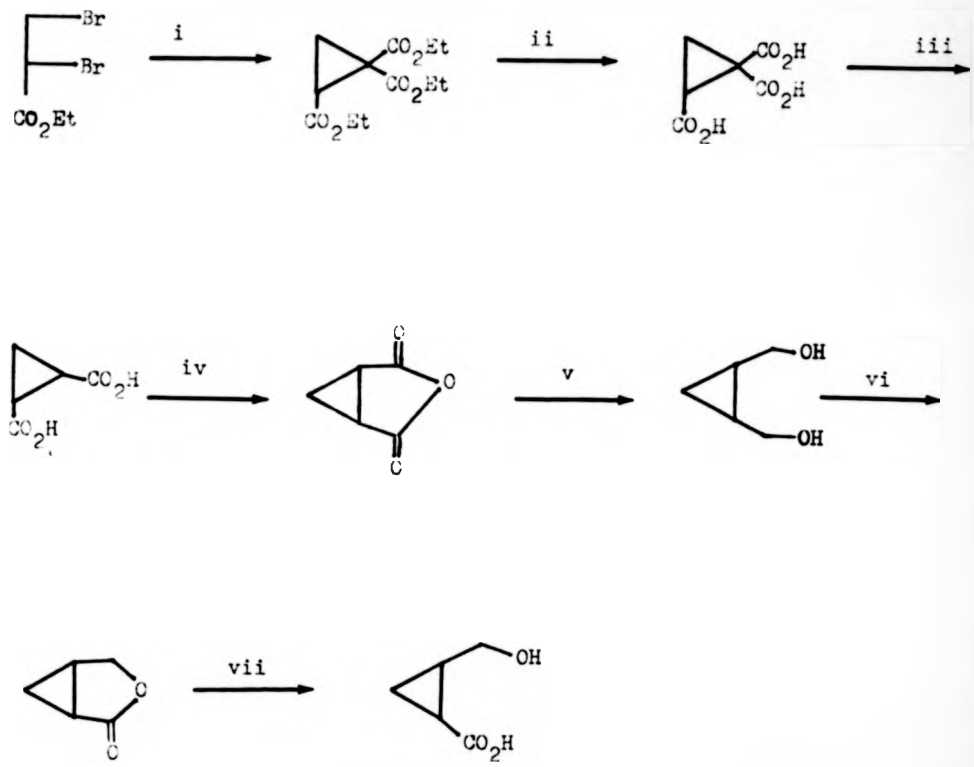
viii = 5% Palladium on charcoal/tetrahydrofuran

Scheme 36. Attempted Synthesis of trans-2-Carboxymethylcyclopropylmethyl(pyridine)cobaloxime




i = $H_2SO_4$/Methanol/65°
ii = N-Bromosuccinimide/$CCl_4$
iii = Silver acetate/$CCl_4$
iv = $H_2SO_4$/methanol
v = $CH_2I_2$/Zn/Cu couple (type II)/ethoxyethane
vi = $PBr_3$/pyridine/ethoxyethane
vii = (Pyridine)cobaloxime(I)/ethanol

Scheme 37. Synthetic Route to cis-2-Carboxycarbonylcyclopropyl-carbinol.




i = Diethyl malonate/NaOEt

ii = Aqueous NaOH

iii = Heat at 230-250°

iv = $Ac_2O$/200°

v = NaOH

vi = $O_2$/Cu

vii = NaOH/Δ

## 6: 2 Experimental

### 6: 2: 1 Attempted Synthesis of trans-2-Methoxycarbonylcyclopropylmethyl-(pyridine)cobaloxime.

**Preparation of 2,2-Dimethyl-4-hydroxymethyl-1,3-dioxalane**

This was prepared according to a literature procedure[136] by reaction of glycerol with acetone in the presence of toluene-4-sulphonic acid catalyst.

**Preparation of 3-O-Benzyl-sn-glycerol**

This was prepared according to a literature procedure[137] by phase-transfer catalysed reaction of benzyl chloride with 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane and subsequent treatment with dil. sulphuric acid to yield 3-O-benzyl-sn-glycerol.

**Preparation of Benzyloxyacetaldehyde**

1-Benzylglycerol (34.4g; 0.189 mol) was stirred with water ($20cm^3$) at $0^oC$. A solution of $NaIO_4$ (50g; 0.234 mol) in water ($600cm^3$) was added in one portion, the reaction mixture turned cloudy, and the suspension was stirred at $0^oC$ for 45 minutes. The precipitated $NaIO_3$ was removed by filtration through a glass wool plug and the filtrate was extracted with ethoxyethane ( 5 x $100cm^3$). The combined organic extracts were dried overnight ($MgSO_4$). Solvent was evaporated off and the residual yellow oil was distilled to yield 14.4g (50.6%) pure material b.p. $120^o$ at 9 mm Hg.

$^1H$ n.m.r. ($CCl_4$) $\delta$ 3.87 (s,3H), 4.51 (s,2H), 7.25 (m,5H), 9.59 (s,1H) p.p.m.

**Preparation of (E)-4-Benzyloxybut-2-enoic Acid**

This was successfully prepared using the Knoevenagel reaction[138] or its

base-catalysed modification, the Doebner reaction[139] of benzyloxyacetaldehyde with diethyl malonate. To a rapidly stirred solution of malonic acid (8.21g; 79 mmol) in pyridine (9.3g; 0.12 mol) at $0^{o}C$, was added freshly distilled benzyloxyacetaldehyde (11.9g; 79 mmol). The mixture was stirred at room temperature for 60h (after 24h the mixture was a semi-solid slurry). This mixture was then heated on a water bath until evolution of $CO_2$ had ceased (10h), and was then poured into water ($30cm^3$). The oily layer was separated and the aqueous layer extracted with ethoxyethane ($25cm^3$). The combined organic layers were washed with 25% v/v aqueous hydrochloric acid ($100cm^3$) and dried ($MgSO_4$). Solvent was evaporated off to yield 9.7g (64%) off white crystals, pure by $^1H$ n.m.r. spectroscopy.

<u>$^1H$ n.m.r. ($CCl_4$)</u> $\delta$ 4.11 (m,2H), 4.52 (s,2H), 6.07 (m,1H), 7.0 (m,1H), 7.23 (m,5H) p.p.m.

<u>i.r. (nujol)</u> 2600 (broad), 1690 $cm^{-1}$

<u>Preparation of (E)-4-Benzyloxybut-2-enoic Acid by the Doebner Reaction</u>

To a $25cm^3$ round-bottomed flask was added malonic acid (3.45g; 33 mmol) pyridine (3.97g; 60 mmol) and two drops of piperidine as catalyst. The solution was stirred at $0^{o}C$ for 10 minutes. To the reaction mixture, was added freshly distilled benzyloxyacetaldehyde (5g; 33 mmol) and the reaction mixture was left at $0^{o}C$ for 24h ( n.b. the reaction mixture was semi-solid at this stage). The mixture was warmed on a steam bath until evolution of carbon dioxide had ceased, (6h) and was then cooled in ice. 50% aqueous sulphuric acid ($20cm^3$) at $0^{o}C$ was then added, and the product extracted into ethoxyethane ($20cm^3$). The aqueous layer was re-extracted with ethoxyethane (2 x $20cm^3$) and the combined organic layers dried ($MgSO_4$). Solvent was evaporated off to yield a viscous oil (9.2g; 85.4%) pure by $^1H$ n.m.r. spectroscopy.

Attempted Wittig Reaction on Benzyloxyacetaldehyde

To a 250cm$^3$ round-bottomed three necked flask fitted with reflux condenser, pressure-equalising dropping funnel, magnetic follower and gas inlet system was added sodium hydride (3.3g; 0.109 mol) (as an 80% dispersion) and anhydrous benzene (23.6 cm$^3$). To the stirred mixture was added triethyl phosphonoacetate (24.7g; 0.109 mol), dropwise, over a 45 minute period, maintaining the temperature below 35°C ( a vigorous evolution of hydrogen was observed). The reaction mixture was stirred at room temperature for a further 1h. To the clear solution was added benzyloxyacetaldehyde (11.65g; 0.109 mol), dropwise, over a 30 minute period. After a few minutes the reaction mixture became very viscous and was worked up by addition of water followed by solvent extraction. The crude product contained at least 4 major components by t.l.c. (silica gel, ethoxyethane eluent). $^1$H n.m.r. spectroscopy showed that the product did not contain the expected ethyl 4-benzyloxybut-2-enoate. No further work was attempted using the Wittig approach.

Preparation of (E)-Methyl Benzyloxybut-2-enoate[140]

To a stirred sample of N,N-diisopropyl-O-methylisourea (29.6g; 0.187 mol), was added slowly, over a period of 5 minutes, (E)-4-benzyloxybut-2-enoic acid (35.9g; 0.187 mol). The reaction was very exothermic. The viscous mixture was stirred for 1h at room temperature, and was then diluted with anhydrous ethoxyethane (150cm$^3$). The diluted solution was stirred for a further 48h at room temperature. The precipitated N,N-diisopropylurea was removed by suction filtration, and washed with ethoxyethane (150cm$^3$). Solvent was evaporated off and the crude mixture distilled b.p. 100-101° at 0.03mmHg to yield pure (E)-methyl benzyloxybut-2-enoate (33.0g; 87.9%). $^1$H n.m.r. ($CCl_4$) $\delta$ 3.66 (s,3H), 4.09 (m,2H), 4.50 (s,2H), 6.04 (m,1H),

6.84 (m,1H), 7.23 (s,5H) p.p.m.

Preparation of trans-Methyl Cyclopropane-1-benzyloxymethyl-2-carboxylate.

To a stirred suspension of zinc-copper couple (type II) (7.5g; 0.115 mol), diiodomethane (6.5 $cm^3$; 20.7g; 77.3 mmol) in anhydrous ethoxyethane (110$cm^3$), was added, via a pressure-equalising dropping funnel, (E)-methylbenzyloxybut-2-enoate (6.25g; 30.3 mmol). dissolved in anhydrous ethoxyethane (25$cm^3$). The mixture was heated under reflux for 7 days until no further conversion to the corresponding cyclopropane was observed (monitored by $^1H$ n.m.r. spectroscopy). Saturated aqueous ammonium chloride (50$cm^3$) was then added cautiously to the cooled solution. The organic layer was removed and the aqueous layer was saturated with sodium chloride. The aqueous layer was re-extracted with ethoxyethane (2 x 50$cm^3$). The combined organic layers were washed with saturated aqueous potassium carbonate (50$cm^3$), saturated aqueous sodium chloride (50$cm^3$), dried ($MgSO_4$) and solvent was evaporated off. The crude product was a mixture of starting olefin and the desired cyclopropane ( 80% of the cyclopropane as estimated by $^1H$ n.m.r. spectroscopy). This crude mixture co-distilled to yield 5.9g (88%) of product b.p. 101-110° at 0.03 mm Hg.

$^1H$ n.m.r. ($CCl_4$) $\delta$ 1.31 (m,2H), 1.45 (m,2H), 3.81 (s, 3H), 4.23 (m,2H), 4.65 (s,2H), 7.40 (s,5H) p.p.m.

Preparation of (E)-Benzyloxybut-2-enoic Acid

Tetrahydrofuran (50$cm^3$, distilled from $LiAlH_4$) in a 500$cm^3$ pressure bottle was briefly cooled in a dry ice bath whilst nitrogen was slowly blown over its surface. 5% Palladium-on-charcoal (5.0g) was added, followed by a similarly cooled solution of (E)-methyl benzyloxybut-2-enoate (12g; 58 mmol) in tetrahydrofuran (50$cm^3$). The pressure bottle was

stoppered and allowed to warm to room temperature. It was then connected to a Parr hydrogenator and hydrogenolysis was effected for 3h at 30 p.s.i initial hydrogen pressure. The uptake of hydrogen was virtually complete after 40 minutes ($\Delta p$ = 16 p.s.i.). The reaction mixture was filtered through Celite, and the pad was washed with ethoxyethane ($50cm^3$). After evaporation of solvent, the crude product was examined by $^1H$ n.m.r. spectroscopy. The product was not the desired alcohol. No methyl ester group was apparent and there was no evidence for a $CH_2$ adjacent to an oxygen function.

Synthesis of trans-2-Methoxycarbonylcyclopropylcarbinol (Scheme 36)

Preparation of (E)-Methylbut-2-enoate

This was prepared by a standard literature procedure[141].

Preparation of (E)-Methyl 4-bromobut-2-enoate

To a $250cm^3$ round-bottomed flask equiped with reflux condenser and drying tube was added recrystallised N-bromosuccinimide (36g; 0.2 mol) and (E)-methylbut-2-enoate (20g; 0.2 mol) in dry, redistilled carbon tetrachloride ($60cm^3$). The mixture was heated under reflux for 12h after which succinimide remained on the surface of the liquid in the flask. The mixture was cooled to room temperature and the succinimide was removed by suction filtration and the precipitate was washed with dry carbon tetrachloride ($100cm^3$). Solvent was evaported off and the residue was fractionally distilled to yield 31g (86%) pure material b.p. 77-78° at 8 mm Hg.

$^1H$ n.m.r. ($CCl_4$) $\delta$3.70 (s,3H), 3.97 (d,2H), 6.0 (d,1H), 6.92 (m,1H) p.p.m.

Preparation of (E)-Methyl-4-Acetoxybut-2-enoate

To a $50cm^3$ round-bottomed flask was added (E)-methyl 4-bromobut-2-enoate (1.39g; 7.5 mmol) in carbon tetrachloride ($20cm^3$). To the solution, was added silver acetate (1.67g; 10 mmol) and the suspension was heated under reflux for 6h. The precipitate (AgBr) was removed by suction filtration and was washed with carbon tetrachloride. The combined organic washings were dried ($MgSO_4$) and solvent was evaporated off. The residue was distilled to yield 0.93g (78%) pure material b.p. 101-103° at 12 mm Hg.

$^1H$ n.m.r. ($CCl_4$) $\delta$ 2.07 (s,3H), 3.60 (s,3H), 4.69 (m,2H) 5.93 (m,1H), 6.83 (m,1H) p.p.m.

Preparation of (E)-Methyl 4-Hydroxybut-2-enoate

To a $250cm^3$ round-bottomed flask was added (E)-methyl 4-acetoxybut-2-enoate (24.4g; 0.15 mol), methanol ($50cm^3$) and 18 M sulphuric acid ($1.1\ cm^3$, 20 mmol). The reaction mixture was stirred at room temperature for 6h and then neutralised with solid $Na_2CO_3$. Water ($100cm^3$) was added and the solution extracted with ethoxyethane ($3 \times 100cm^3$). The combined organic layers were dried ($MgSO_4$) and solvent was evaporated off. The crude product was distilled b.p. 108-111° at 9 mm Hg to yield 14.6g (78%) pure material.

$^1H$ n.m.r. ($CCl_4$) $\delta$ 3.70 (s,3H), 4.25 (m,2H), 5.7 (-OH, broad) 6.0 (m,1H), 6.90 (m,1H) p.p.m.

Preparation of *trans*-2-Methoxycarbonylcyclopropylcarbinol

To a $500cm^3$ round-bottomed three necked flask fitted with reflux condenser, gas inlet system and pressure-equalising dropping funnel was added the zinc-copper couple type (II) (7.5g; 115 mmol) in ethoxyethane

($110cm^3$) under nitrogen. To the stirred suspension was added diiodomethane (20.7g; 77 mmol) followed by the dropwise addition of (E)-methyl 4-hydroxybut-2-enoate (3.52g; 30.3 mmol) in ethoxyethane ($24cm^3$) over a 30 minute period. The mixture was heated under reflux for 24h. Saturated aqueous ammonium chloride ($50cm^3$) was added and the ethoxyethane layer separated and was washed with water ($50cm^3$), saturated aqueous sodium chloride ($50cm^3$) and dried ($MgSO_4$). Solvent was evaporated off and the residual oil distilled b.p. 66-68° at 0.05 mm Hg to yield 2.1 g (70%) material. This material was shown to contain ca 5% starting material (E)-methyl 4-hydroxybut-2-enoate by $^1H$ n.m.r. spectroscopy.

<u>$^1H$ n.m.r. ($CCl_4$)</u> $\delta$1.1 - 1.6 (m,4H), 3.70 (s,3H), 3.0 (-OH,broad) 4.20 (m,2H) p.p.m.

<u>Preparation of 1-Methoxycarbonylcyclopropylmethylbromide</u>

This was prepared in a method analogous to that used in the preparation of cyclopropylmethylbromide (chapter 3), to yield 1.5 g (52%) of bromides. The bromides obtained were a mixture of the desired cyclopropane (90%) and (E)-methyl 4-bromobut-2-enoate (10% as estimated by $^1H$ n.m.r. spectroscopy).

<u>$^1H$ n.m.r. ($CCl_4$)</u> $\delta$0.9 - 1.4 (m,4H), 3.68 (s,3H), 4.10 (m,2H) p.p.m.

<u>Attempted Preparation of trans-2-Methoxycarbonylcyclopropylmethyl(pyridine)-cobaloxime.</u>

Bromo(pyridine)cobaloxime (1.34g; 2.6 mmol) and methanol ($20cm^3$) were stirred under nitrogen in a Schlenk tube for 45 minutes. Potassium tetrahydroborate (0.38g; 2.6 mmol) was added, followed by <u>trans</u>-2-methoxycarbonylcyclopropylmethylbromide (0.5g; 2.6 mmol) and the reaction mixture was stirred at 0°C for 6h. Ice-water ($50cm^3$) was added and the mixture

was extracted with dichloromethane (3 x 100cm$^3$). The combined organic layers were dried ($MgSO_4$) and solvent was evaporated off to yield a dark brown material and an oil shown to be recovered bromide by $^1$H n.m.r. spectroscopy. The brown precipitate obtained was not an alkylcobaloxime.

6:2:2 Synthetic Intermediates en route to cis-2-Carboxycyclopropylcarbinol (Scheme 37).

Preparation of Triethyl Cyclopropane-1,1,2-tricarboxylate

A modification of a literature procedure was used[142]. To a 2 litre three-necked round-bottomed flask fitted with reflux condenser, and pressure-equalising dropping funnel was added sodium (4.6g; 0.2 mol) in absolute ethanol (60g). Ethyl 1,2-dibromopropionate (26g; 0.1 mol) was added cautiously over 5 minutes to the stirred reaction mixture (violent reaction!), followed by diethyl malonate (16g; 0.1 mol). After 1 – 2h a precipitate of sodium bromide was observed, and, when the solution was neutral to litmus paper (between 1 and 4h), water (100cm$^3$) was added. The solution was evaporated on a rotary evaporater until most of the absolute alcohol had been evaporated off. To the resulting slurry, was then added water (150cm$^3$) and the dark upper layer containing the triester was separated, and the aqueous layer was extracted with ethoxyethane (2 x 100cm$^3$). The combined organic layers were dried ($MgSO_4$) and solvent evaporated off. The product was fractionally distilled to yield 20.3g (77%) pure material b.p. 158-159° at 9 mm Hg. $^1$H n.m.r. ($CCl_4$) $\delta$1.25 (m,9H), 1.55 (m,1H), 1.83 (m,1H), 2.45 (m,1H), 4.15 (m,6H) p.p.m.

Preparation of Cyclopropane-1,1,2-tricarboxylic Acid

To a 500cm$^3$ round-bottomed three necked flask fitted with reflux condenser,

pressure-equalising dropping funnel, and magnetic follower was added water ($100cm^3$). To the rapidly stirred solution, was added sodium hydroxide (100g; 2.5 mol) followed by the slow dropwise addition of triethyl cyclopropane-1,1,2-tricarboxylate (100g; 0.36 mol). The reaction mixture was heated under reflux overnight (15h). Water ($150cm^3$) was added and the apparatus arranged for downward distillation. Ethanol was then distilled off from the reaction mixture. The aqueous layer was then acidified and continuously extracted with ethoxyethane over several days. The ethereal solution was dried ($MgSO_4$) and solvent was evaporated off to yield 40.6 g (61%) pure material m.p. 181° (lit.[142] m.p. 183°). (This product was recrystallised from the minimum amount of boiling water).

$^1H$ n.m.r. ($D_2O$) $\delta$1.45 (m,1H), 1.55 (m,1H), 2.25 (m,1H) p.p.m.

Preparation of Cyclopropane-1,2-dicarboxylic Acid

To a $10cm^3$ pear-shaped flask equipped for downward distillation was added cyclopropane-1,1,2-tricarboxylic acid (2g; 0.012 mmol). The flask was heated at 220-230° until evolution of $CO_2$ was judged complete, the crude product was then distilled at 12 mm Hg. The product, cyclopropane-1,2-dicarboxylic acid 0.87g; (56%) crystallised upon cooling to room temperature. The product was recrystallised from 45 times its volume of ethoxyethane to yield pure material m.p. 174° (lit.[143] m.p. 175°).

$^1H$ n.m.r. ($CCl_4$) $\delta$1.53 (m,2H), 2.63 (m,2H) p.p.m.

Attempted Selective Hydrolysis of the Triethyl Cyclopropane-1,1,2-tricarboxylate

To a $10cm^3$ round-bottomed flask fitted with a drying tube and magnetic

follower was added triethyl cyclopropane-1,1,2-tricarboxylate (0.9314g; 5 mmol) in absolute ethanol ($2cm^3$). Potassium hydroxide (0.2805g; 5 mmol) was added and the reaction mixture was stirred at room temperature for 40h. A white precipitate was observed which was removed by filtration with suction. This solid was very hygroscopic and was dried in a desiccator *in vacuo*.

$^1H$ n.m.r. ($D_2O$) δ1.20 (m,6H), 1.38 (m,1H), 1.60 (m,1H), 3.65 (m,4H) p.p.m.

The product is thus the 2,2-diethoxycarbonylcyclopropanecarboxylic acid.

## 6:2. Use of 2,6,7-Trioxabicyclo[2.2.2.]octane as a Carboxy Protecting Group

1-(3'-Iodopropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2.]octane was prepared by D.A.Howes[144].

### Preparation of 1-[3'σ-(pyridine)cobaloxime]propyl-4-methyl-2,6,7-trioxabicyclo[2.2.2.]octane

This was prepared from the (3'-iodopropyl)-4-methyl-2,6,7-trioxabicyclo-[2.2.2.]octane by either the disproportion method or using bromo(pyridine)-cobaloxime in methods analogous to those employed in the preparation of but-3-enyl(pyridine)cobaloxime (Chapter 3).

$^1H$ n.m.r. ($CDCl_3$) δ 0.75 (s,3H), 1.03 (m,2H), 1.55 (t,4H), 2.1 (s,12H) 3.83 (s,6H), 7.3 (t,2H), 7.7 (t,1H), 8.50 (d,2H) p.p.m.

Found C 47.75, H 6.22, N 12.65 %; calculated for $C_{22}H_{34}N_5O_7Co$ C 47.40, H 6.51, N 12.58%.

### Acid Hydrolysis of 1-[3'σ-(pyridine)cobaloxime]propyl-4-methyl-2,6,7-trioxabicyclo[2.2.2.]octane

To a $50cm^3$ conical flask was added the 1-[3'σ-(pyridine)cobaloxime]-propyl-4-methyl-2,6,7-trioxabicyclo 2.2.2. octane (0.180g; 0.3 mmol) followed by dichloromethane ($10cm^3$). 0.5M aqueous hydrochloric acid ($5cm^3$) was added and the reaction mixture stirred at room temperature for 30 minutes (after which time the aqueous layer was highly coloured). The mixture was neutralised with solid $Na_2CO_3$ to yield 0.15g (82%) of 7,7-di(hydroxymethyl)-5-oxa-4-oxo-octyl(pyridine)cobaloxime.

<u>$^1H$ n.m.r. ($CDCl_3$)</u> δ 0.84 (s,3H), 1.27 (m,2H), 1.54 (t,2H), 2.13 (s,12H), 2.27 (t,2H), 3.55 (5,4H), 3.3-40 (s, broad,2-OH), 4.10 (s,2H), 7.31 (t,2H), 7.73 (t,1H), 8.53 (d,1H) p.p.m.

<u>Found</u> C 46.59 H 6.41 N 12.39 % <u>calculated</u> for $C_{22}H_{36}O_8N_5Co.1H_2O$ C 46.89 H 6.8 N 12.42%.

<u>Preparation of 3-Carboxypropyl(pyridine)cobaloxime</u>

The 7,7-di(hydroxymethyl)-5-oxa-4-oxo-octyl(pyridine)cobaloxime (0.253g; 0.42 mmol) was dissolved in dichloromethane ($2cm^3$) and stirred with 0.5M aqueous potassium hydroxide ($0.5cm^3$) at room temperature. After 2h. the aqueous layer was highly coloured. The aqueous layer was removed and made slightly acid with 10M hydrochloric acid (pH 5 by narrow range paper) when the cobaloxime precipitated. The cobaloxime was filtered with suction and dried <u>in vacuo</u> to yield 0.131g (62.3%) pure material.

<u>$^1H$ n.m.r. ($d^6$DMSO)</u> δ 1.0 (m,2H), 1.20 (t,2H), 1.95 (m,2H), 2.0 (s,12H), 7.45 (t,2H), 7.80 (t,1H), 8.27 (d,2H) p.p.m.

<u>Preparation of 3-Methoxycarbonylpropyl(pyridine)cobaloxime</u>

7,7-di(hydroxymethyl)-5-oxa-4-oxo-octyl(pyridine)cobaloxime (175 mg; 0.314 mmol) was dissolved in methanol ($5cm^3$) and 2M aqueous sodium hydroxide ($2cm^3$) was added. The mixture became warm and darkened.

After shaking for 2 minutes, 2M aqueous HCl was added to neutrality and the solution evaporated to dryness at room temperature. The orange solid was extracted into dichloromethane (2 x 5cm$^3$) and the combined dichloromethane extracts were washed with water (2 x 2cm$^3$), dried ($MgSO_4$) and solvent was evaporated off. The orange solid was recrystallised from acetone containing 0.5% v/v pyridine, to yield 115 mg (78%) of the cobaloxime methyl ester.

<u>$^1$H n.m.r. ($CDCl_3$)</u> $\delta$1.27 (m,2H), 1.51 (m,2H), 2.12 (s,12H), 2.18 (m,2H), 3.58 (s,3H), 7.30 (t,2H), 7.72 (t,1H), 8.54 (d,2H) p.p.m.

## 6:3 Results and Discussion

No cobaloximes with $^1$H n.m.r. data consistent with their containing a carboxyl-substituted cyclopropylcarbinyl group were isolated.

The Simmons-Smith reaction used to prepare 2-methoxycarbonylcyclopropylcarbinol yields as final product a mixture containing starting alcohol (<u>ca</u> 10%) (E)-methyl 4-hydroxy-but-2-enoate and the desired cyclopropane (as estimated by $^1$H n.m.r. spectroscopy). The components of this mixture are very close in boiling points, and the standard method for their separation (spinning-band distillation) is unsatisfactory. The mixture boiled in the range 108 - 110$^\circ$ at 0.03 mm Hg, and considerable decomposition of some of the components occurred when the crude material was heated for a prolonged period. Considerable difficulty is also encountered running a large glass distillation apparatus at the reduced pressures required to effect efficient volatalisation of the products. Thus, the Simmons-Smith procedure employed here, requires optimisation to convert all the olefinic starting material to cyclopropyl products.

Alternatively, a better separation of alkene from cyclopropyl product may be possible by employing argentised silica gel chromatography[145], for example. This procedure is likely to retard the alkene to a much greater extent than the cyclopropane.

6:3(a) Reaction of Methyl 4-bromobut-2-enoate with Silver Acetate

A reaction was initially performed by heating under reflux a 2:1 mole ratio of potassium acetate to methyl 4-bromobut-2-enoate in methanol. The reaction mixture was worked up in the usual manner (addition of water followed by solvent extraction) and the product was analysed by $^1H$ n.m.r. and i.r. spectroscopy. Spectral evidence shows that the product is a mixture of cis- and trans-isomers of methyl 4-acetoxybut-2-enoate. The relative proportions of the two isomers depends upon the time for which the mixture was heated e.g. after 3h ca 40% of the cis-isomer was noted and after 15h ca 60% cis-isomer was noted. Longer reaction times gave no apparent increase in the cis/trans ratio. An $S_N2$ displacement of bromide gives only the trans-acetoxy isomer. Formation of the cis-isomer, may occur via an $S_N2'$ substitution to methyl 2-acetoxybut-3-enoate, followed by allylic rearrangement to cis-methyl 4-acetoxybut-2-enoate.

In another experiment a 2:1 mixture of silver acetate and methyl 4-bromobut--2-enoate was heated under reflux for 15h in methanol. The reaction mixture was worked up and the product was analysed by i.r. and $^1H$ n.m.r. spectroscopy. The substitution pattern about the double bond was entirely trans. However, the product of this reaction contains two components; methyl 4-acetoxybut-2-enoate and methyl 4-methoxybut-2-enoate. The latter is probably formed by capture of an intermediate carbonium ion by methanol.

By using a 1.1:1 molar ratio of methyl 4-bromobut-2-enoate to silver acetate and heating overnight in boiling $CCl_4$, pure (E)-methyl 4-acetoxybut-2-enoate is formed.

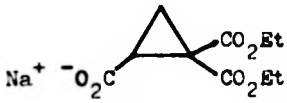
6:3 (b) Methanolysis and Hydrolysis of (E)-Methyl 4-acetoxybut-2-enoate

Initially the methanolysis of methyl 4-acetoxybut-2-enoate was studied with 5 mole % sodium methoxide in methanol. After work up, the product, as analysed by i.r. and $^1H$ n.m.r. spectroscopy, contained no double bond. Probably Michael addition of methanol across the double bond occurred resulting in a $\gamma$-acetoxy-$\beta$-methoxy-substituted molecule.

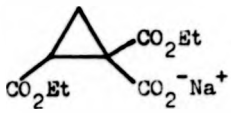
For the hydrolysis of the methyl 4-acetoxybut-2-enoate, 5% aqueous hydrochloric acid in methanol was found to be the reagent of choice, and gives the methyl 4-hydroxybut-2-enoate in good yield without serious side reactions taking place.

6:4 The Cyclopropane-1,2-dicarboxylic Acid Intermediate Postulated for the $\alpha$-Methyleneglutarate Mutase Reaction

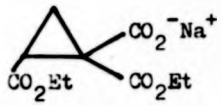
One attempted approach for the synthesis of this intermediate was the selective hydrolysis of one of the 1-carboxyl groups of the triester derived from cyclopropane-1,1,2-tricarboxylic acid. The 1-carboxylate group may be more reactive towards base because of its proximity to the other 1-carboxyl grouping. The product isolated from reaction of 1 mole equivalent of the triester with 1 mole equivalent of base was a single product (as identified by $^1H$ n.m.r. spectroscopy). This product is the sodium salt of an acid, diester, either 1, 2 or 3: over page.




1




2



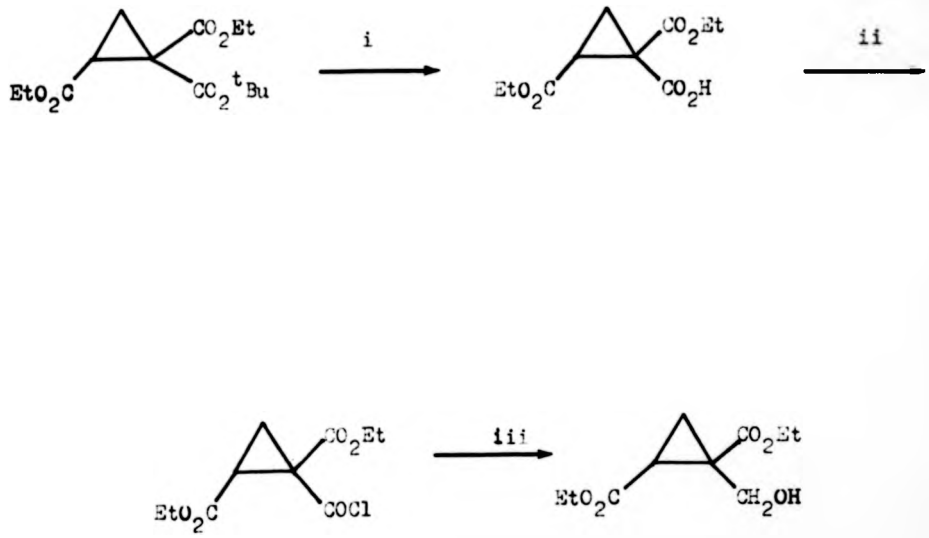

3

$^1$H n.m.r. spectroscopy could not distinguish between the possibilities. However, if 1 were formed, then addition of DCl should result in a marked shift of the resonance of the methine proton of the cyclopropane ring which is adjacent to a carboxylate anion in one situation and to a protonated analogue in the other. Indeed, addition of DCl resulted in a marked shift ( $\delta$ 0.95p.p.m.) of this methine proton resonance, indicating 1 had been formed and not the desired products 2 or 3.

An alternative approach to 1,2-diethoxycarbonylcyclopropane-1-carboxylic acid would be to use a mixed malonate condensation with ethyl,t-butyl malonate and ethyl 1,2-dibromopropionate as outlined in Scheme 38 . This would result in the production of 1-t-butoxycarbonyl-1,2-diethoxy-carbonylcyclopropane:


Advantage can then be made of the differential hydrolysis of t-butyl and ethyl ester groupings. Thus, in dilute acid solution, t-butyl esters are cleaved ($S_N1$ reaction) whereas ethyl esters are hydrolysed only slowly. Hence, the 2-carboxyl substituted acid, diester, might be obtained. Reaction of this compound with thionyl chloride to yield the corresponding acyl chloride followed by selective reduction (e.g. with $NaBH_4$) of the acyl chloride moiety leads to alcohol (Scheme 38 ). Thence, the alkyl-cobaloxime is available using standard intermediates.

Scheme 38. Possible Route to 1,2-Diethoxycarbonylcyclopropane-1-methanol




i = Dil.HCl.

ii = Thionyl chloride.

iii = $NaBH_4$.

## REFERENCES


1. (a) "Cobalamin, Biochemistry and Pathophysiology", ed. B.M.Babior, Wiley, New York, 1975.

   (b) Biochemistry, 1974, 13, 1555.

2. "Vitamin $B_{12}$", ed. E.Lester Smith, Menthuen, London, 1965.

3. F.A.Kuehl, C.H.Shunk, M. Moore and K. Folkers, J.Am.Chem.Soc., 1955, 77, 4418.

4. British Medical Encyclopaedia of Medical Practice, 2nd Ed., 1, 446, Butterworths.

5. G.A.Whipple, Arch.Intern. Med., 1922, 29, 711.

6. G.R.Minot and W.P.Murphy, J.A.M.A., 1926, 87, 470.

7. E.J.Cohn, G.R.Minot, G.A.Alles and W.T.Salter, J. Biol. Chem., 1928, 77, 325.

8. W.B.Emery and L.F.J.Parker, Biochem. J. 1946, 40, IV.

9. R. West, Science, 1948, 107, 398.

10. E.L. Rickes, N. G. Brink, F.R.Konuiszy, T.R.Wood and K. Folkers, Science, 1948, 107, 396.

11. E. L. Smith and L.F.J.Parker, Biochem. J., 1948, 43, VIII.

12. J. W. Corcoran and D. Shemin, Biochem. Biophys. Acta, 1957, 25, 661.

13. K. H. Fontes, J.E. Page, L.F.J.Parker and E.L.Smith, Proc.Roy. Soc. (B), 1949, 136, 592.

14. D. Perlman, Adv. Appl. Microbiol., 1959, 1, 87.

15. L. Mervyn and E. L. Smith, Progr. Ind. Microbiol., 1964, 5, 151.

16. K. Folkers and D.E.Wolf, Vitamins and Hormones, 1954, 12, 1.

17. E. L. Smith, Biochem. Soc. Symposia, 13, 3.

18. A.W.Johnson and A. Todd, Vitamins and Hormones, 1957, 15, 1.

19. R. Bonnett, Chem. Revs., 1963, 63, 573.

20. C. Brink, D.C.Hodgkin, J. Lindsey, J. Pickworth, D.Robertson and J. G. White, Nature, 1954, 174, 1169.

21. R. Bonnett, J.R.Cannon, V.M. Clark, A.W.Johnson, L.F.J.Parker, E. L. Smith and A. Todd, J.C.S., 1957, 1158.

22. P. G. Lenhert and D.C.Hodgkin, Nature, 1961, 192, 937.

23. R.B.Woodward, Pure Appl. Chem., 1973, 33, 45.

24. A.Eschenmoser, Quart. Rev., 1970, 24, 366; Pure Appl.Chem.Suppl., 1971, 2, 69. Naturwiss. 1974, 61, 513.

25. R.C.Bray and D.Schemin, J. Biol. Chem., 1963, 238, 1501.

26. A.R.Battersby, M. Ihara, E. McDonald, J.R.Redfern and B.T.Golding, J.C.S. Perkin(I), 1977, 158.

27. A.I.Scott. Acc.Chem. Res., 1978, 11, 29.

28. K. Bernhauer, F.Wagner, H. Michna, P. Rapp and H. Vogelmann, Z.physiol. Chem., 1968, 349, 1297; F. Wagner, Ann. Rev. Biochem., 1966, 35/1, 405.

29. A.R.Battersby, S.Kishimoto, E. McDonald, F.Satoh and H.K.W.Wurziger, J.C.S. Perkin(I), 1979, 1927.

30. E.J.Corey, N.J.Cooper, M.L.H.Green, Proc.Nat.Acad.Sci., 1977, 74,811.

31 G.N.Schrauzer and J.W.Sibert, J.Am.Chem.Soc., 1970, 94, 1022.

32. B.M.Babior, Acc. Chem. Res., 1975, 8, 376.

33. H.F.Kung, T.C.Stadtman, J.Biol.Chem., 1971, 246, 3378.

34. J. Retey, A.Umani-Ronchi and D.Arigoni, Experimentia, 1966, 22,72.

35. P. A. Frey, G. L. Karabatsos and R. H. Abeles, Biochem. Biophys. Res. Comm., 1965, 18, 551.

36. J. Retey, A.Umani-Ronchi and D.Arigoni, Experimentia, 1966, 22, 502.

37. B.M.Babior, J.Biol. Chem., 1970, 245, 6125; R.B.Silverman, D.Dolphin and B.M.Babior, J.Am. Chem.Soc., 1972, 94, 4028.

38. B.T.Golding and L. Radom, J.Am.Chem.Soc., 1976, 98, 6331.

39. B.T.Golding, P.J.Sellars and C.S.Sell, J.C.S. Chem. Comm., 1976, 773.

40. Dinah Coates, M.Sc.Dissertation, University of Warwick, 1977.

41. F.M.Moore, B.T.M.Willis and D.C.Hodgkin, Nature, 1976, 214, 130.

42. R. Bonnett, J.M.Godfrey and D.R.Redman J.C.S.(C), 1969, 1163.

43. V.Koppenhagen, Dissertation, University of Stuttgart, 1967.

44. R. Bonnett, J.M.Godfrey, V.B.Math, J.C.S.(C), 1971, 3736.

45. S.L.Tackett, J.W.Collat, J.C.Abbott, Biochemistry, 1963, 2, 919.

46. B. Jaselskis, H. Diehl, J.Am.Chem.Soc., 1954, 76, 4345.

47. G.N.Schrauzer, J.W.Sibert, Arch. Bioch.Biophys., 1969, 130, 257.

48. J.W.Collat and J.C.Abbott, J.Am.Chem.Soc., 1964, 86, 2308.

49. R. Breslow and K.L.Khanna, J.Am.Chem.Soc., 1976, 98, 1297, 6765.

50. G.J.H.Grate and G.N.Schrauzer, J.Am.Chem.Soc., 1979, 101, 4601.

51. R.B.Silverman and D.Dolphin, J.Am.Chem.Soc., 1973, 95, 1686.

52. G.N.Schrauzer, J.W.Sibert and R.J.Windgassen, J.Am.Chem.Soc., 1968, 90, 6681.

53. D.A.Clarke, R.Grigg and A.W.Johnson, J.C.S. Chem.Comm., 1966, 208.

54. A.Bigotto, E.Zangrando and L.Randaccio J.C.S.Dalton, 1976, 96.

55. D.L.McFadden and A.T.McPhail, J.C.S.Dalton, 1974, 363.

56. G.N.Schrauzer, Angew.Chem.Int. Ed., 1976, 15, 417; Acc. Chem. Res., 1968, 1, 97.

57. A.D.Bury, M.P.Atkins, B.T.Golding, M.D.Johnson and P.J.Sellars, J.Inorg. and Nuc.Chem., submitted for publication.

58. J.M.Wood and D.G.Brown, Structure and Bonding, 1972, 11, 47.

59. G.Costa, Coord. Chem.Rev., 1972, 8, 63.

60. G.N.Schrauzer, L. P. Lee and J. W. Sibert, J.Am.Chem.Soc., 1970, 92, 2997.

61. G.Bidlingmaier, H. Flohr, U.M.Kempe, T.Krebs and J.Retey, Angew.Chem. Int.Ed., 1975, 14, 822.

62. H. Flohr, W. Pannhorst and J.Retey, Angew. Chem. Int.Ed. 1976, 15,561.

63. B.T.Golding, T.J.Kemp, E.Nocchi and W.P.Watson, Angew. Chem.Int.Ed. 1975, 14, 813.

64. B.T.Golding and P.J.Sellars, J.C.S. Perkin(II), submitted for publication.

65. G.Costa, G.M.Nestroni, G. Tauzher and L.Stefani, J.Organomet.Chem., 1965, 6, 181.

66. E.Childers and G.W.Struthers, Analytical Chemistry, 1955, 27, 737.

67. S.Chemally and J.M. Pratt, J.C.S. Chem.Comm., 1978, 988.

68. H.E.Simmons and R.D.Smith, J.Am.Chem.Soc., 1958, 80, 5323.

69. E.LeGoff, J.Org.Chem., 1964, 29, 2048.

70. R.S.Shank and H.Schecter, J.Org.Chem., 1959, 24, 1825.

71. J.Furukawa, N.Kawabata and J.Nishimura, Tetra..Lett.,1968, 3495.

72. E.Buchner, Ann. 1893, 273,214.

73. E.V.Dehlmlow, Angew.Chem. internat. Edit., 1974, 13, 170.

74. R.C.Woodworth and P.S.Skell, J.Am.Chem.Soc.,1957, 79, 2542.

75. V.VanRheenen, R.C.Kelly and D.Y.Cha, Tetra. Lett., 1976, 1973.

76. A.Karagiorgas, M.Sc.Dissertation, University of Warwick, 1978; M. Foster, unpublished results.

77. G.N.Schrauzer, Inorganic Synthesis, 1968, 11, 61.

78. J.B.Stothers, "Carbon-13 NMR Spectroscopy", Academic Press. 1972.

79. M. Green and R.I.Hancock, J.Chem.Soc.(A), 1967, 2054.

80. A.N.Nesmeyanov, N.E.Kolobova, I.B.Zlotina, M.Ya.Solodova and K.N.Anisimou, Chem. Abs., 1977, 86, 55802.

81. J.M. Brown, J.C.S. Perkin(II), 1973, 1993.

82. H. Yamazaki, T.Nishido, Y.Matsumoto, S.Sumida and H.Hagihara, J.Organomet.Chem., 1966, 6, 86.

83. C.Giannotti, B.Septe and D.Benlian, J.Organomet.Chem., 1972, 39, 5C.

84. G.Costa, G.Tauzher and A.Puxeddu, Inorg. Chim.Acta, 1969, 3, 41.

85. T.L.Brown, L.M. Ludwick and R.S.Stuart, J.Am.Chem.Soc., 1972, 94,384.

86. G.N.Schrauzer and R.J.Windgassen, J.Am.Chem.Soc., 1966, 88, 3738.

87. A.W.Herbinger and T. L. Brown, J.Am.Chem.Soc., 1972, 94, 388.

88. K.L.Brown and A.W.Awtry, Inorg. Chem., 1978, 17, 111.

89. D.Dodd and M.D.Johnson, J.Am.Chem.Soc., 1974, 96,2279; C.J.Cooksey, D.Dodd, M.D.Johnson and B.L.Lockmann, J.C.S. Dalton, 1978.

90. A.Bury, M.R.Ashcroft and M.D.Johnson, J.Am.Chem.Soc. 1978, 100,3217.

91. M.F.Atkins, A.Bury, B.T.Golding, M.D.Johnson and P.J.Sellars, J.Am.Chem.Soc.. 1980, 102, 3630.

92. H.O.Pritchard, R.G.Sowden, A.F.Trotman-Dickenson, Proc.Roy.Soc.. 1953, A218, 416.

93. T.Chambers and G.B.Kistiakowskey, J.Am.Chem.Soc.. 1934, 56, 399.

94. G.A.Olah, D.P.Kelly, C.L.Jevel and R.D.Porter, J.Am.Chem.Soc.. 1970, 92, 2544.

95. J.D.Roberts and R.H.Mazur, J.Am.Chem.Soc.. 1951, 73, 2509; R.H.Mazur, W.R.White, D.A.Semenow, C.C.Lee, M.S.Silver and J.D.Roberts, J.Am.Chem. Soc.. 1959, 81, 4390.

96. Z.Majerski, S. Borcic and D.E.Sunko, Tetrahedron, 1969, 24, 301; J.C.S.Chem.Comm.. 1970, 1636.

97. K.B.Wiberg and G.Szeimies, J.Am.Chem.Soc.. 1968, 90, 4195; ibid, 1970, 92, 571.

98. Z. Majerski and P. V.R.Schleyer, J. Am.Chem.Soc.. 1971, 93, 655.

99. K.B.Wiberg, B.A.Hess and A.J.Ashe, "Carbonium Ions" Vol.3., ch.26, Wiley-Intescience, New York, 1972.

100. J.E.Baldwin and W.D.Feglesong, J.Am.Chem.Soc.. 1968, 90, 4303,4311.

101. M.E.H.Howden and J.D.Roberts, Tetrahedron Suppl.2.. 1963, 19, 403.

102. J.S.Storal and J.D.Roberts, J.Am.Chem.Soc.. 1978, 100, 8018.

103. J.S.Storal, Issa Youarri, J.D.Roberts, G.K.Sarya Prakash, D.J.Donovan and G.A.Olah, J.Am.Chem.Soc.. 1978, 100, 8016.

104. M.Simmonetta and S.Winstein, J.Am.Chem.Soc.. 1954, 76, 18.

105. W.G.Woods, R.A.Carboni and J.D.Roberts. J.Am.Chem.Soc.. 1956, 78,5653; Tetrahedron Suppl.2, 1963, 19, 423.

106. M.J.S.Dewar and A.P.Marchand, Ann.Rev.Phys.Chem.. 1965, 16, 321.

107. M.Suzuki, S.I.Murahashi, A.Sonoda and I.Moritani. Chem.Letts.. (Tokyo), 1974, 267.

108. J.Y.Godet, M.Pereye, J.C.Pommier and D.Chevolleau, J.Organomet. Chem., 1973, 55, C15.

109. J.K.Kochi, P.J. Krusu and D.R.Eaton, J.Am.Chem.Soc., 1969, 91.1877.

110. J.K.Kochi, P.S.Krusic and D. R.Eaton, J.Am.Chem.Soc., 1969, 91.1879.

111. W.M. Horspool, Photochem., 1973, 4, 577.

112. P.A.Levene and A.Walti, Org.Synth.Coll.Vol.II, 545.

113. B.T.Golding, D.R.Hall and S.Sakrikar, J.C.S.Perkin(I), 1973,1214.

114. P.Dowd, K.Kang and M.Shapiro, J.Am.Chem.Soc., 1975, 97. 4754.

115. M. D. Johnson, personal communication.

116. D.A.Seeley and J.McElwee, J.Org.Chem., 1973, 38, 1691.

117. D.J.Pasto and C.C.Cumbo, J.Org.Chem., 1965, 30, 1271.

118. J. Nishimura, N.Kawabata and J.Furukawa, Tetrahedron. 1969, 25, 2647.

119. E.C.Friedrich, S.N.Falling and D.E.Lyons, Synth.Comm., 1975, 5, 33.

120. P.J.Sellars, personal communication.

121. L. G. Marzilli, P.J.Toscano, L.Randaccio, N.B.Pahor and M.Calligaris, J.Am.Chem.Soc., 1979, 101, 6754.

122. J.F.Endicott, Inorg.Chem., 1977, 16, 494.

123. A.G.Davies, B.Muggleton, J.Y.Godet, M.Pereyre and J.C.Pomier, J.C.S.Perkin(II), 1976, 1719.

124. M.A.Casting, M.Pereyre, M.Ratier, P.M.Bloom and A.G.Davies, J.C.S. Perkin(II), 1979, 589.

125. F.R.Jenson, V.Madon and D.H.Buchanon, J.Am.Chem.Soc., 1970, 92, 1414; H.L.Fritz, J.H.Espenson, D.A.Williams and G.A.Molander, ibid.1974, 96. 2378.

126. M.Tada and M.Okabe, Chem.Soc.Jap.Chem.Letts., 1980, 2, 201.

127. Unpublished results, see also M.P.Atkins, B.T.Golding and P.J.Sellars, Proc. Eur. Symp. Vitamin $B_{12}$ Intrinsic Factors, 3rd, 1979, 587.

128. M.Ashcroft and M.D.Johnson, personal communication.

129. B.T.Golding, T.J.Kemp and E.Nocchi, J.C.S. Dalton, 1977, 1266.

130. J.H.Espenson, J.Chem.Soc.Chem.Comm., 1971, 653; Inorg.Chem., 1979, 18, 2853.

131. J. R. Barcello and C.Otero, Spectrochim.Acta, 1962, 18, 1231.

132. A.L.Crumbliss and P.L.Gaus, Inorg. Chem., 1975, 14, 486.

133. B.N.Figgis, Techniques of Inorganic Chemistry, Volume 4, Weissberger Ed. Interscience.

134. A.V.Ablov, N.M.Samus and D.A.Bologa, Russ. J.Inorg.Chem., 1963, 8,440.

135. M.P.Atkins, B.T.Golding, D.A.Howes and P.J.Sellars, J.C.S. Chem.Comm., 1980, 207.

136. M.Renoll and M.S.Newman, Org. Synth.Coll. Vol.III, 502.

137. B.T.Golding and P.Y.Ioannou, Synthesis, 1977, 423.

138. E.Knoevenagel, Annalen, 1894, 281,94.

139. C.Doebner, Ber., 1909, 42, 4072.

140. L.J.Mathias, Synthesis, 1979, 11, 561.

141. "Textbook of Practical Organic Chemistry", Ed. Vogel, 3rd edn., 1958, 927.

142. M.Conrad and M.Gutzeit, Ber., 1884, 17, 1185.

143. H.L.deWaal and G.W.Perold, Ber., 1952, 85, 574.

144. D.A.Howes, dissertation, University of Warwick, to be submitted.

145. L.J.Morris, J.Lipid Res., 1966, 7, 717.