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SOLVOLYTIC STUDIES OF β -ACETOXYALKYLCOBALOXIMES

by

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A dissertation submitted to the

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for the degree of

DOCTOR OF PHILOSOPHY

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A C K N O W L E D G E M E N T S

The work described in this thesis was carried out in the School of Molecular Sciences, University of Warwick. The results presented here are original except where specific acknowledgement is made and have not been presented for any other degree.

I am grateful to Professor V.M. Clark for the use of the laboratories of the School of Molecular Sciences. I am also grateful to him and Dr. T.J. Kemp for providing funds during my last year.

My everlasting thanks must go to Dr. B.T. Golding who supervised this work. He was always available for discussion and constantly provided new ideas. He also read the draft of this thesis. Through his patience, understanding and guidance he has taught me more than just chemistry. He has always been a source of inspiration and knowledge.

I would also like to thank the technicians in the department, all my friends and colleagues who made working and living so very enjoyable.

My thanks to Miss Doreen Wearing who took so much trouble over the typing, and to W.P. Watson who did the proof-reading; also Mr. A.N. Whitehead for the photographs.

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S U M M A R Y

Evidence is presented in this thesis for the possible involvement of a novel olefinic π -complex of cobalt(III) in the solvolysis of β -acetoxyalkylcobaloximes. The enzymatic reactions catalysed by coenzyme B₁₂ are described in the introduction. Evidence obtained from an extensive study of these reactions, and reported in literature, is discussed in terms of various mechanisms for coenzyme B₁₂ action. The similarity between biacetyldioxime complexes of cobalt and the B₁₂ coenzymes is described and, on the basis of studies on the former (reported in Chapters II and III), the suggested intermediacy of an olefinic π -complex of cobalt(III) in some of the enzymatic reactions can be supported.

The hydrolysis, ethanolysis and deuteromethanolysis of β -acetoxyalkylcobaloximes are discussed in Chapter II. The evidence obtained, and results of studies on cobaloximes reported in literature, are interpreted in terms of a scheme which requires the involvement of the intermediate mentioned above. However, two possible alternatives to this complex are also considered. The similarity of these solvolyses with the acid catalysed deoxymercuration reactions and solvolyses of substituted ferrocenes is pointed out.

Chapter III deals with the solvolyses of chiral and specifically labelled cobaloximes and also of cobaloximes with different trans-ligands. The results of these experiments are shown to be in favour of the π -complex as the key intermediate in these solvolyses.

ABBREVIATIONS

b.p.	boiling point
C.D.	Circular Dichroism
cm	centimetre
DMG	Dimethylglyoxime
e.s.r.	electron spin resonance
g	gram
g.l.c. (G.L.C.)	gas liquid chromatography
I.R.	Infra-Red
L	Ligand
M	Mol
mg	milligram
MHz	Mega Herz
ml	milli litre
mM	milli Moles
mp	melting point
MS	Mass Spectra
nm	nanometre
n.m.r.	nuclear magnetic resonance
τ	chemical shift
T.L.C.	Thin Layer Chromatography
U.V.	Ultra-Violet

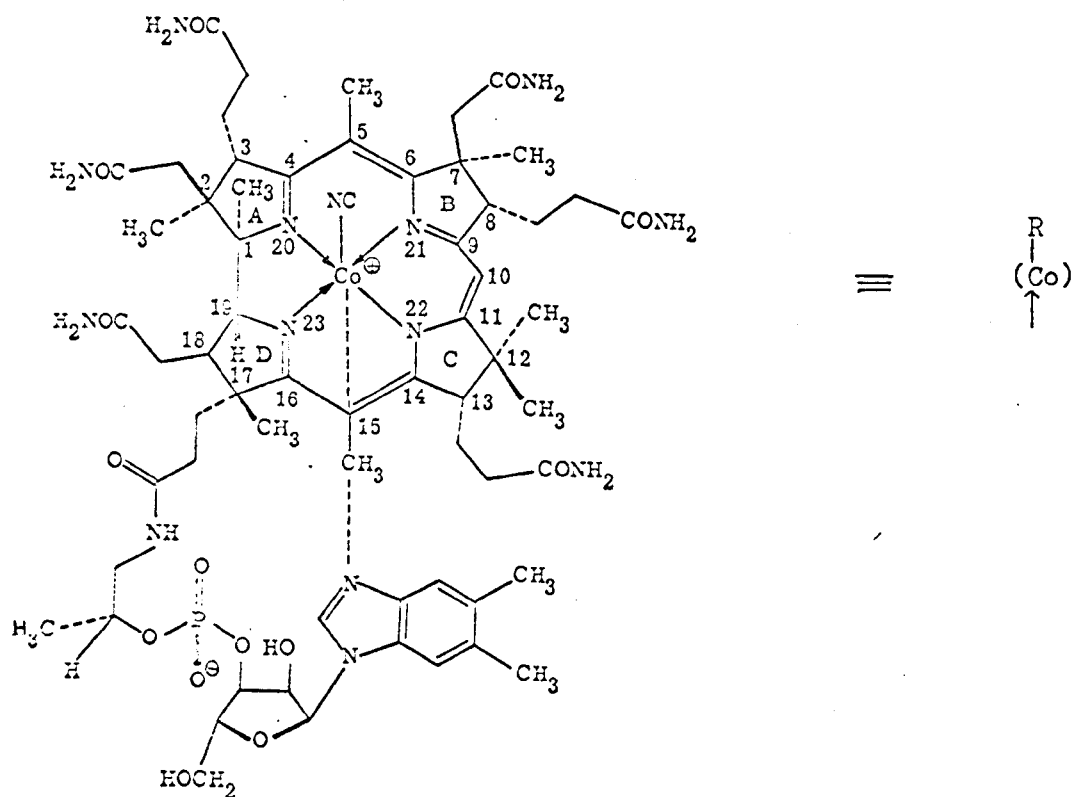
CHAPTER I

The research described in this thesis concerns an aspect of the chemistry of σ -alkylbis (biacetyldioximato) complexes of cobalt(III). The study of these complexes - hereafter referred to as 'cobaloximes' - developed from an interest in the chemistry and biochemistry of vitamin B₁₂ and its natural congeners. As will be discussed later, there is considerable evidence that cobaloximes simulate many of the reactions of the cobalamins and hence serve as good models. It will be relevant to begin with a discussion of the chemistry of cobalamins.

The history of vitamin B₁₂ (see figure I) dates from about 1926, when it was demonstrated that 'pernicious anaemia'* could be therapeutically controlled by ingestion of whale liver¹. This 'anti-pernicious factor', which came to be known as vitamin B₁₂, was isolated in 1948^{3,4}. After significant contributions to its structural elucidation in the classical style, this problem was finally resolved beyond doubt in 1955 by X-ray crystallography⁵. This structure has now been confirmed by total synthesis⁶. Vitamin B₁₂ is biosynthesised almost exclusively by micro-organisms. Commercially, it is made by fermentation of Streptomyces species and

* A macrocyclic anaemia in which the red blood cells become abnormally large while immature and are few in number; the bone marrow is megaloblastic².

FIGURE I



R = CN, vitamin B₁₂ Co(III)
 vitamin B_{12r} Co(II)
 vitamin B_{12s} Co(I)

R = CH₃, methylcobalamin

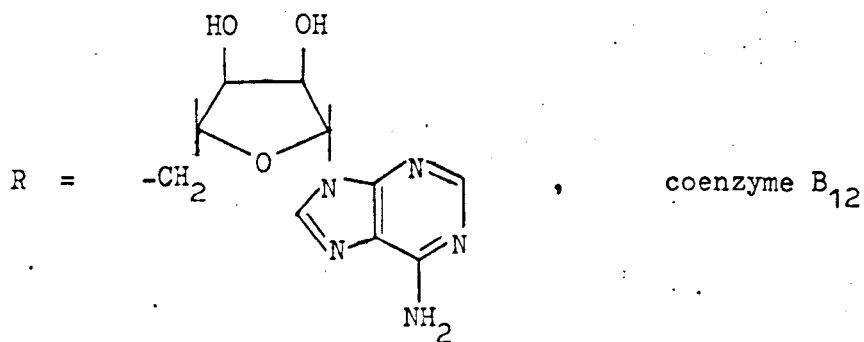
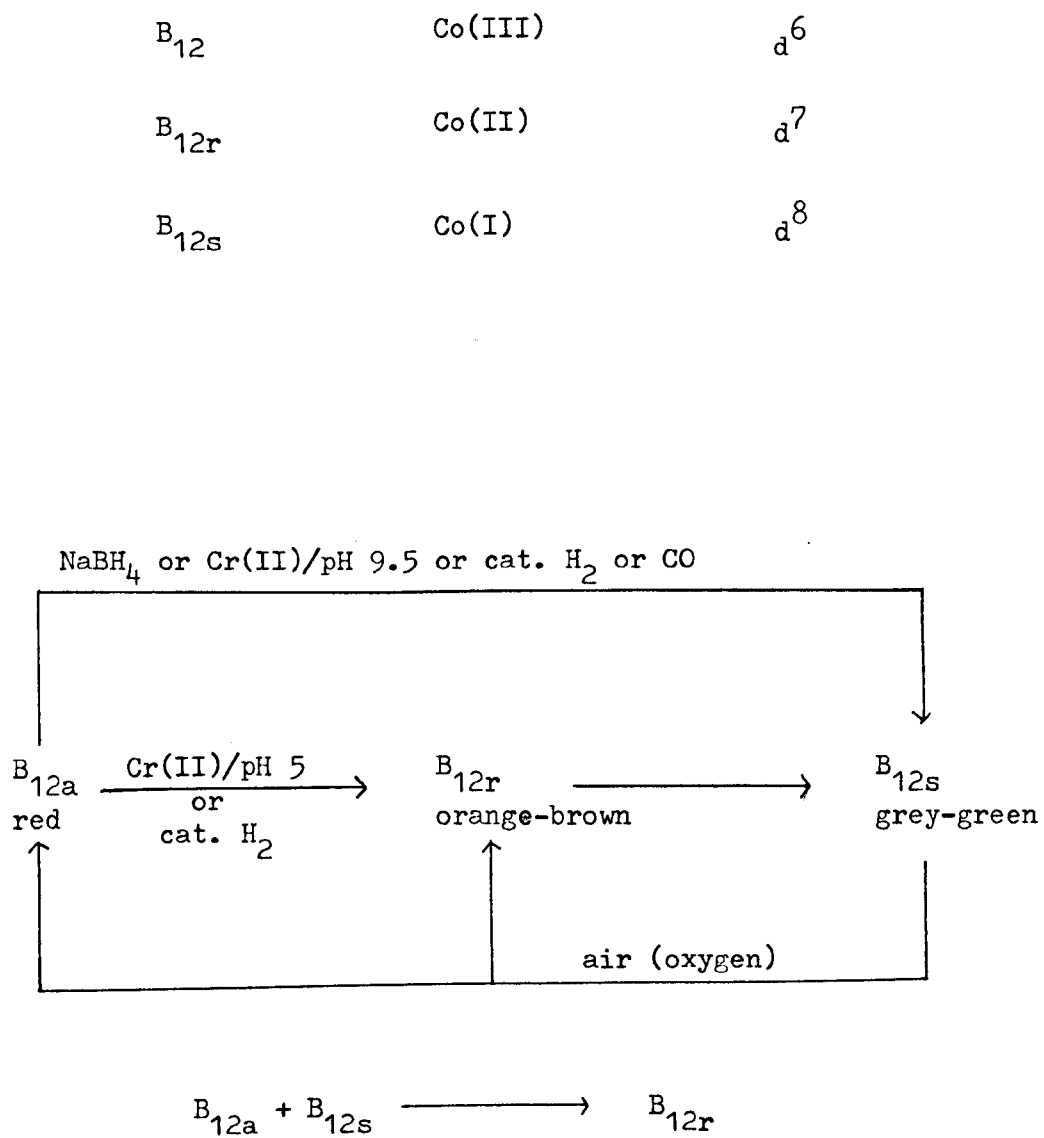


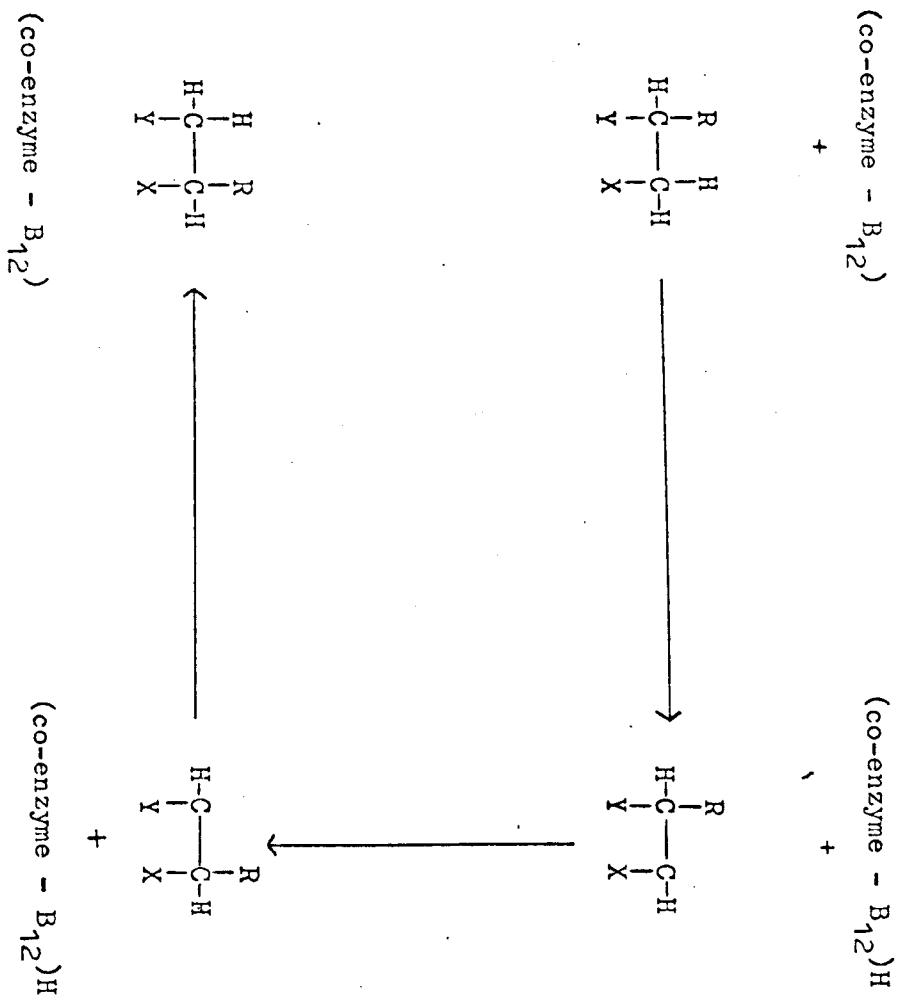
FIGURE II

other micro-organisms, especially the propionibacterium species.

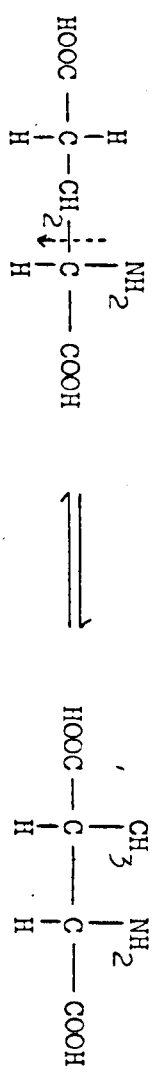
The accepted nomenclature for vitamin B₁₂ is shown in fig.I. Hence, vitamin B₁₂ may be called cyanocobalamin. The tetra-pyrrole ring liganded to cobalt is known as the corrin ring and hence cobalamins are also sometimes referred to as corrinoids. In 1958 a new naturally occurring cobalamin was isolated from several bacterial sources and animal liver^{8,9,10}. On the basis of X-ray crystallographic studies¹¹, it was shown to be 5'-deoxyadenosyl cobalamin. This is sometimes referred to as coenzyme B₁₂ because of its role as a coenzyme in a group of biological reactions to be discussed. Another cobalamin, also of biochemical importance, is methyl cobalamin, discovered in 1963¹². This differs from the cyanocobalamin only in that the cyano group is replaced by a methyl group. Usually, cobalamins are hexa-coordinated with the tetra-coordinating corrin ring in the xy-plane, and the other two ligands on the z-axis, of the cobalt ion. When one of the axial ligands is strongly electron-donating, the other axial ligand may be lost to form a stable five-coordinated cobalt species in solution. Vitamin B₁₂, sometimes referred to as B_{12a}, is a cob(III)alamin, since the oxidation state of the cobalt ion is +3. It can be reduced to two other oxidation states: Co(II) in B_{12r} (cob(II)alamins), and Co(I) in B_{12s} (cob(I)alamins). Electron spin resonance studies indicate that B_{12r} is the only paramagnetic species amongst these (figure II).

The discovery of a cobalt-carbon σ -bond in coenzyme B₁₂¹¹ aroused tremendous interest. This provided the first and rare example of a naturally occurring organometallic molecule, and inspired new research into the organometallic chemistry of cobalt.

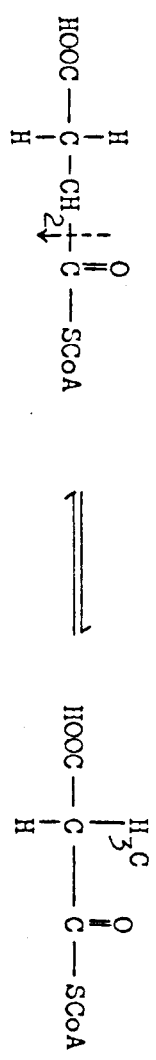
SCHEME I



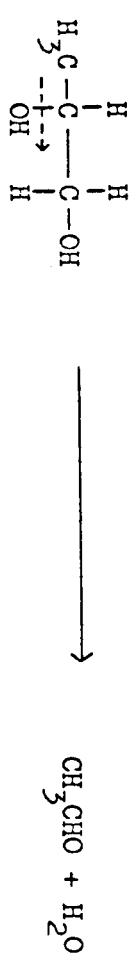
SCHEME II



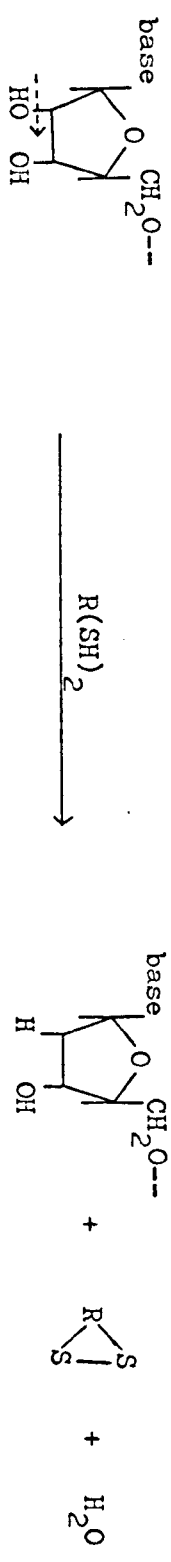
Glutamate mutase



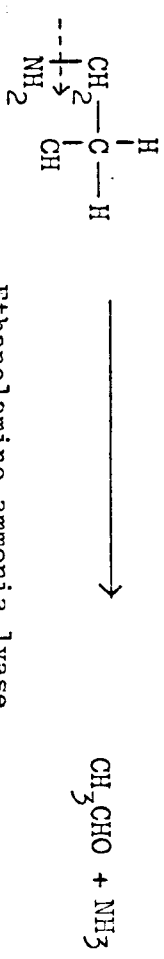
Methylmalonyl CoA mutase



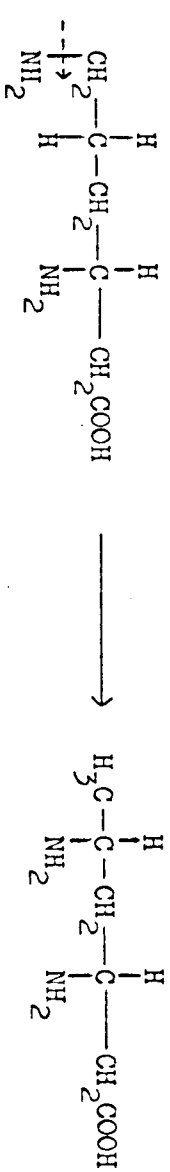
Propanediol dehydrase



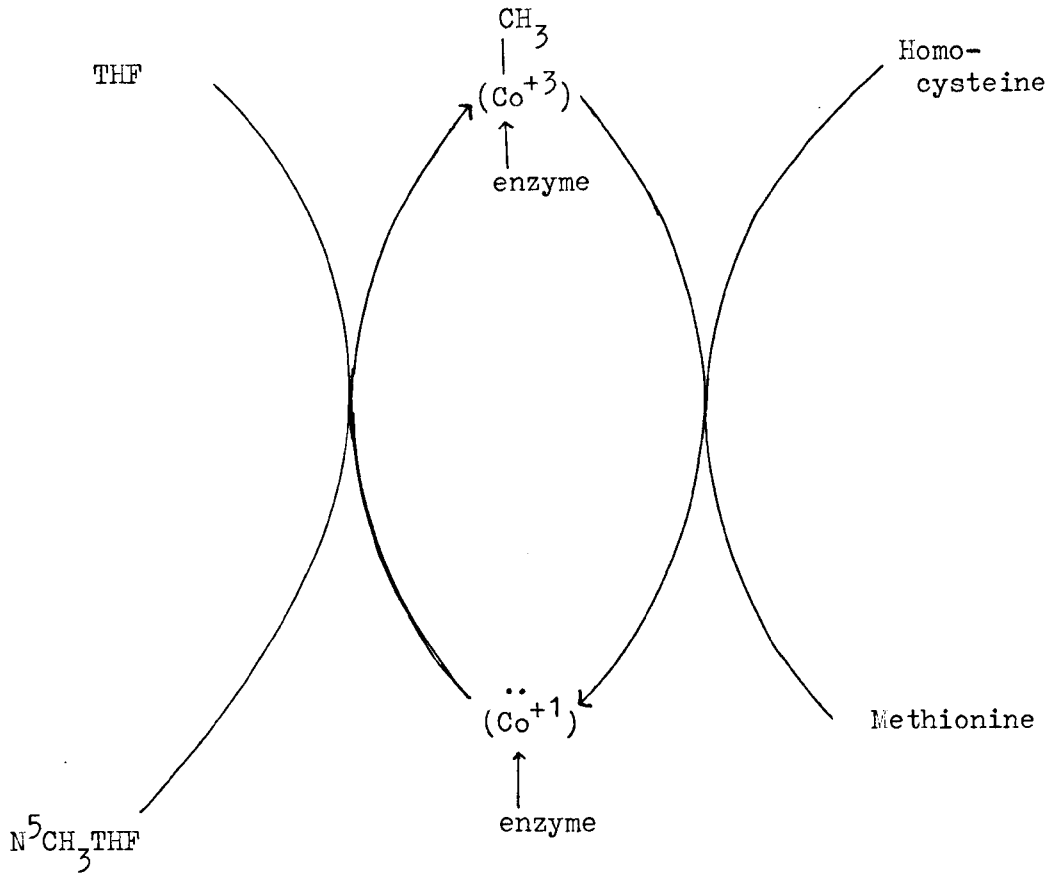
Ribonucleotide reductase



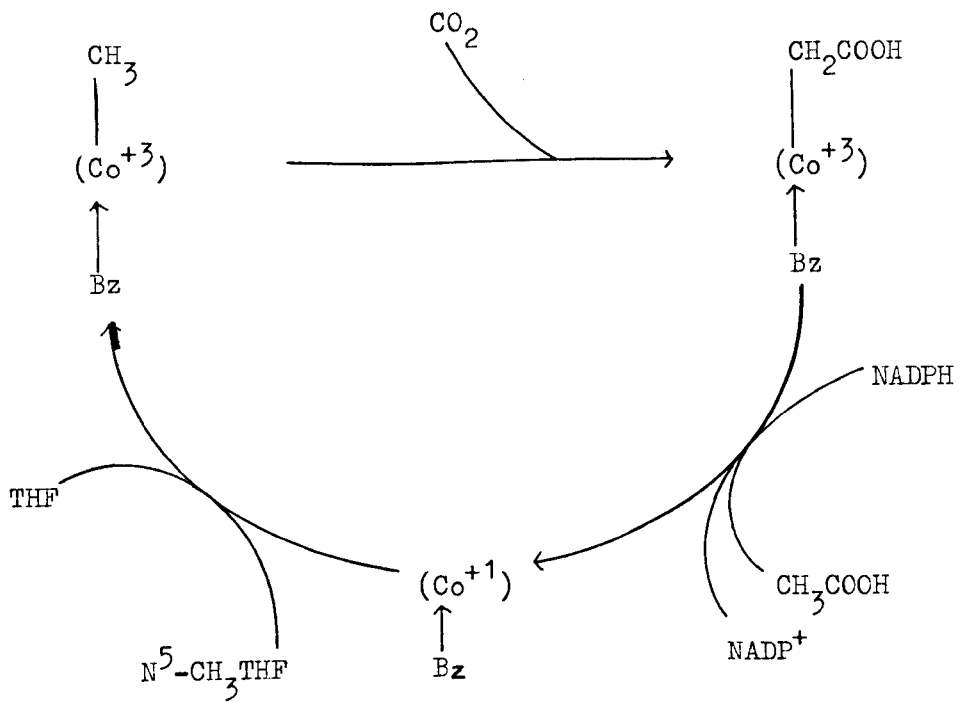
Ethanolamine ammonia lyase



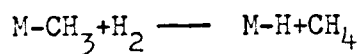
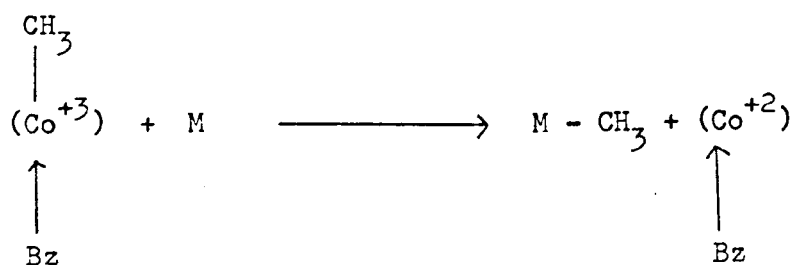
L-β-lysine mutase

SCHEME III

Methionine Synthetase



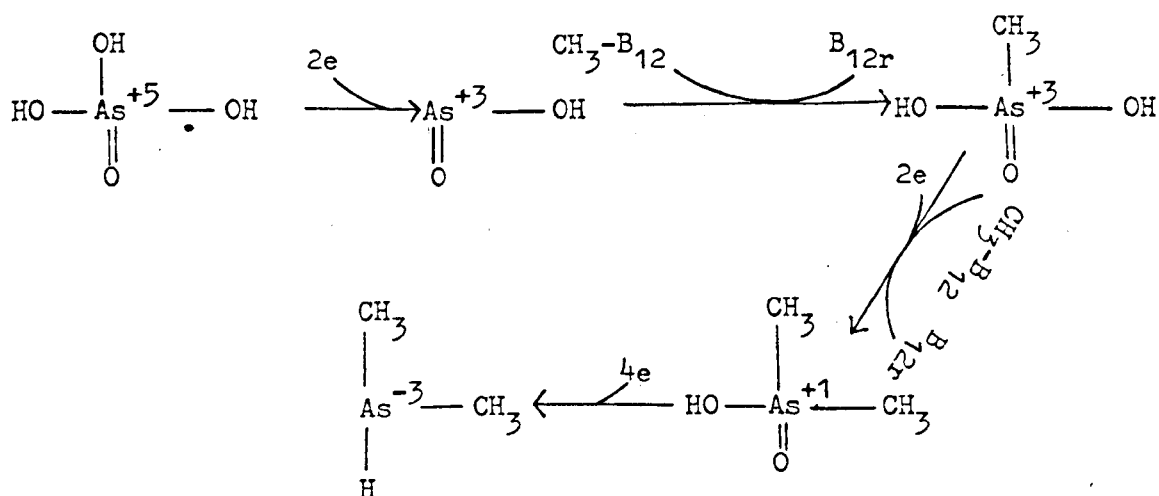
Acetate Synthetase

SCHEME III contd.

Methane Synthetase

Bz = Benzimidazole, THF = Tetrahydrofolate

NADPH = Nicotinamide adenine dinucleotide, reduced form.

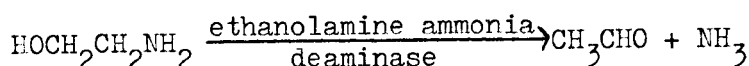
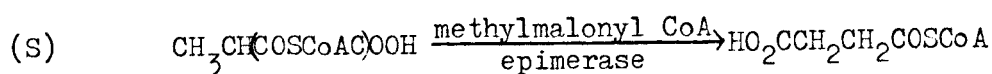
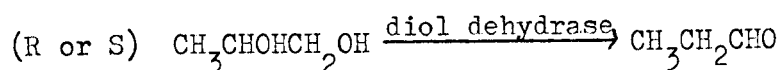


Synthesis of dimethylarsine from arsenate and methyl cobalamin.

Furthermore, it has not been possible, so far, to find analogies in conventional organic chemistry for most of the reactions catalysed by the cobalamins. These reactions are essentially of two types:-

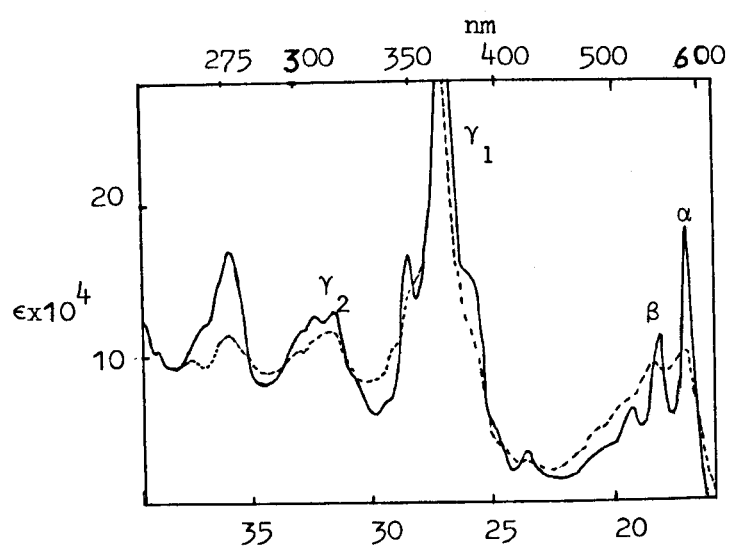
- (a) the 'rearrangement reactions';
- (b) the 'synthetic reactions'.

All the reactions in the first category are catalysed by coenzyme B₁₂. All, but one, can be described by a general scheme (scheme I) in which a hydrogen atom exchanges with a group attached to an adjacent carbon atom. Examples of this type of reaction are:-



The exception mentioned above is the ribonucleotide reductase system. How this reaction differs from the others in this group will be discussed later. In the synthetic reactions, vitamin B₁₂ activated as methyl cobalamin, functions as the catalyst. These reactions involve transfer of the cobalt-bound methyl group to other metal ions, such as Hg(II) ¹³ and As(III) ¹⁴, and synthesis of methane ¹⁵, acetic acid ¹⁶ and methionine ¹⁷. These reactions are summarised in schemes II and III.

The unique feature in all these reactions is the cobalt-carbon σ -bond. Cleavage of this bond is an important step and, hence, the factors that influence this are also important. The strength of

FIGURE III

Absorption spectra of dicyanocobinamide in ethanol at -180° (—) and in water at room temperature (----), pH7 (cf. ref. 23).

this bond will be determined by its electronic environment which, in turn, is influenced by the other ligands attached to the cobalt ion. Spectroscopic studies have been an invaluable aid to an understanding of the factors that influence this cobalt-carbon bond. It was observed that the absorption spectra of all corrins, whether they are naturally occurring - with or without the metal ion - or synthetic^{18,19}, bear a striking resemblance to each other. The reason for this similarity is that the spectral absorptions arise mainly from the corrin chromophore^{20,21,22} (Fig.III). Another important observation was the similarity between corrin spectra and typical metalloporphyrin spectra²³. In the visible region the two spectra are of equal intensity, whilst in the ultraviolet, the porphyrin spectra are about ten times more intense than the corrin spectra.

There are three important bands in the corrin spectra which provide considerable information about the corrins. Of these, the α -band (≈ 550 nm) is the most important for it is directly related to the net charge on the metal²³. Hence, the position of this band is determined by both the oxidation state of the cobalt ion and the nature of the axial ligands. This is well illustrated by the observed movement of this band from the red for Co(I) to the blue for Co(II) complexes. The influence of the axial ligands is demonstrated by its movement from ≈ 600 nm for the ligand pair CH_3^- , CN^- to just above 450 nm for the single bond 'base off' system with the CH_3^- ligand^{21b}. The positions of the γ -(≈ 370 nm) and β -bands (≈ 550 nm) indicate the degree of covalency of the cobalt bond^{24,25}. As this bond becomes more covalent, the charge on the corrin nitrogen atoms increases²⁶, and these bands move to longer wavelengths.

Important electronic effects, namely the cis- and trans-effects²¹, have been observed in the cobalamins. Transmission of electronic effects of the axial ligand along the z-axis and into the plane of the corrin ring, through the cobalt ion, constitute the trans-effect and the cis-effect respectively. Three types of trans-effects are possible²¹:-

(a) ground-state effect in which only the bond-lengths and force constants within the same molecule are affected;

(b) thermodynamic or equilibrium trans-effect, which affects the equilibrium constant between two complexes;

(c) kinetic trans-effect.

As the electron-donating power of the axial ligand increases, this tends to increase the stability of the five-coordinated species with respect to the six-coordinated species. Consequently, an equilibrium between the two is established and this is responsible for the observed temperature-dependency of the corrin absorption spectra²⁷. Increase in the polarisability of one axial ligand causes an increase in the other trans metal-ligand bond length. Evidence for this is provided by the changes in the stretching frequencies of the cyanide ligand. For the free CN^- the stretching frequency has a value of 2079 cm^{-1} . This value for the CN^- in benzimidazole cyanocobalamin is 2132 cm^{-1} , and falls to 2082 cm^{-1} in ethyl cyanocobalamin²¹. Changes in the stability constants of the complexes also reflect the influence of the axial ligand. Similar cis- and trans-effects have also been observed in haemoglobins and iron porphyrins²⁸.

Proton n.m.r. spectra have provided considerable information about cobalamins and have permitted the study of changes in molecular conformation. Alkyl groups attached to cobalt exhibit a high field chemical shift. This may be due to an increased electron density on the alkyl group giving it a carbanion-like character²⁹, or to chromophore anisotropy. The changes in the chemical shifts of the C-1 methyl protons³⁰, and the C-10 proton of the corrin ring, reflect conformational changes in the corrin ring. Ring-current from the benzimidazole group contributes to the shielding of the C-1 methyl protons. This ring current can be influenced by the nature of the axial ligand due to the trans-effect and this in turn would affect the chemical shift of the protons involved. Also, the nature of the axial ligand affects the net charge on the C-10 carbon atom^{31,32}, via the cis-effect and, hence, the chemical shift of the proton attached to it. A linear relationship has been observed between the τ -value of this proton and the position of the γ -band³¹.

Proton n.m.r. study of the cobalamins, however, has cast some doubt on the so-called cis-effects. While changes in the axial ligand seem to influence the π - π^* transitions^{24,33} of the corrin ring, changes in the corrin ring do not seem to influence the chemical shifts of the axial ligands. The electronic spectrum of methyl-10-chlorocobalamin is markedly different from that of the parent methyl cobalamin. The chemical shifts of the methyl groups, on the other hand, are -0.06 δ in methyl cobalamin and -0.01 δ in methyl-10-chlorocobalamin. Thus, it seems that although the electronic environment in the corrin ring has been altered by substitution at C-10, the electron density at the cobalt alkyl has not been significantly changed. Essentially, the changes that

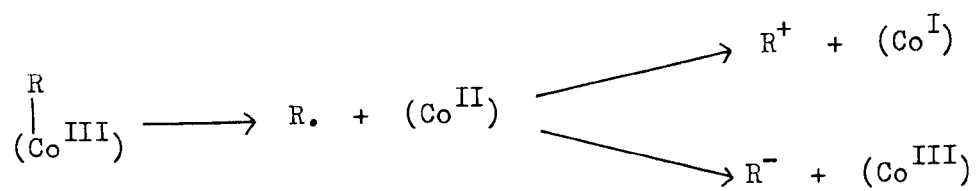
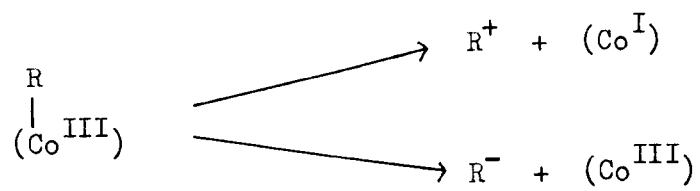
occur in the corrin ring could be of three types³¹:-

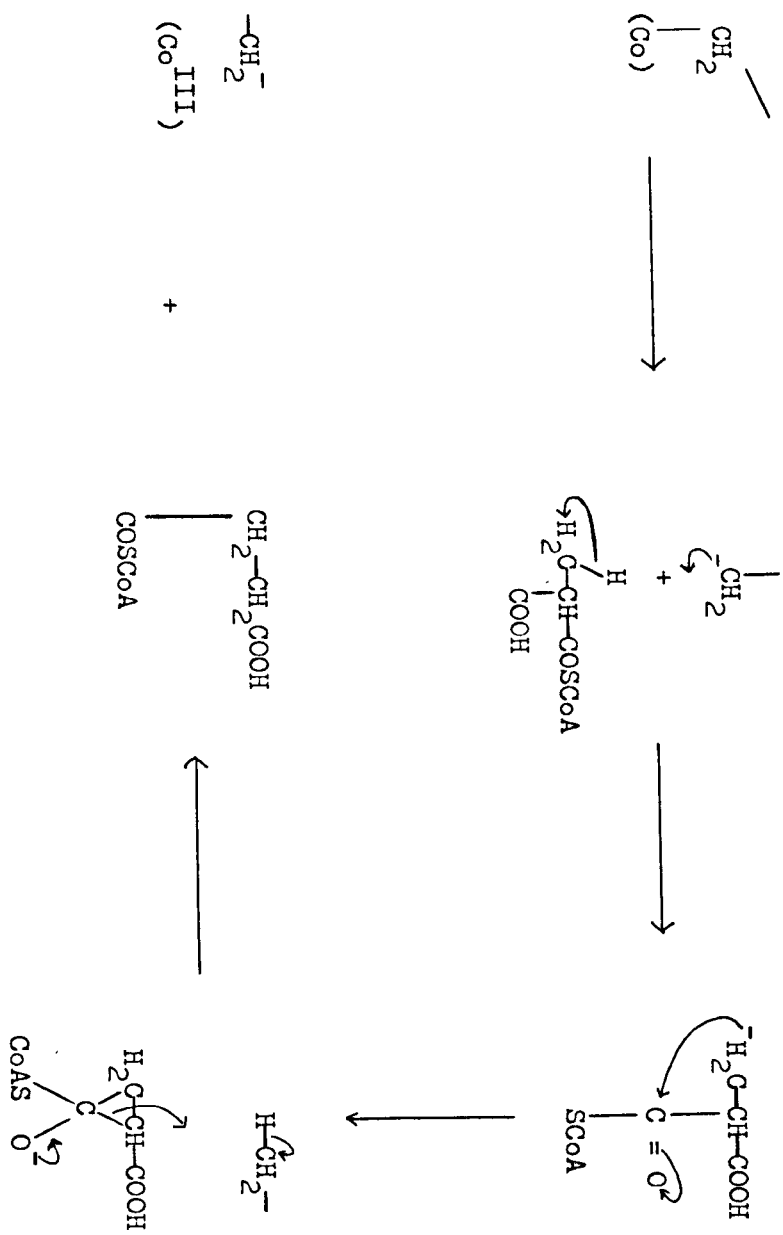
- (a) Changes in the populations of different low-lying vibrational states. These changes cause a movement of intensity from one vibrational component to another, within the same transition.
- (b) Changes in the conformation of the corrin ring.
- (c) Electronic changes.

All these changes are closely interrelated and cannot be separated one from the other. Thus, a conformational change causes a change in the stretching and bending force constants. These, in turn, alter the populations of different vibrational states as well as the electron density and hybridisation at each atom. Furthermore, these changes must involve the cobalt ion and its axial ligands. Hence, it is suggested³⁴ that the so-called cis-effect may actually be due to changes in the conformation of the corrin ring as the axial ligands are varied, rather than a transmission of electronic effects through the metal. Additional evidence for conformational changes caused by varying the axial ligands is provided by the wide variation in the circular dichroism of the cobalamins³¹.

The polarisation of the cobalt-carbon bond, in the B₁₂ coenzymes, will to a large extent determine the manner in which it could undergo fission. This could occur in four ways:-

- (a) Heterolytic scission of the bond with electron-transfer to the C-5'-deoxyadenosyl moiety to give Co(III) species.
- (b) Heterolytic scission with transfer of electrons to cobalt to give Co(I).

SCHEME IV

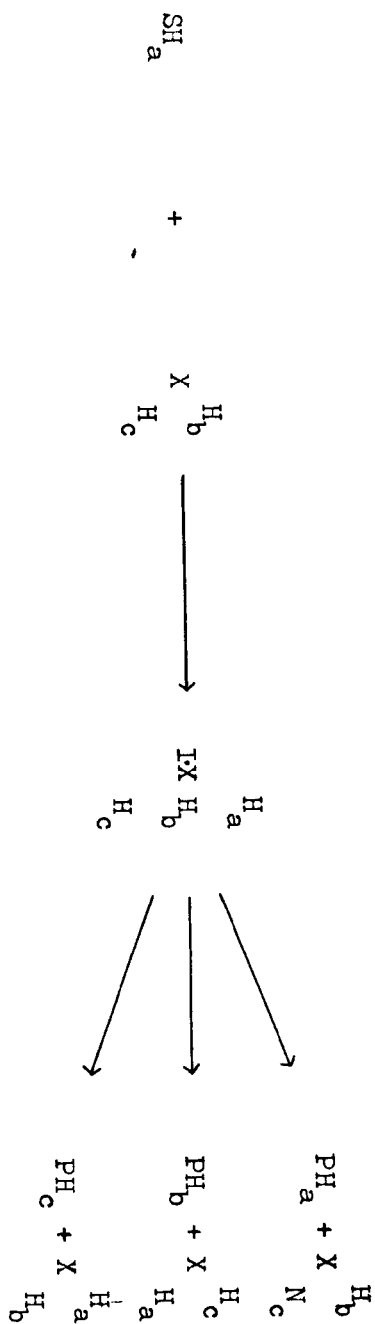


(c) Homolytic scission resulting in Co(II).

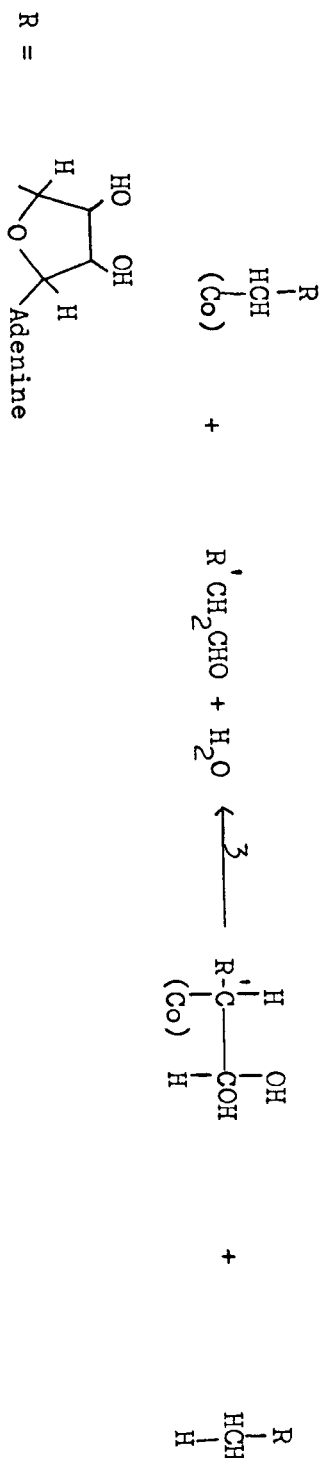
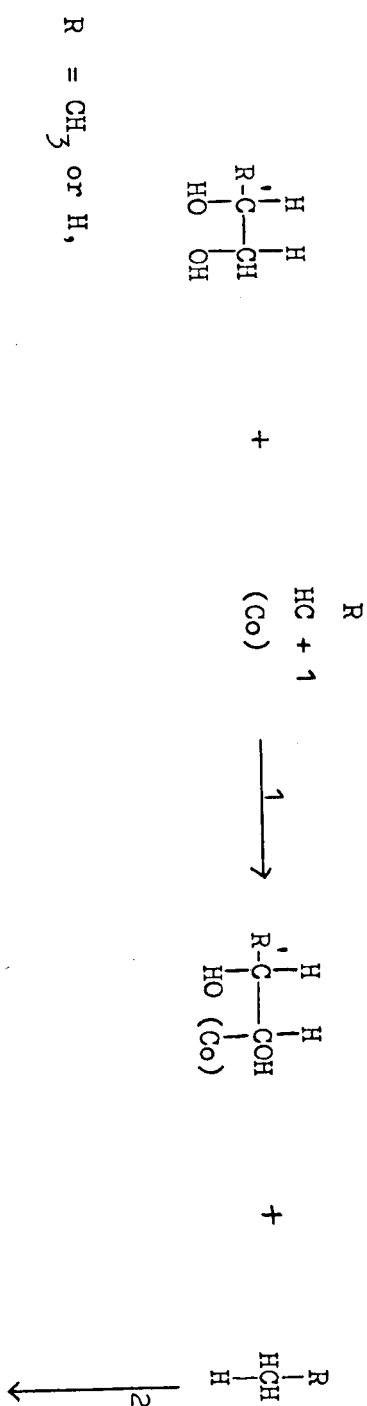
(d) Homolytic scission followed by rapid electron transfer to give either Co(I) or Co(III). (See scheme IV.)

An essential step in all the 'rearrangement reactions' is an intermolecular hydrogen transfer which can only occur after the cobalt-carbon bond has cleaved. A very large number of mechanisms have been proposed for this, centred around one or other of these different cobalt species. An early mechanism proposed for the methyl malonyl CoA mutase system invoked Co(III) and 5'-deoxyadenosyl carbanion ³⁵ (scheme V). This scheme had an analogy in the chemistry of cyclopropanone derivatives³⁶. The proposed 5'-deoxyadenosyl carbanion would require the migrating hydrogen species to be a proton - which is probably precluded by later results. On the basis of experiments on model compounds, a revised version of this scheme has recently been proposed³⁷ (see later). Evidence for a Co(I) intermediate has also been obtained. An e.s.r. signal was observed in the ribonucleotide reductase. However, the rate of appearance of this signal was substantially slower than the hydrogen transfer. Hence, it was concluded that Co(I) was the obligatory intermediate, which was subsequently oxidised to Co(II) ³⁸. N₂O is known to react selectively with Co(I) ³⁹, but not with Co(II) or Co(III) chelates. Consequently, when substantial inhibition of propanediol dehydrase was observed, in the presence of N₂O, this was interpreted in terms of a Co(I) intermediate⁴⁰. It is interesting to note that a similar inhibition was not observed in the case of ribonucleotide reductase. This may corroborate the proposed intermediacy of Co(I) in that reaction. For, if Co(I) is oxidised to Co(II) faster than its reaction with N₂O, then no inhibition due to

SCHEME VI



SCHEME VII

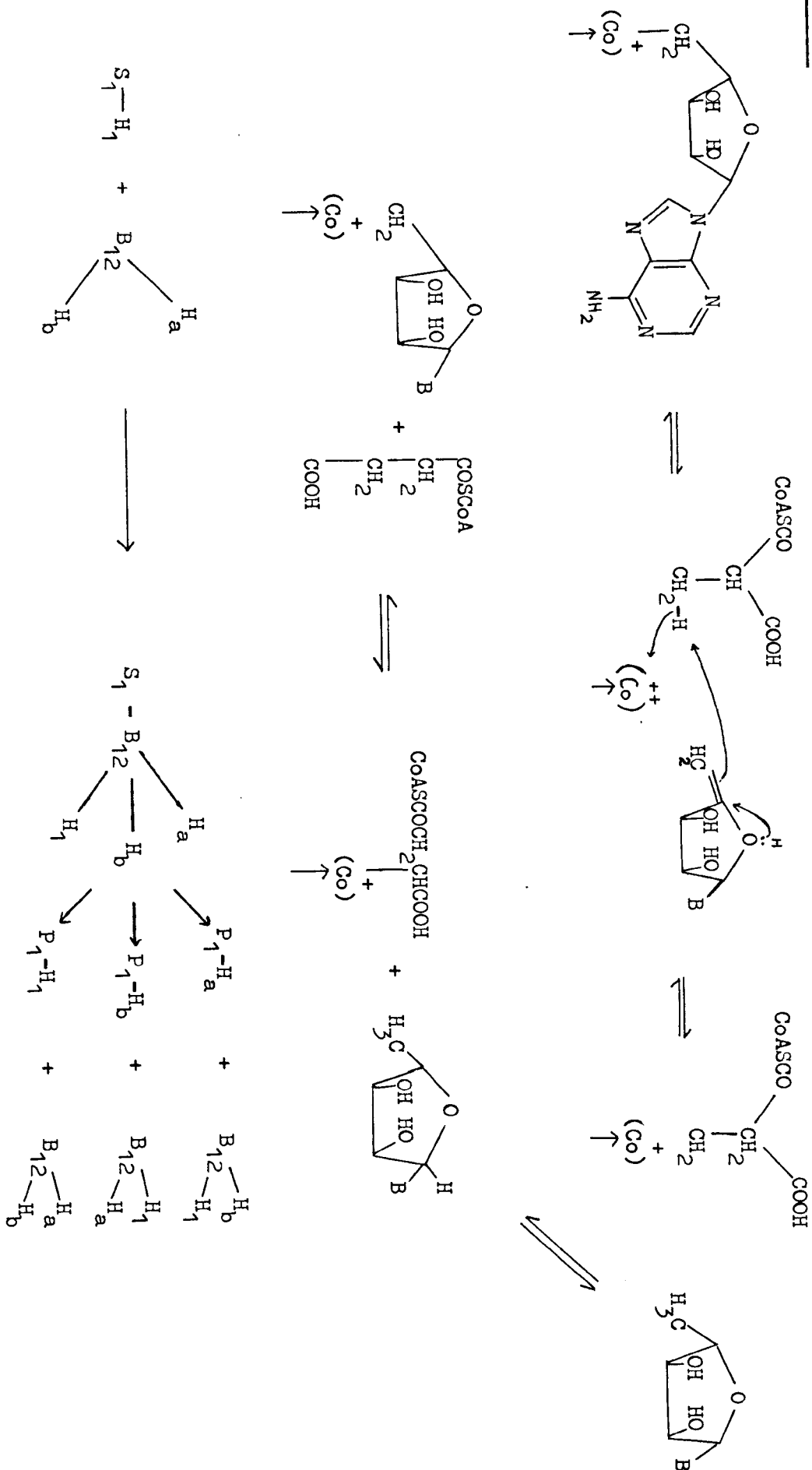


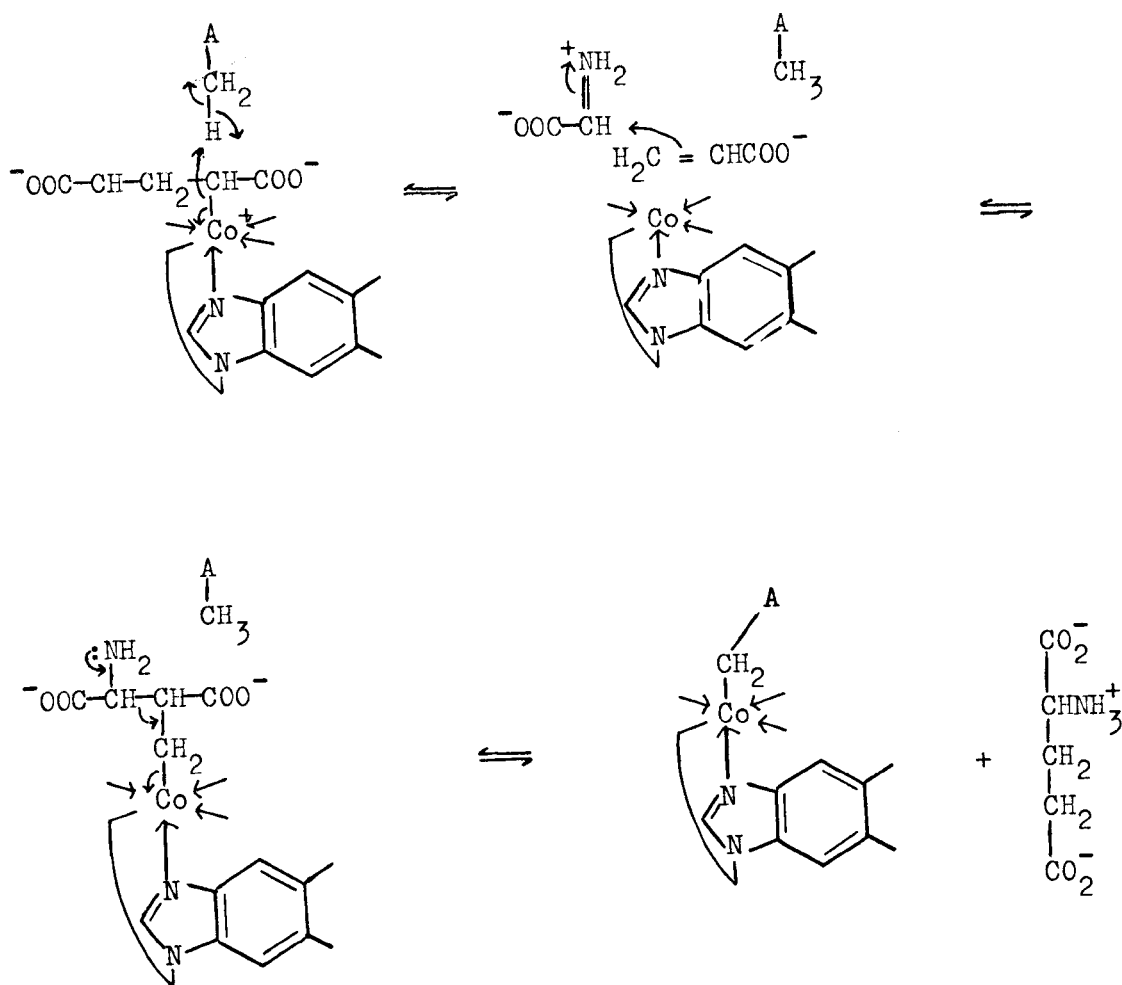
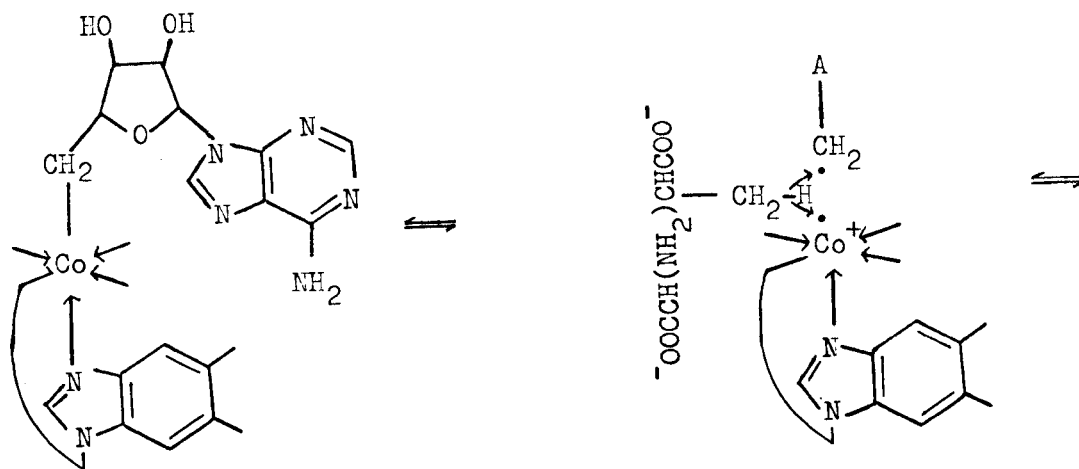
N_2O would be observed. However, considerable other evidence seems to be in favour of a Co(II) species as a key intermediate in general.

Investigation of the coenzyme B_{12} -catalysed dehydration of propane-1,2-diol has produced some very interesting results. Most enzymic reactions are stereospecific for a particular stereoisomer of a substrate⁴¹. The diol-dehydrase, however, utilises both R- and S-propane-1,2-diol with approximately equal ease, although it does distinguish between the two pro-chiral hydrogens at C-1 in the diol. Labelling studies on this system have provided a wealth of information. The use of R- and S-propane-1,2-diols, specifically mono-deuterated at C-1, indicated deuterium transfer to C-2 during the transformation to propionaldehyde, accompanied by a large kinetic isotope effect only with the R-isomer⁴². Inversion of configuration at C-2 during this process was demonstrated by the use of R- and S-propanediols, dideuterated at C-1. The 1,2- 2H_2 -propionaldehyde formed was oxidised to propionic acid, the absolute configuration of which was established by comparison with a synthetic sample of known configuration. When tritiated substrates and coenzymes were used, evidence was obtained for an intermolecular hydrogen transfer via the coenzyme⁴³. ^{18}O -labelled propanediols showed that propane-1,1-diol is an intermediate in the transformation, which is dehydrated stereospecifically^{44,45}. A rigorous kinetic study with labeled substrates and coenzyme has demonstrated the intermediacy of 5'-deoxyadenosine⁴⁶ (scheme VI).

On the basis of all this evidence, a scheme was proposed⁴⁶ which seems to be consistent with all known experimental facts (scheme VII). This mechanism is iso-energetic and it was pointed

SCHEME VIII





out that steps 1 and 3, involving alkyl metal transfer, do not necessarily have to be one-step reactions. It has been observed that when 5'-deoxyinosyl cobalamin is used in the propanediol dehydrase system, some 5'-deoxyinosine is released to the solution⁴⁷. A similar observation had been reported in the case of ethanolamine ammonia lyase system⁴⁸. These observations provide some basis for the proposed intermediacy of 5'-deoxyadenosine in the diol dehydrase system. However, there could be another explanation for the observations made with 5'-deoxyinosyl cobalamin. Cleavage of the cobalt-carbon bond could yield, say, Co(II) and 5'-deoxyinosyl radical. If this radical is weakly held by the enzyme, some of it would be leaked to the solution where it would abstract a hydrogen radical to form 5'-deoxyinosine.

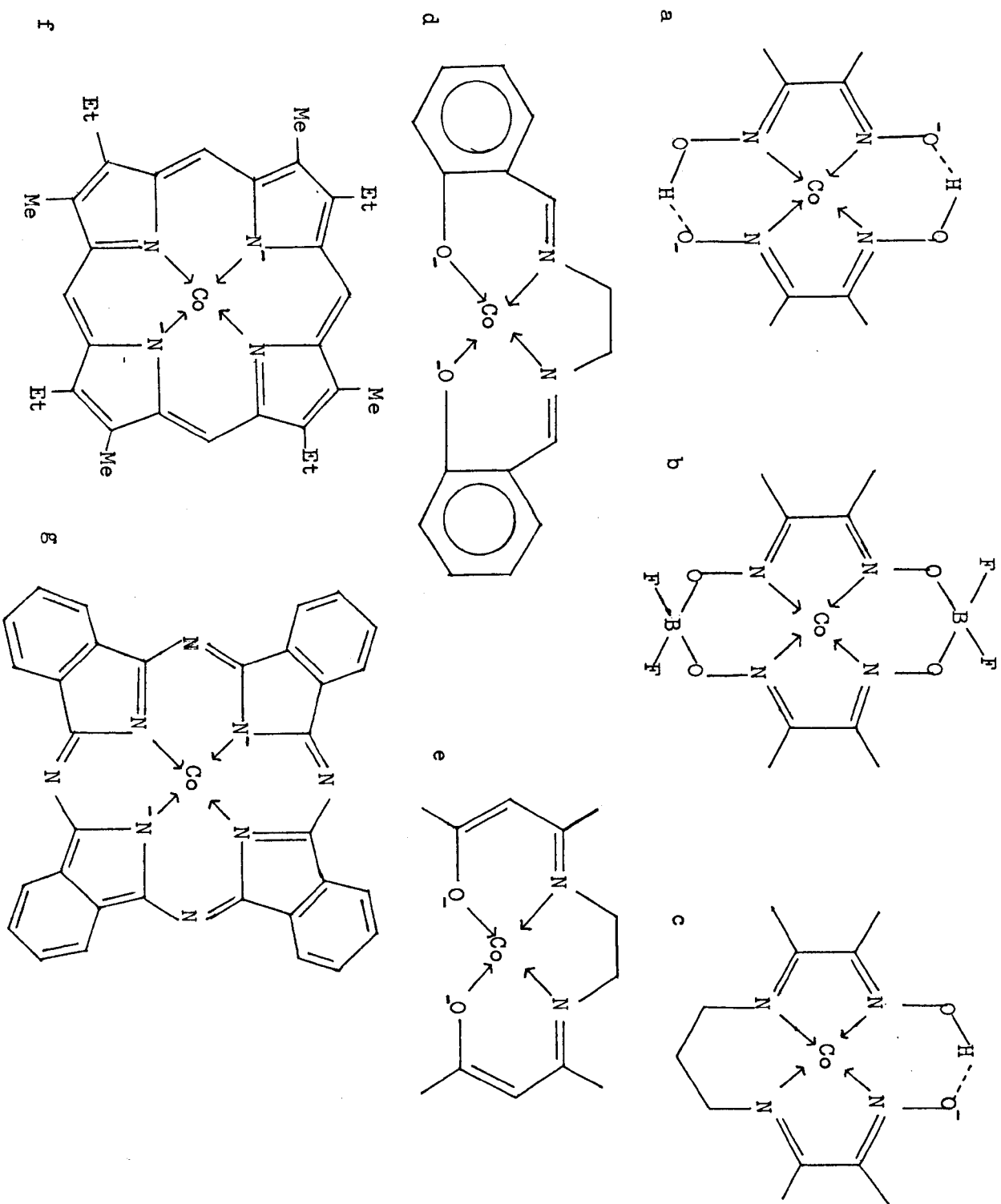
The observations made in the other rearrangement reactions are similar to those in the diol dehydrase system. The mechanistic scheme proposed for the diol-dehydrase, in which 5'-deoxyadenosine is considered to be the hydrogen carrier⁴⁶, is very similar to that proposed earlier for the methyl malonyl CoA mutase system⁴⁹ (scheme VIII). The essential features of this scheme are hydrogen scrambling in the intermediate 5'-deoxyadenosine and isomerisation in the cobalt-bound substrate. These are also the essential features of the scheme proposed for diol dehydrase. The only difference is the proposed participation of the lone pair on oxygen in scheme VIII. A recent mechanism proposed for the glutamate-mutase system also requires the intermediacy of 5'-deoxyadenosine as the hydrogen carrier. However, this scheme differs from the other two in that the isomerisation occurs through a fragmentation, the different fragments being kept in proximity by the enzyme (scheme IX).

FIGURE IV

Possible model compounds for coenzyme B₁₂

- (a) alkyl**bis**(biacetyldioxime)cobalt(III) complexes
(cobaloximes)
- (b) BF₂-bridged cobaloximes
- (c) cobalt**bis**(biacetylmonooximeimino)-1,3-propane
- (d) cobalt**bis**(salicylaldehyde)-ethylene diimine
- (e) cobalt**bis**(acetylacetone)ethylene diimine
- (f) cobalt phthalocyanin
- (g) Aetioporphyrine(I)cobalt

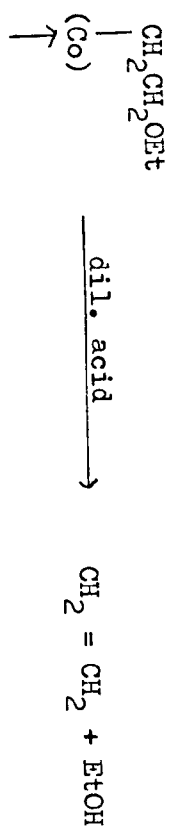
FIGURE IV



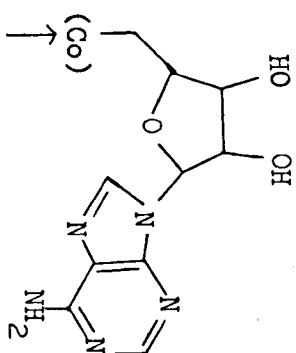
The one exception in these reactions, as mentioned before, is ribonucleotide reductase. In this reaction, extracts from Lactobacillus leichmanii convert ribonucleotides to deoxy ribonucleotides. This reaction differs from the other rearrangement reactions in that exchange with solvent protons, and between free and bound 5'-deoxyadenosyl cobalamin, occurs rapidly during catalysis⁵⁹. Also, retention is observed, in the replacement of a hydrogen group by a hydrogen atom which occurs at the C-2' position of the ribose moiety of the substrate ribonucleotide.

The reactivity of the cobalt-carbon bond is the common denominator in all these reactions. The electronic environment of this bond, and the factors that influence it, have already been discussed. However, the sensitivity of coenzyme B₁₂ to light and chemical reagents, the complexity of its spectra and its cost, limit the amount of work that can be done with it. Consequently, model compounds assume considerable importance if a greater understanding of the cobalamin catalysed reactions is to be achieved. A remark made by R.H. Abeles is worthy of note:- "An enzymatic reaction is not meaningfully defined until it can be related to known non-enzymatic reactions and this cannot yet be done for reactions involving cobalamins. For these reactions, it may well be that the relevant non-enzymatic chemistry has not yet been discovered."⁴⁵. Model compounds can perform this important task of setting up a relevant non-enzymatic chemistry. Any potential cobalamin model would have to possess an equatorial ligand system that is similar to the corrin ring. A number of such model compounds are now known and they are summarised in Figure IV. The various models have their respective advantages and disadvantages. However, the most

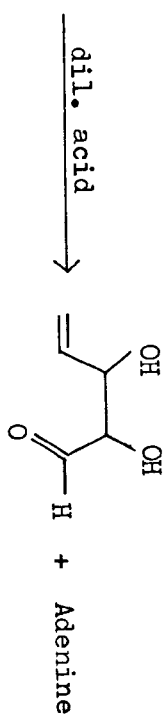
SCHEME XI



(β -Hydroxyethylcobalamin)



(5'-deoxyadenosylcobalamin)



extensively studied model system amongst these has been the bis (biacetyldioximato) complexes of cobalt(III) - 'cobaloximes'. It was found that the reactions of these complexes, more than those of most of the other models, very closely resemble various coenzyme B₁₂ reactions. The nature of the axial bond involving the cobalt atom in cobaloximes was demonstrated to be very similar to that in cobalamins on the basis of extended self-consistent HMO calculations⁵². Also, these were the only models to exhibit some enzymic activity. This statement needs to be qualified. Amongst the various models tried, only methyl cobaloximes were found to substitute for methyl cobalamin in methane synthesis by Methanobacillus omelianskii⁵³. However, this reaction cannot proceed, when methyl cobaloximes are used, unless catalytic amounts of vitamin B_{12r} are present. This indicates that the methyl cobaloximes could be involved in methyl transfer to the cobalamin rather than in the enzymic reaction itself.

The research reported in this thesis evolved from an original scheme for the action of coenzyme B₁₂ (scheme X). The postulated opening of the ribose ring, on protonation, to form the π -complex is supported by the acid catalysed decomposition of 5'-deoxyadenosyl cobalamin to give free adenine and an unsaturated pentose (see scheme XI). The most interesting feature of this scheme is the proposed intermediacy of a π -olefin complex of Co(III). This π -complex has ample analogy in the organometallic chemistry of many transition metals⁵⁴. It is known that β -acetoxy mercurials undergo acid-catalysed decomposition to give ethylenes⁵⁵. A π -olefin complex of Hg(II) for these reactions was proposed as early as 1939⁵⁶. Incontrovertible evidence for the existence of such species as an intermediate in these reactions has only recently been obtained⁵⁷.

This decomposition has similarities to that of β -acetoxyalkyl cobaloximes described in Chapters II and III. It has been suggested that π -complexes formed between metallocenium cations and biological electron donors would be of great use in the study of the structure and function of nucleic acids and proteins⁵⁸. The nature of bonding between oxygen and haemoglobin has long been under discussion. It is important to note, in the context of this thesis, that one of the models considered seriously, involved the oxygen molecule π -complexed to Fe(II) in the haem⁵⁹. The biological activity of ethylene⁶⁰ is quite well established. However, its linkage to various metallo-enzymes is not fully understood. On the basis of empirical rules proposed for ethylene action, and comparison with stability constants of silver-olefin complexes, it has been suggested that ethylene must bind to a metallic receptor site in tissue⁶¹. A π -olefin complex of Co(III) may serve as a model for this system.

As described in Chapters II and III, experiments were originally performed with a view towards obtaining evidence in support of this scheme. However, it has been shown that a carbocyclic analogue of coenzyme B₁₂, in which the ribose ring oxygen is replaced by a methylene group, has about 40 per cent of the activity of the coenzyme⁶². Consequently, the validity of this scheme became rather doubtful. Although this scheme itself may not be valid, according to recent proposals, a cobalt-olefin complex could nevertheless be involved as a key-intermediate. In the schemes VII and VIII, for diol dehydrase and methyl malonyl CoA mutase respectively, step 2 involves isomerisation of the cobalt bound substrate. In the course of this, the cobalt ion migrates from one

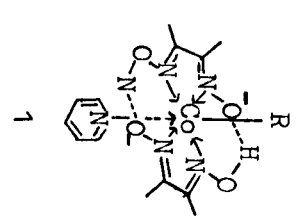
carbon atom to an adjacent carbon atom. This isomerisation is essentially reversible, although the equilibrium favours the product to a certain extent. Hence, this reaction must involve an intermediate in which the probabilities of migration in either direction, to give product or substrate, are similar. This could be achieved by a π -complex of Co(III).

The evidence to be presented in Chapters II and III, rigorously establishes the intermediacy of π -complexes of Co(III), in the solvolytic chemistry of cobaloximes. It is quite probable that such species derived from cobalamins are also capable of existence and are intermediates in the acid catalysed decomposition of β -ethoxy ethyl cobalamin and 5'-deoxyadenosyl cobalamin⁶³ (scheme XI).

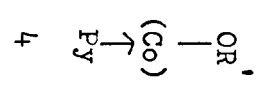
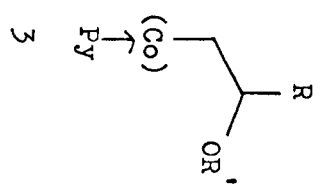
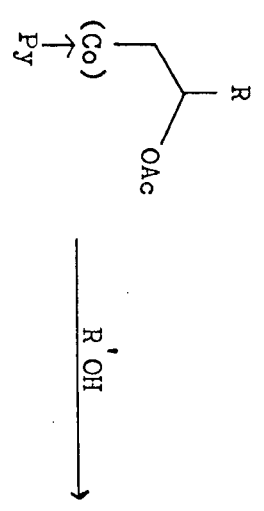
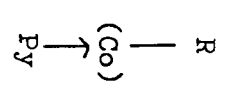
CHAPTER II

Organometallic chemistry provides considerable evidence for the formation of β -carbonium ions, and π -complexes, in the reactions of various transition metal-alkyl systems⁵⁴. The possible involvement of such species in the solvolyses of β -acetoxyalkyl biacetyldioximato complexes of Co(III) was investigated. The rates of solvolyses of various primary toluene-sulphonates are known, and provide an indication of the stability of the respective carbonium ions. It was felt that the tosylate of β -hydroxyethyl cobaloxime (5) would serve a similar purpose. However, all attempts to synthesise this compound failed. During this work, β -acetoxyethylcobaloxime (2a, R = -H), the anticipated product of acetolysis of the elusive tosylate (5), was synthesised by routine acetylation of β -hydroxyethylcobaloxime and found to be remarkably reactive under neutral solvolytic conditions⁶⁴. β -Acetoxy-*n*-propylcobaloxime (2b, R = -CH₃) was analogously prepared and found to be even more reactive than the β -acetoxyethylcobaloxime. The solvolyses of these cobaloximes were found to be, in general, very clean reactions with half-lives of a few hours at 25°C. The solvolytic products, obtained in high yields, have been identified as alcohols from hydrolyses and ethers from alcoholyses. The structures of the products have been confirmed by their spectroscopic properties and in most cases by comparison with samples prepared by independent syntheses. Equation I in scheme XII summarises the

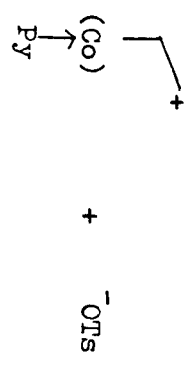
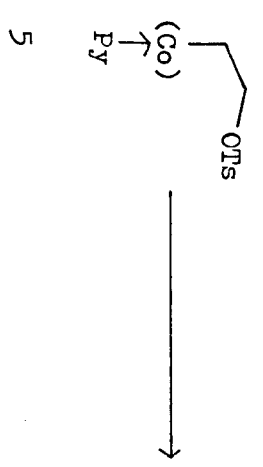
SCHEME XII



≡



a, R = H
b, R = CH₃



I

II

Aliquots were withdrawn at regular intervals, evaporated to dryness and the residue dissolved in CDCl_3 to record ^1H n.m.r. spectra. The percentage of different products in the reaction at the time of each aliquot was calculated from the spectra. Values of $\log_{10} \left(\frac{100}{\% \text{ Rem}} \right)$ were plotted against t (seconds). A straight line for initial reaction (1-2 half lives) was obtained and its slope gave the values of k recorded in the first table. The percentages for des-alkylcobaloximes given in the second table were measured from ^1H n.m.r. spectra after 12 half lives.

Possible errors in k :

- (a) evaporation of aliquots took time;
- (b) errors in measuring integrals for the appropriate peaks ($\pm 5\%$).

Kinetic data for trityl acetate:-

Hydrolysis* in 80% dioxan-water - $t = 25^\circ\text{C}$; $k = 2.1 \times 10^{-4} \text{ sec}$;

$\Delta E^\ddagger = 23.6 \text{ k.cal./mol.}$

Ethanolysis* in absolute ethanol - $t = 25^\circ\text{C}$; $k = 4.17 \times 10^{-3} \text{ sec}^{-1}$.

* C.A. Bunton and A. Konasiewicz: J. Chem. Soc. (1955), 1354.

* C.G. Swain: J. Amer. Chem. Soc. (1955), 77, 3731.

TABLE ISolvolyses of β -acetoxyethyl(pyridine)cobaloximes

Solvent	T °C	k (sec ⁻¹)
dioxan:water (65:35)	25	7.8×10^{-5}
dioxan:water (1:1)	25	8.13×10^{-5}
dioxan:water (1:1)	40	4.73×10^{-4}
CD ₃ OD:CDCl ₃ (2:3)	35.9	8.2×10^{-6}
CD ₃ OD:CDCl ₃ (1:1)	35.9	1.3×10^{-5}
CD ₃ OD:CDCl ₃ (3:2)	35.9	2.78×10^{-5}

% Des-alkylcobaloxime formed under the different conditions

Solvent	T °C	% des-alkyl
dioxan:water (65:35)	25	13.5
dioxan:water (1:1)	25	25.5
dioxan:water (1:1)	40	30.9
CD ₃ OD:CDCl ₃ (2:3)	35.9	15.1
CD ₃ OD:CDCl ₃ (1:1)	35.9	9.4
CD ₃ OD:CDCl ₃ (3:2)	35.9	9.5

TABLE II

Chemical shifts for β -substituted ethylcobaloximes.

Cobaloxime	$\text{C}(1)\text{-H}$	DMG-CH_3	$\text{C}(2)\text{-H}$	$\text{-}\overset{\text{O}}{\parallel}\text{C-CH}_3$	-OCH_3	$\text{-OCH}_2\text{-}$	$\text{-CH}_2\text{-CH}_3$	Pyridine		
								$\alpha\text{-H}$	$\beta\text{-H}$	$\gamma\text{-H}$
$\text{Py-(Co)}-\overset{1}{\text{CH}}_2\overset{2}{\text{CH}}_2\text{OAc}$	8.51 (t)	7.86 (s)	6.29 (t)	8.05 (s)	-	-	-	1.43 (d)	2.65 (d)	2.31 (t)
$\text{Py-(Co)}-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$	8.40 (t)	7.87 (s)	6.87 (t)	-	-	6.62 (q)	8.91 (t)	-	-	-
$\text{Py-(Co)}-\text{CH}_2\text{CH}_2\text{OH}$	8.32 (t)	7.86 (s)	6.96 (t)	-	-	-	-	-	-	-
$\text{PPh}_3\text{-(Co)}-\text{CH}_2\text{CH}_2\text{OAc}$	8.15 (m)	8.15 (d)	6.27 (m)	8.15 (m)	-	-	-	PPh_3 2.65(d)	-	-
$\text{PPh}_3\text{-(Co)}-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$	8.38 (m)	8.17 (d)	6.12 - 5.25(m)	-	-	(6.12)- 6.52(m)	8.8 (t)	2.5 - 2.75(d)	-	-
$\text{PPh}_3\text{-(Co)}-\text{CH}_2\text{CH}_2\text{OH}$	8.18 (m)	8.18 (d)	7.05 (q)	-	-	-	-	2.69 (d)	-	-

reactions discussed in this chapter. The solvolyses follow first order kinetics for disappearance of the acetate (2). Kinetic data obtained are collected in table I.

The β -substituted alkyl cobaloximes have very similar infra-red, ultra-violet and visible spectra. The ^1H n.m.r. spectra, however, are generally first order spectra with well-distinguished peaks which can easily be assigned to the different protons. The various products formed during the solvolyses can also be seen in, and their relative concentrations determined from, these spectra. The progress of the solvolyses of the cobaloximes was therefore most conveniently followed by ^1H n.m.r. spectroscopy. However, the errors involved in such a method of assessment are quite large and, hence, the data presented in table I can only be used for a qualitative discussion of the solvolyses.

A consideration of the ^1H n.m.r. spectra of these cobaloximes is necessary before a discussion of the solvolyses. The chemical shifts of the various protons in these compounds are given in table II. The large singlet at $\approx 7.8\tau$ represents the protons in the four methyl groups attached to the two molecules of biacetyldioxime. The rapid rotation of the alkyl side-chain about the Co-C axis renders the magnetic environment, about each of these methyl groups, equivalent and hence they have the same chemical shift. The $\alpha\text{-CH}_2$ protons appear as a triplet, at $8.3\text{--}8.4\tau$, on account of coupling with the $\beta\text{-CH}_2$ protons. The latter, for the same reason, appear as a triplet. This triplet appears further downfield at $6\text{--}7\tau$. In the β -acetoxyethylcobaloxime these protons are, as expected, furthest downfield at 6.22τ . As the acetoxy group is

successively replaced by ethoxy, methoxy and hydroxy groups, the chemical shift of the β -CH₂ protons increases to 6.96 τ . This triplet, therefore, provides a very useful means of ascertaining the extent of solvolysis at any given time. The rate of decrease of the triplet at 6.22 τ corresponds to the rate at which the β -acetoxyethylcobaloxime disappears in the reaction. This is complemented by the rate of increase of the triplet at 6.87-6.96 τ , which parallels the rate of appearance of the solvolytic product.

A by-product in the solvolyses is free acetic acid. The methyl protons in this have a chemical shift of 7.9 τ ⁶⁵, whilst the acetate methyl protons, of the starting material, are at 8.02 τ . This offers yet another handle on the reaction and, by comparing the relative heights of the two peaks, it is possible to estimate the extent of the reaction.

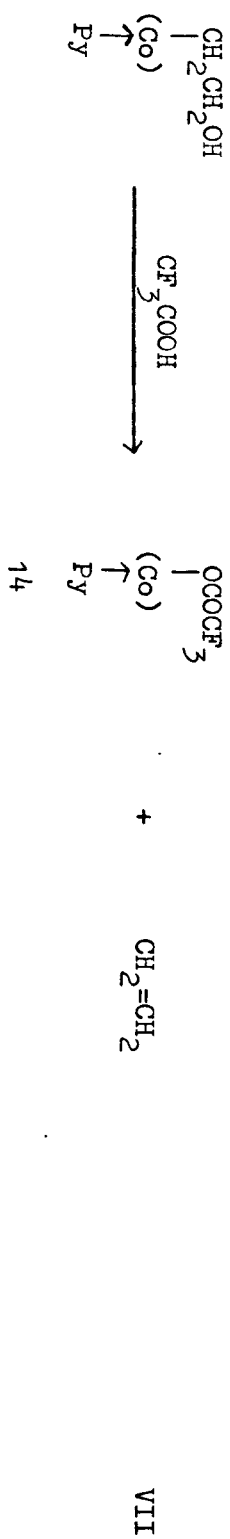
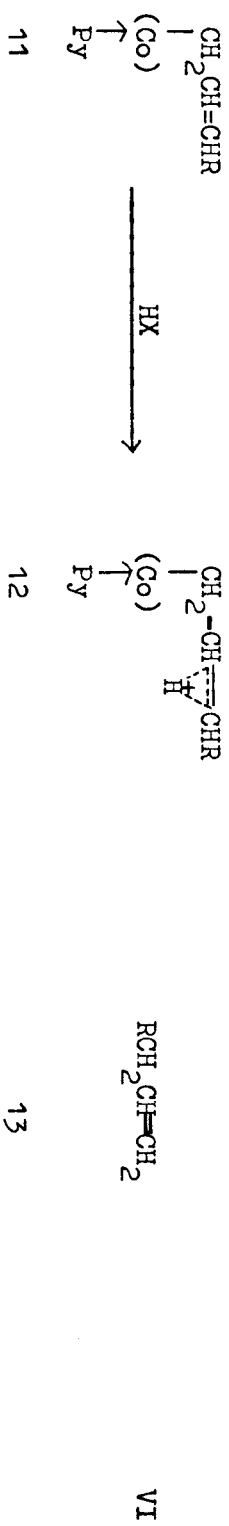
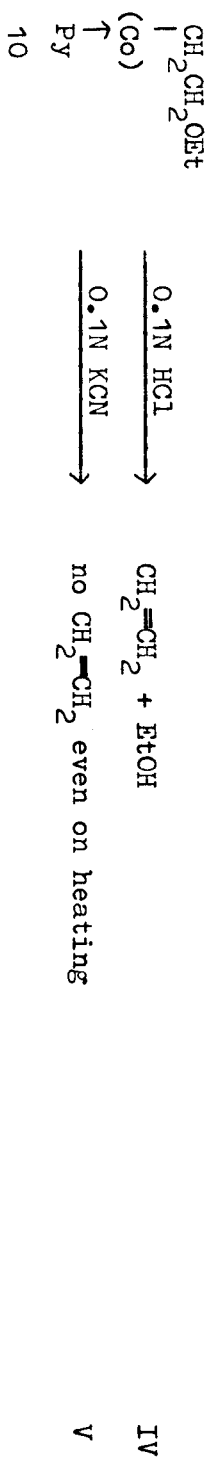
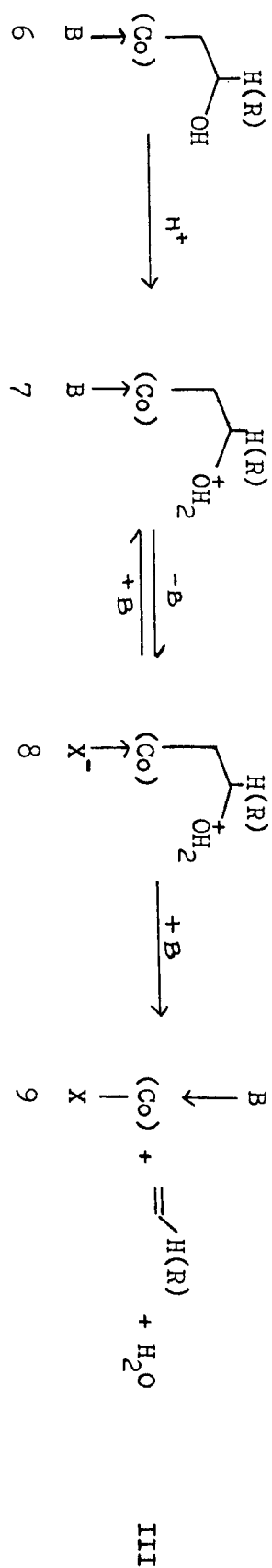
The chemical shifts of the pyridine protons in β -acetoxyethylcobaloxime, and for free pyridine, are also indicated in table II. Comparing these two sets of values, it is apparent that the α -protons on the pyridine are least affected, the γ -protons more and the β -protons the most. This implies that liganding to cobalt has the effect of reducing electron density on the β -carbon atom in the pyridine, far more than on the α - or γ -carbon atoms. This is similar to the situation in nitro-benzene, where the nitro-substituent reduces the electron density at the *m*-position far more than at the *o*- or *p*-positions. In almost all alkylcobaloximes the chemical shifts of the pyridine protons are more or less similar and are not significantly altered when substituents on the trans-alkyl ligand are changed. However, substitution of the Co-C bond

by a Co-O or a Co-X bond (X = halogen) has a profound effect on the pyridine protons and the methyl protons of the biacetyldioxime moiety. Whilst the β - and the γ -protons on the pyridine remain virtually unaltered, the α -protons move upfield to $\approx 1.7 \tau$. In other words, replacement of the alkyl ligand by a more electro-negative ligand apparently has the effect of increasing the electron density at the α -carbon atom of the pyridine. Cobaloximes in which the Co-C bond is replaced by a Co-O or a Co-X (X = halogen) bond will be referred to as des-alkylcobaloximes. In these complexes, the methyl protons of the biacetyldioxime unit are deshielded and appear downfield as a singlet at $\approx 7.5 \tau$. This singlet, and the new pyridine doublet at $\approx 1.7 \tau$, are a measure of the des-alkylcobaloximes formed during the solvolyses. The rate at which they are formed can be computed from the rate of increase of the singlet at $\approx 7.5 \tau$. Thus, n.m.r. spectra recorded during the solvolyses provide the following information simultaneously:

- (a) rate of disappearance of the starting material;
- (b) rate of formation of the solvolytic products; and
- (c) rate of formation of the des-alkylcobaloximes as by-products.

Ethanolysis, methanolysis and hydrolysis of β -acetoxyalkylcobaloximes were studied under different conditions. Depending on these conditions, differing amounts of des-alkylcobaloximes ((4) in scheme XII) are formed. The hydrolysis of β -acetoxyethylcobaloxime was carried out in dioxan-water systems in which the proportion of water was successively increased from 20% to 50%. As the solvent

SCHEME XIII



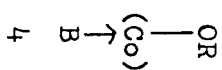
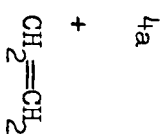
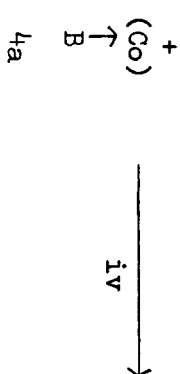
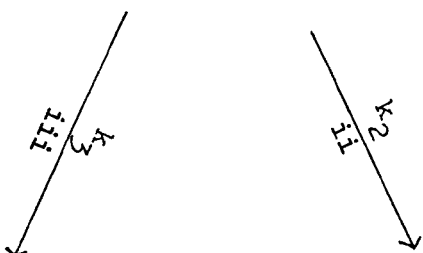
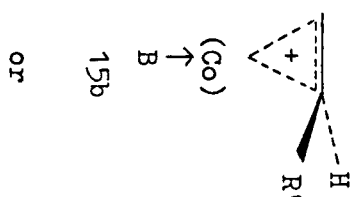
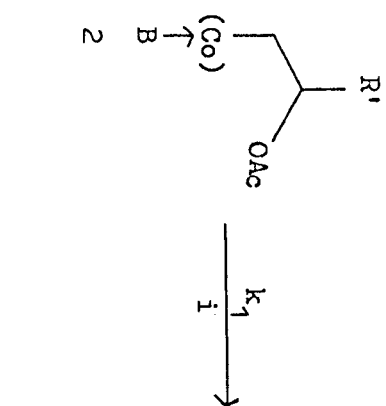
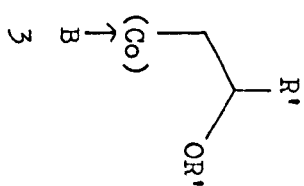
polarity (E_T for H_2O = 63.1; E_T for dioxan = 36.0) ⁶⁶ is increased, the relative amount of the des-alkylcobaloxime was found to increase. Hydrolysis in dioxan containing 35% water results in only about 13% of the des-alkyl product. On the other hand, if the proportion of water is increased to 50%, the yield of des-alkylcobaloxime increases to about 25%. Both of these solvolyses were performed at 25°C. Raising the temperature does not seem to have as much effect as change in solvent polarity. Hydrolysis in dioxan:water (1:1) at 40°C gives about 30% of the by-product as opposed to the 25% reported above. In deuteromethanolyses, the proportion of deuteromethanol in deuteriochloroform was increased from 40% to 50% to 60%, but the amount of des-alkylcobaloxime obtained is only in the region of 10%. Although these figures are only approximate, they indicate a definite variation in the product distribution with a change in the solvolyses conditions. Any mechanism postulated for these solvolyses must offer an explanation for this variation.

It has been suggested that the acid-catalysed decomposition of β -hydroxyethylcobaloxime ⁶⁷ involves trans attack of the acid anion on the initially formed oxo-cation (cf. scheme XIII). Thus, (8) is formed from (7) by base ligand exchange and, according to reaction III in scheme XIII, it is (8) which undergoes decomposition to give (9) and an ethylene molecule. This mechanism is based on the general mechanism for ligand-substitution reactions in octahedral complexes. Such a scheme could be operative in the solvolyses. Reaction III depends on the equilibrium between (7) and (8), and the ease with which the latter can be formed. The formation constants of (8) will therefore be important, and the rate at which it is formed will more or less be the rate at which the

cobaloximes will undergo decomposition. Accordingly, it was reported⁶⁷ that decomposition of β -hydroxyethylcobaloxime in the presence of 0.5M HCIO_4 proceeded at a scarcely perceptible rate. In direct contradiction of this observation, no appreciable difference was seen in the rate of decomposition, as judged from manometric determination of ethylene evolution, whether 0.2M aqueous HCl or HCIO_4 was used as a reagent⁶⁸. Furthermore, if the nucleophilicity of the acid anion is an important factor in this decomposition, as claimed⁶⁷, then no significant reaction should be seen on treatment of β -hydroxyethylcobaloxime with trifluoroacetic acid since it has a weakly nucleophilic counter anion. In fact, when a solution of the former was treated with 1.1 equivalent of the latter, a rapid reaction was observed and after a few minutes extensive ethylene evolution had occurred with formation of a new cobaloxime - trifluoroacetoxycobaloxime, which has been isolated in $\approx 95\%$ yield. It was identified from its spectral properties - the analysis agreeing with the proposed structure ((14) in scheme XIII). The ^1H n.m.r. spectrum was that of a des-alkylcobaloxime (see discussion at the beginning of the chapter). In the infra-red spectrum, the carbonyl absorption was found to be at 1714 cm^{-1} , which is in accord with that observed for other organometallic trifluoroacetates⁶⁹. However, this value is quite different from 1790 cm^{-1} recorded for various organic trifluoroacetates⁷⁰. The low value for the carbonyl stretching frequency of (14) is perhaps analogous to the stabilisation of carbonium ions β to cobalt, which is under discussion here, since it is likely that the carbonyl carbon atom of a trifluoroacetoxy group bears appreciable positive charge.

A further objection to scheme XIII is that it fails utterly

SCHEME XIV



to explain the survival of the alkyl-cobalt moiety in the solvolytic reactions described. The acid catalysed decompositions of β -ethoxyethylcobaloxime (10) and allylcobaloxime (11) have also been suggested to occur via an analogous pathway to that of scheme XIII⁶⁷. It was suggested that (11) is protonated to give a non-classical carbonium ion (12) which is stabilised by the electron-releasing alkyl substituent. This then breaks up to give the alkene (13). These decompositions can be rationalised within the mechanistic framework of the solvolytic chemistry discussed below.

In the case of the solvolytic reactions it is very significant that the major product is the solvolytic product for this indicates that the carbon atom β to the cobalt is the reaction centre. These solvolyses can be either of the S_N1 or S_N2 types. The S_N2 pathway is isoenergetic for a new C-O bond is formed at the same time as another C-O bond is being broken. The transition state could be assisted by the π -system of electrons in the biacetyldioxime unit. The S_N1 pathway involves a slow first step, in which a carbonium ion intermediate is formed, followed by a rapid second step, in which this intermediate is captured by the solvent to give the product. Of the two possibilities, S_N1 and S_N2 , the latter seems much less likely.

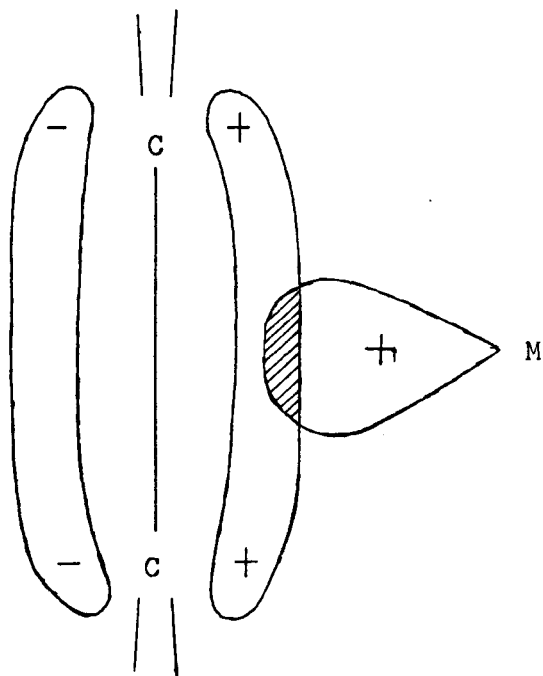
The intermediate in the S_N1 pathway is described above as a simple carbonium ion. There are two other alternatives to this which are shown in scheme XIV. The solvolyses of β -acetoxyalkylcobaloximes are discussed in terms of this scheme. The intermediate (15) is formed in the rate-determining step. This is then either captured by the solvent to give the solvolytic product (3), or

breaks down to give the des-alkylcobaloxime (4).

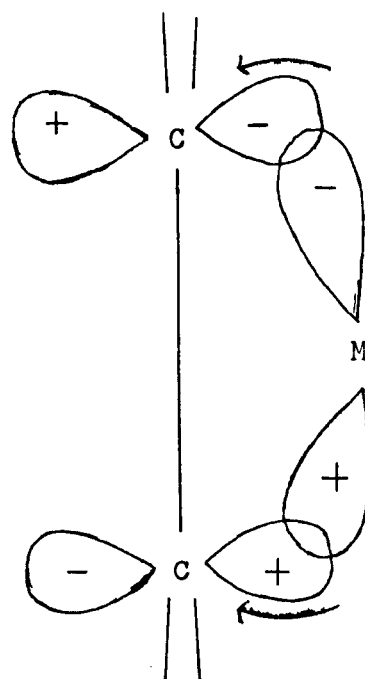
The carbonium ion, species (15a), can be stabilised by interaction with both the transition metal-ion and the equatorial π -system. The stabilisation afforded by the latter could be in terms of electron donation from the π -system of the biacetyldioxime unit. Interaction with the metal ion could involve overlap of the filled d-orbitals of cobalt with the formally vacant p-orbital of the carbonium ion. Stabilisation of a β -carbonium ion, by interaction with a transition metal-ion, is known as the β -effect. The overlap integrals between a 3d orbital of iron and a 2p orbital of carbon were calculated as a function of internuclear distance⁷¹. From this it was deduced that direct interaction between the metal and C- β is possible.

The charged transition state (15c) is stabilised by σ - π hyperconjugation. This does not require changes in the C-C or C-metal bonds or migration of the metal ion towards the electron deficient centre. It has been suggested⁷² that in all such reactions, where a metal-carbon bond enhances the formation of a β -carbonium ion, the major driving force is a carbon-metal σ - π hyperconjugation. This suggestion was made on the basis of a comparison of the Hammett σ_p^+ values of certain metallic groups on the benzene ring as determined by charge-transfer spectra, with σ_p^+ values obtained from reactions - both sets of values agreeing quite closely.

The species (15b) is a novel intermediate olefinic complex. A large number of such olefin complexes of the elements of Groups

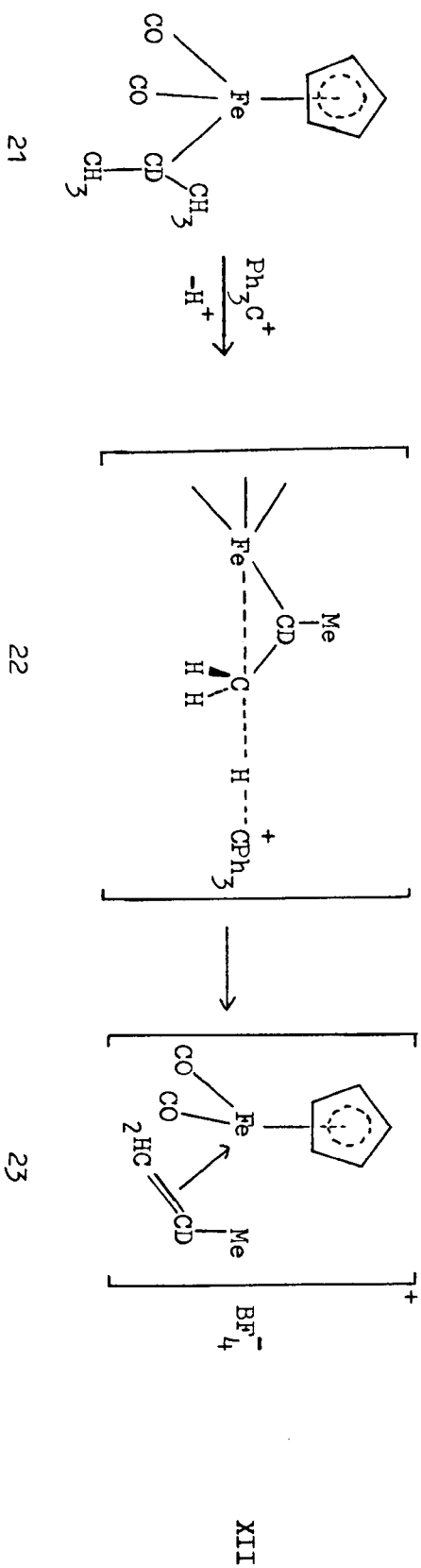
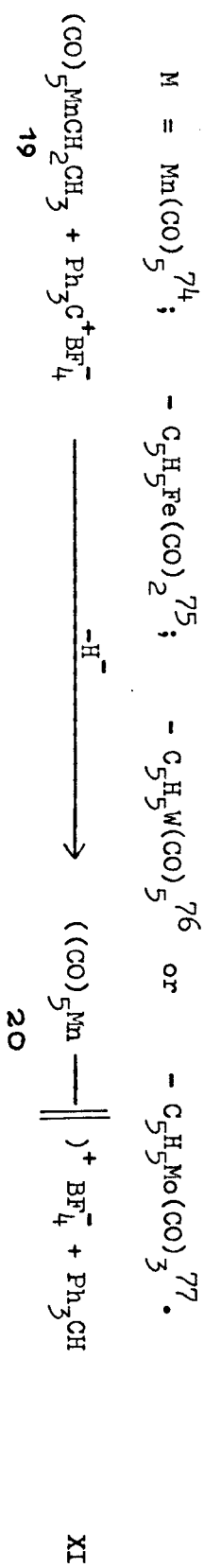
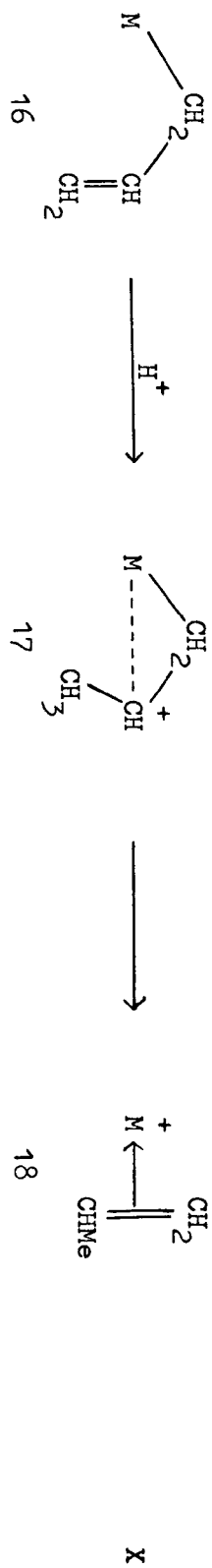
FIGURE V

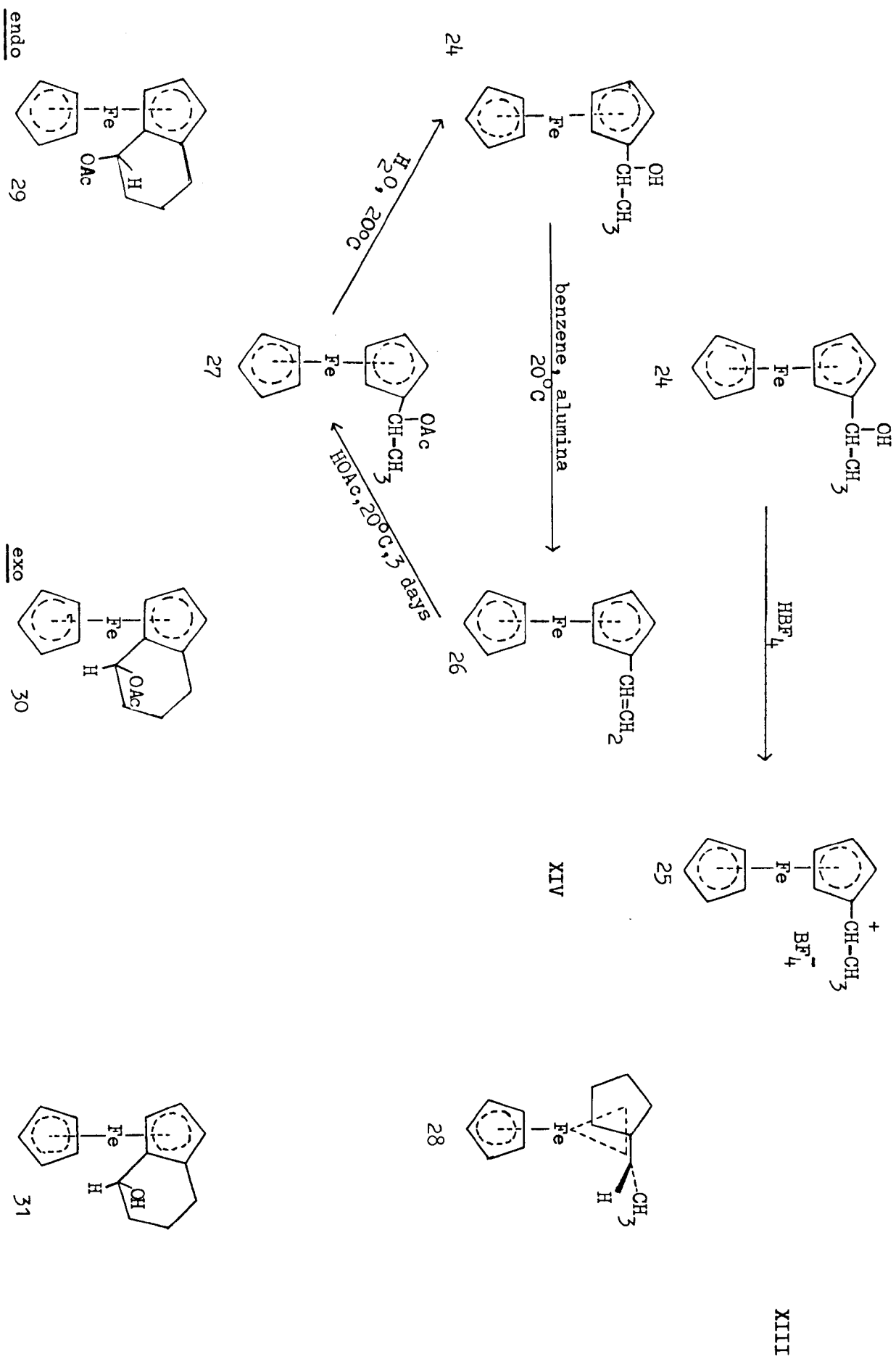
Donation from filled
 π -orbitals to vacant metal
 orbital.



Back bonding from filled
 metal orbital to acceptor
 π^* -orbitals.

SCHEME XV



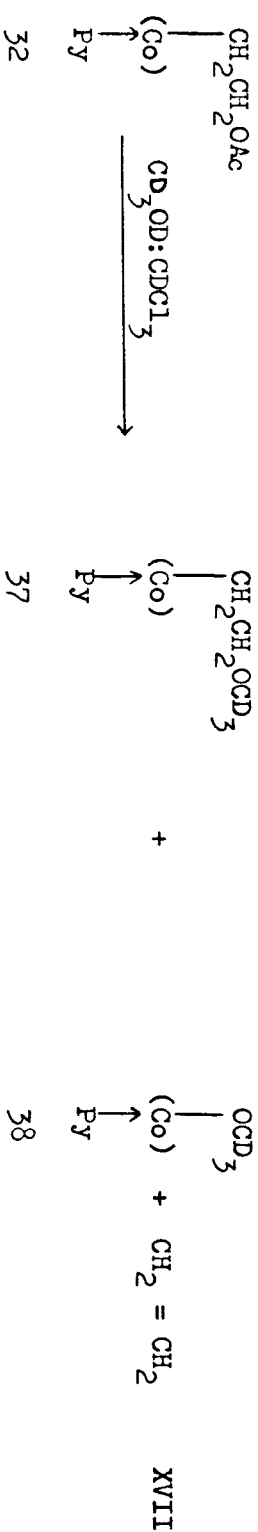
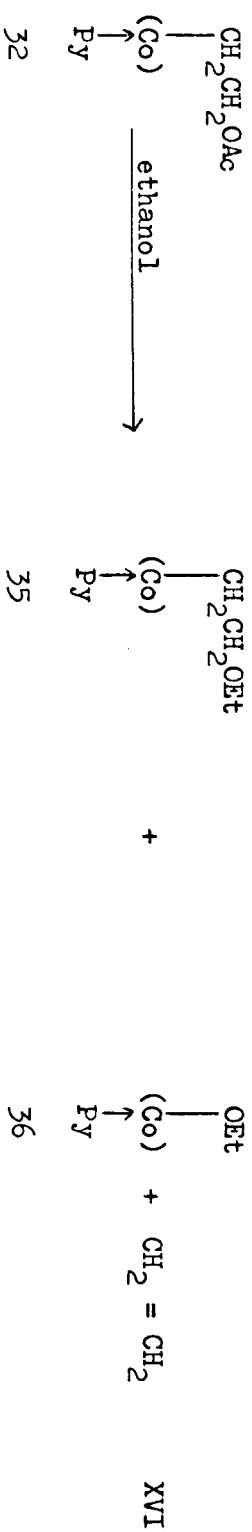
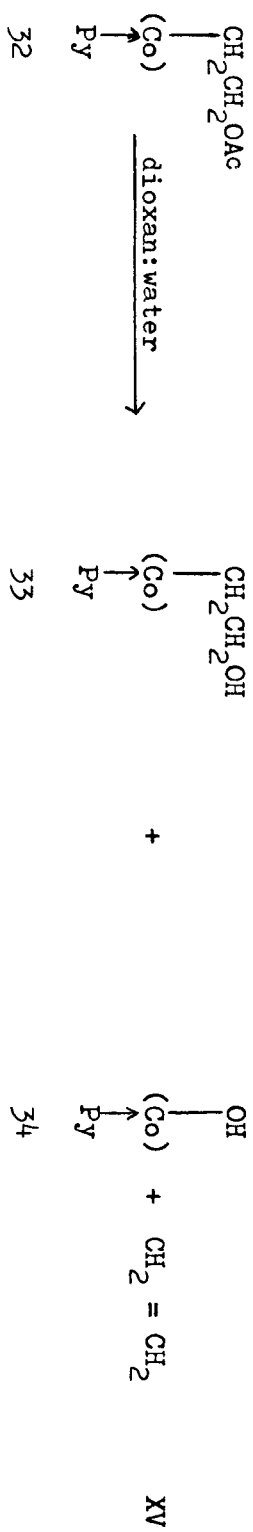


VI-VIII are now well characterised. The bonding in such complexes is generally attributed to interactions between π -electrons in the olefin and hybrid orbitals of the metal. As shown in figure V, this involves overlap of the π -electron density of the olefin with a σ -type acceptor orbital on the metal atom and a 'back bond' resulting from flow of electron density from filled metal d_{xy} or other $d\pi$ - $p\pi$ hybrid orbitals into anti-bonding orbitals on the carbon atoms.

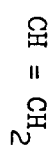
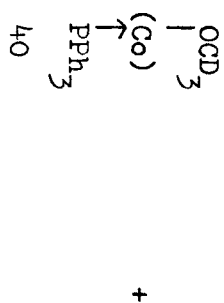
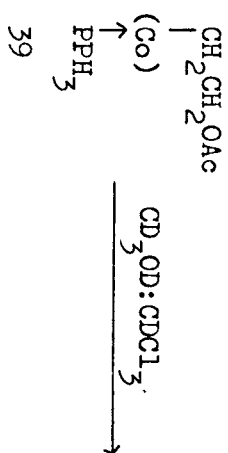
The formation of an olefinic π -complex of cobalt as an intermediate, in the solvolyses of β -acetoxyalkylcobaloximes involves a σ - π rearrangement. Such rearrangements have been observed in several organometallic systems⁷³ and may occur extremely rapidly. A number of unusual protonation reactions of various σ -alkenyl transition metals are known and are indicated in reaction X in scheme XV. Hydride abstraction reactions observed for a number of transition metal-alkyl complexes (alkyl = ethyl, n-propyl or i-propyl) also involve a σ - π rearrangement⁷⁴ (cf. reactions XI and XII). Reaction XII is strong evidence that the hydride ion is abstracted from the β -carbon atom resulting in a carbonium ion, at that carbon atom, which is necessary for the subsequent σ - π rearrangement.

The solvolyses of the acetoxyalkylcobaloximes via an olefinic π -complex have their closest analogy in the solvolyses and other reactions of certain substituted ferrocenes (see later). The similarity with deoxymercurations has already been mentioned (cf. Chapter I). However, in the cobaloxime system the loss of ethylene from the olefinic π -complex is kinetically slower than its capture by solvent. The reverse is generally true of deoxymercurations⁷⁵.

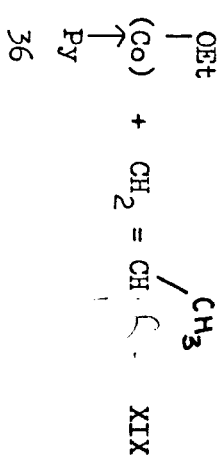
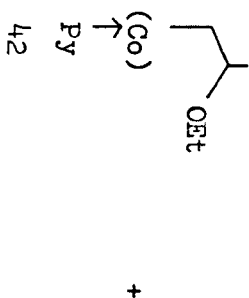
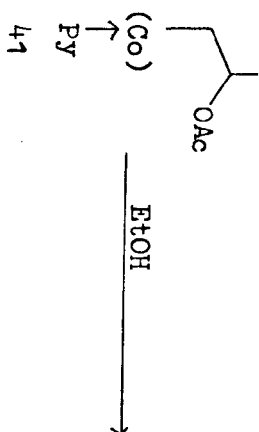
SCHEME XVII



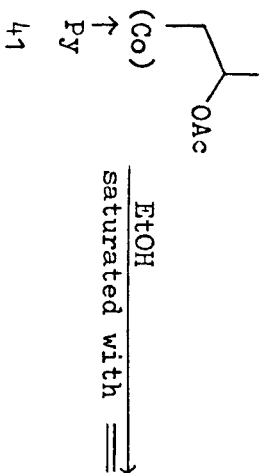
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XVIII

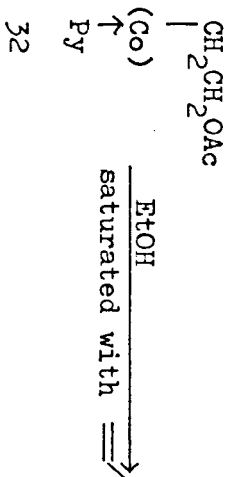


XIX



no crossed products

XX



no crossed products

XXI

Substituted ferrocenes undergo reactions in which carbonium ions in a β -position with respect to the metal play a significant role. Some of these reactions are summarised in scheme XVI. The acid catalysed decomposition of (27) to give (24) is faster than the solvolysis of trityl acetate⁷⁹. The reaction sequence XIII and the solvolyses of (29) and (30) provide substantial evidence for the intermediacy of a π -complex. The dehydration of (24) to (25) is very facile⁸⁰ and under the same conditions no dehydration is observed with β -phenyl ethyl alcohol. (29) and (30) are, respectively, the endo- and exo-isomers. It was observed that the exo reacts faster than the endo by a factor of about 2500 and in both cases the exclusive product is the exo-alcohol (31)⁸¹. Thus, this is evidence that there is a direct interaction of the transition metal with the reaction centre. It has been suggested⁸² that the relative rates of (29) and (30), and the stereospecificity of the solvolyses, can be interpreted in terms of the intermediate (28) - an olefinic π -complex of iron.

The solvolyses discussed in this chapter are shown in scheme XVII. Comment has already been made on the formation of ethers, (35), (37) and (42), as the major product of the reaction. This and the variation in the amounts of des-alkylcobaloxime can be readily explained by the mechanism set out in scheme XIV. The stability of the intermediate (15) determines its relative turnovers in steps (ii) and (iii). The factors that influence the stability of (15) will therefore determine the product distribution. Some of the factors that affect the stability of the intermediate are temperature, solvent polarity and the nature of the trans-ligand. The effect of solvent polarity and temperature on the product

distribution have already been mentioned. As the solvent system becomes more and more polar, its ability to stabilise ionic species increases. In scheme XIV, (4a) is a charged intermediate, while in (15) the positive charge is delocalised at least over three atoms. Consequently, as the solvent polarity increases, (15) may be destabilised in preference to (4a). This increases the turnover of the intermediate in step (iii) relative to step (ii) and higher amounts of the des-alkylcobaloxime are formed. The effect of the trans-ligand will be discussed later. If k_2 and k_3 simply represent the rates at which (3) and (4) are formed, then two possibilities arise:

- (a) $k_2 > k_3$ — in this case (3) will be the major product;
- (b) $k_3 > k_2$ — in this case (4) will be the major product.

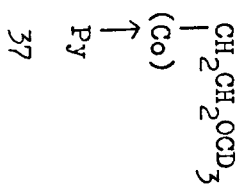
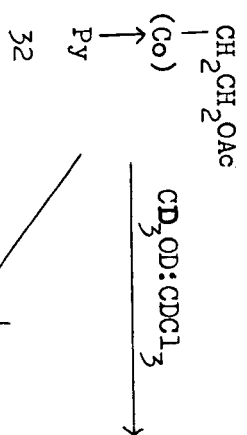
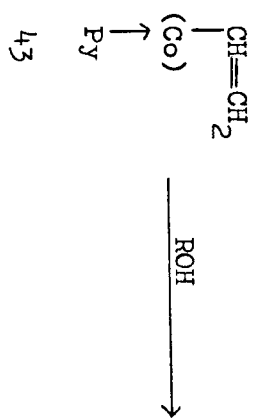
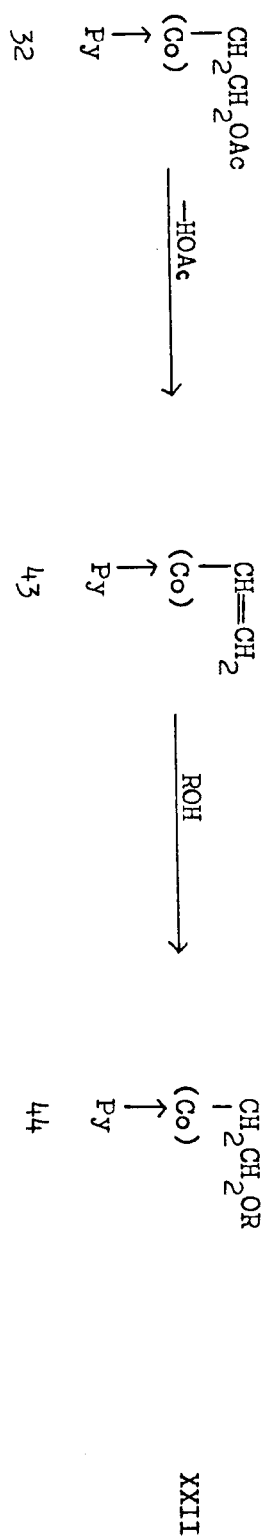
In both cases the first step, the formation of the intermediate, is the slow step. Consequently, the first possibility represents a first order reaction for loss of starting material. This holds for most of the solvolyses studied. The only exception is that shown in reaction XVIII of scheme XVII. Here, the major product is a des-alkylcobaloxime. Ethanolysis of cobaloxime (39) also results in formation of des-alkyl product(s) (e.g. (4b)), only traces if any of the expected solvolytic product being formed. Here $k_3 > k_2$ and the intermediate (15) is destabilised relative to (4a). Perhaps this is due to the greater ability of triphenyl phosphine to stabilise the coordinatively unsaturated species (4a).

It is not possible at this stage to make a distinction among the possibilities (15a), (15b) or (15c). Any one of them can

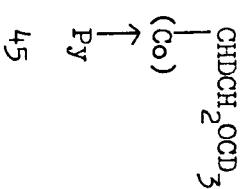
explain the observed results of solvolyses. In the next chapter rigorous evidence will be presented for the intermediacy of (15b). The kinetic data obtained from the ethanolysis of β -acetoxyethylcobaloxime (34) in absolute ethanol at 25°C are : $E_a = 19.9 \pm 1.2$ k. cal. mole⁻¹; $S^\ddagger = -18.2 \pm 4.2$ cal. deg.⁻¹ mole⁻¹; $k = 4.37 \pm 0.06 \times 10^{-6}$ s⁻¹ ⁸³. The large negative value for the entropy of activation suggests that there is a restriction of rotation about the C-C bond in the CH₂-CH₂ unit of the intermediate, whether it is (15a), (15b) or (15c). The acid catalysed decompositions mentioned earlier (cf. scheme XIII) can be better explained in terms of (15) as an intermediate. Protonation of the ethoxyethylcobaloxime (10) or the allylcobaloxime (11) would give rise to intermediates analogous to (15) which then break down to give the observed products. The acid catalysed decomposition of β -hydroxyethyl (pyridine) cobaloxime also follows this pathway. In all these three decompositions the reaction is equilibrium-controlled.

A fragmentation-recombination mechanism would not be inconsistent with the facts mentioned so far. In this case the intermediate would be (4a). This could either be captured by the ethylene and solvent to give the solvolytic product, or it could lose ethylene completely to give the des-alkylcobaloxime. This implies that step (iii) in scheme XIV is reversible. To check this possibility the ethanolysis of β -acetoxyethylcobaloxime (32) in ethanol saturated with propene, and the ethanolysis of β -acetoxy-n-propylcobaloxime (41), were studied. If the fragmentation-recombination mechanism was valid, then in each case crossed products, viz. (42) and (35), should be obtained. No crossed products were seen and in each case only the single expected solvolytic product was formed.

SCHEME XVIII



XVII

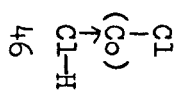
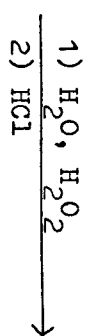
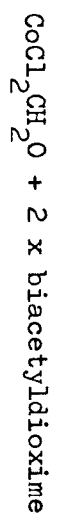


Hence, the fragmentation-recombination mechanism must be ruled out. A corollary of this is that when the intermediate (15) loses ethylene, this loss is irreversible.

There is one other possible pathway by which the solvolyses could occur. This involves the intermediacy of a σ -vinyl cobaloxime as shown in scheme XVIII. The solvent adds across the double bond in (43) to give the solvolytic product. If this is valid, then deuteromethanolysis of β -acetoxyethylcobaloxime should give the product (45). No such product is formed and (37), containing deuterium only in the methoxy group of the side-chain, is obtained. Thus, this mechanism too has to be eliminated.

The possibilities of S_N1 and S_N2 pathways have been mentioned earlier in the chapter. It was also stated that S_N1 was the more likely of the two. This implies that solvolyses of the acetate (2) involve alkyl-oxygen fission. From the hydrolyses alone it is not possible to deduce whether alkyl-oxygen fission or acyl-oxygen fission occurs. However, the fact that ethers are formed from the alcoholyses clearly indicates that acyl-oxygen fission is very unlikely. Direct experimental evidence for an alkyl-oxygen fission can be obtained as follows. Hydrolysis of β -acetoxyethylcobaloxime (32) with H_2O^{18} will give the ^{18}O -labelled β -hydroxyethylcobaloxime if the hydrolysis has occurred via alkyl-oxygen fission. In the case of acyl-oxygen fission, however, no ^{18}O will be incorporated. On treatment with acid, this cobaloxime will undergo decomposition resulting in a des-alkylcobaloxime, ethylene and H_2O^{18} . This ^{18}O -labeled water can be scavenged by dicyclohexylcarbodiimide⁸⁴ to give the N,N' -dicyclohexyl urea, which can be separated from the

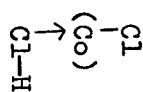
SCHEME XIX



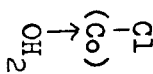
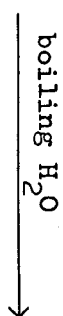
46

(dark green)

XXIII



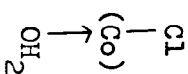
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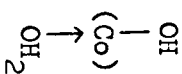
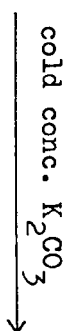
47

(grey green)

XXIV



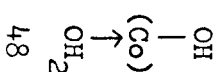
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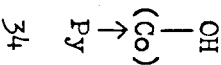
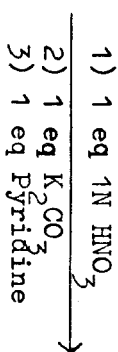
48

(brownish yellow)

XXV



48



34

(brownish red)

XXVI

reaction mixture by chromatography. Analysis of the mass spectrum of this urea would reveal whether the ^{18}O -label was incorporated in it and to what extent. Presence of ^{18}O in the urea would preclude acyl-oxygen fission in the solvolyses of β -acetoxyalkylcobaloximes. A preliminary experiment, along these lines, was attempted using ordinary water for the hydrolysis. A very small amount of a white crystalline substance was isolated from the reaction mixture after treatment with dicyclohexylcarbodiimide. The infra-red spectrum of this was found to be very similar to that of a genuine sample of N,N'-dicyclohexyl urea. Thus, after the conditions have been optimised, this approach should provide evidence in favour of alkyl-oxygen fission.

The formation of des-alkylcobaloximes as by-products in solvolyses, has been discussed earlier in the chapter. It was considered necessary to identify at least one of them by comparison with a sample prepared independently. It was felt that the des-alkylcobaloxime formed in the hydrolyses of β -acetoxyalkylcobaloximes could be hydroxocobaloxime resulting from the capture of (4a) by water. An independent synthesis of this cobaloxime was attempted according to scheme XIX. As shown, this is an extension of a method reported for the preparation of hydroxo-aquocobaloxime⁸⁵. The product so obtained had the same chromatographic and spectroscopic properties as the hydroxocobaloxime isolated from hydrolysis. However, the synthetic product did not give a satisfactory analysis. An attempt was also made to convert the trifluoroacetoxycobaloxime into the hydroxocobaloxime. The former was treated with a variety of bases, such as aqueous hydroxide, benzylamine, etc., but surprisingly, formation of hydroxocobaloxime was not observed. The

inability of the trifluoroacetoxycobaloxime to react with benzylamine further emphasises its dissimilarity with organic trifluoroacetates.

In summary, the conclusions reached from a study of solvolyses of β -acetoxylethylcobaloximes are :

- (a) the solvolyses involve an alkyl-oxygen fission in the acetate;
- (b) a β -carbonium ion — a simple, or non-classical or one stabilised by σ - π hyperconjugation — is involved as an intermediate;
- (c) the solvolyses are most probably S_N1 type of reactions;
- (d) there is restriction of rotation about the C-C bond in the alkyl side-chain of the intermediate;
- (e) these acetates are of similar reactivity to trityl-acetates.

CHAPTER III

The solvolyses of β -acetoxyalkylcobaloximes can be interpreted in terms of the intermediates shown in scheme XIV discussed in Chapter II. In this chapter are described experiments which establish the validity of this scheme to a high degree of certainty. This evidence comes from a study of the reactions shown in scheme XX. Again, as in the case of the solvolyses discussed in the previous chapter, these reactions were followed by ^1H n.m.r. spectroscopy. Additional and equally important evidence for reaction XXVIII came from circular dichroism spectra and measurement of optical rotations. It will be pertinent to begin with a discussion of the ^1H n.m.r. spectra of the cobaloximes (49) - (58).

The chemical shifts of the various protons in these cobaloximes are given in the tables (III) and (IV). Assignments of chemical shifts with the β -acetoxyethylcobaloximes have already been discussed in Chapter II. In table (III) are given the chemical shifts of β -acetoxyethylcobaloximes with different base ligands. The three pyridines used as ligands are 4-dimethylaminopyridine, pyridine and 4-cyanopyridine in decreasing order of their electron-donating power. This variation in electron-donating ability has almost no effect on the chemical shifts of the methyl protons in the

SCHEME XX

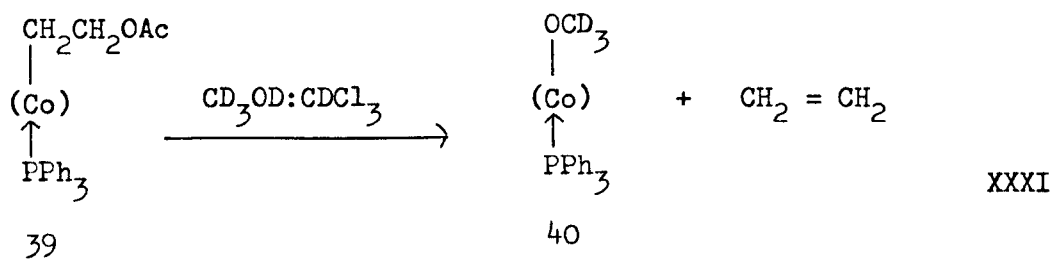
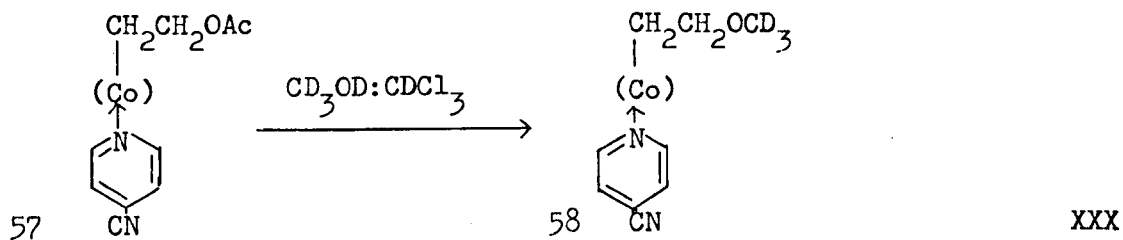
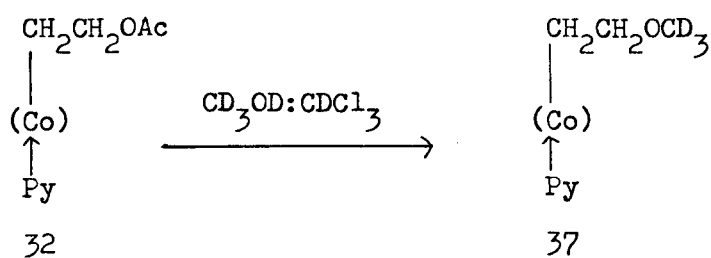
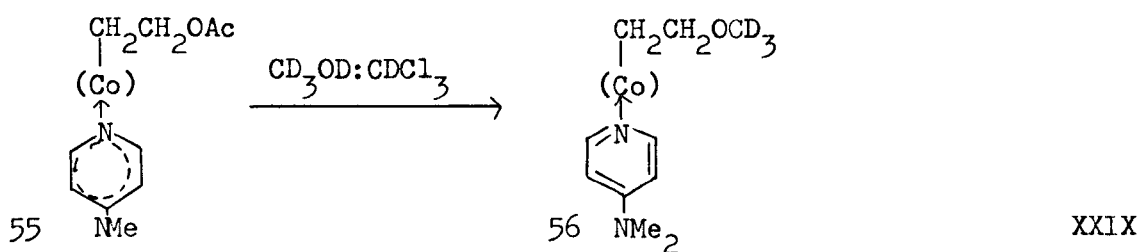
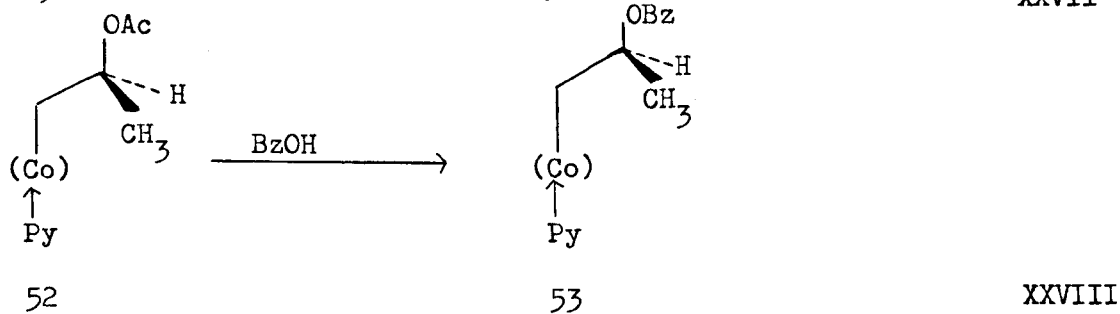
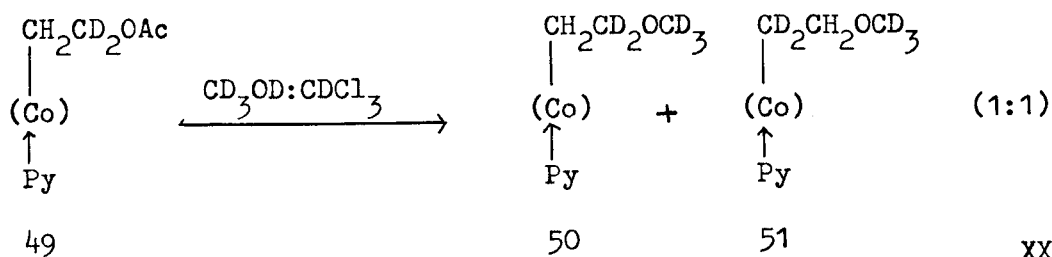


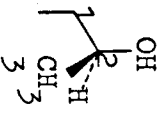
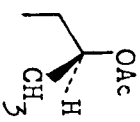
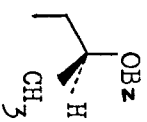
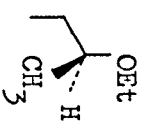
TABLE III

Chemical shifts for the β -substituted ethylcobaloximes.

Cobaloxime	C(1)-H	DMG-CH ₃	C(2)-H	$\text{-}\overset{\text{O}}{\parallel}\text{C-CH}_3$	-OCH_3	$\text{-OCH}_2\text{-}$	N- (CH ₂) ₂	Pyridine		
								α -H	β -H	γ -H
Py — (Co)- ¹ CH ₂ ² CH ₂ OAc	8.51 (t)	7.86 (s)	6.29 (t)	8.05 (s)	-	-	-	1.43 (d)	2.65 (d)	2.31 (t)
Py — (Co)-CH ₂ CH ₂ OCH ₃	8.43 (t)	7.86 (s)	6.93 (t)	-	6.81 (s)	-	-	1.44 (d)	2.71 (d)	2.25 (t)
Py — (Co)-CH ₂ CD ₂ OCD ₃	8.43 (s)	7.86 (s)	-	-	-	-	-	1.44 (d)	2.71 (d)	2.25 (t)
Py — (Co)-CD ₂ CH ₂ OCD ₃	-	7.86 (s)	6.93 (t)	-	-	-	-	1.44 (d)	2.71 (d)	2.25 (t)
(4-CN)-Py — (Co)-CH ₂ CH ₂ OAc	8.43 (t)	7.86 (s)	6.32 (t)	8.06 (s)	-	-	-	1.21 (d)	2.45 (d)	-
(4-CN)-Py — (Co)-CH ₂ CH ₂ OCD ₃	8.35 (t)	7.86 (s)	6.99 (t)	-	-	-	-	1.2 (d)	2.41 (d)	-
(4-NMe ₂)-Py — (Co)-CH ₂ CH ₂ OAc	8.61 (t)	7.86 (s)	6.24 (t)	-	-	-	7.01 (s)	1.94 (d)	3.57 (d)	-
(4-NMe ₂)-Py — (Co)-CH ₂ CH ₂ OCD ₃	8.58 (t)	7.90 (s)	7.02 (t)	-	-	-	7.02 (s)	2.03 (d)	3.12 (d)	-

TABLE IV

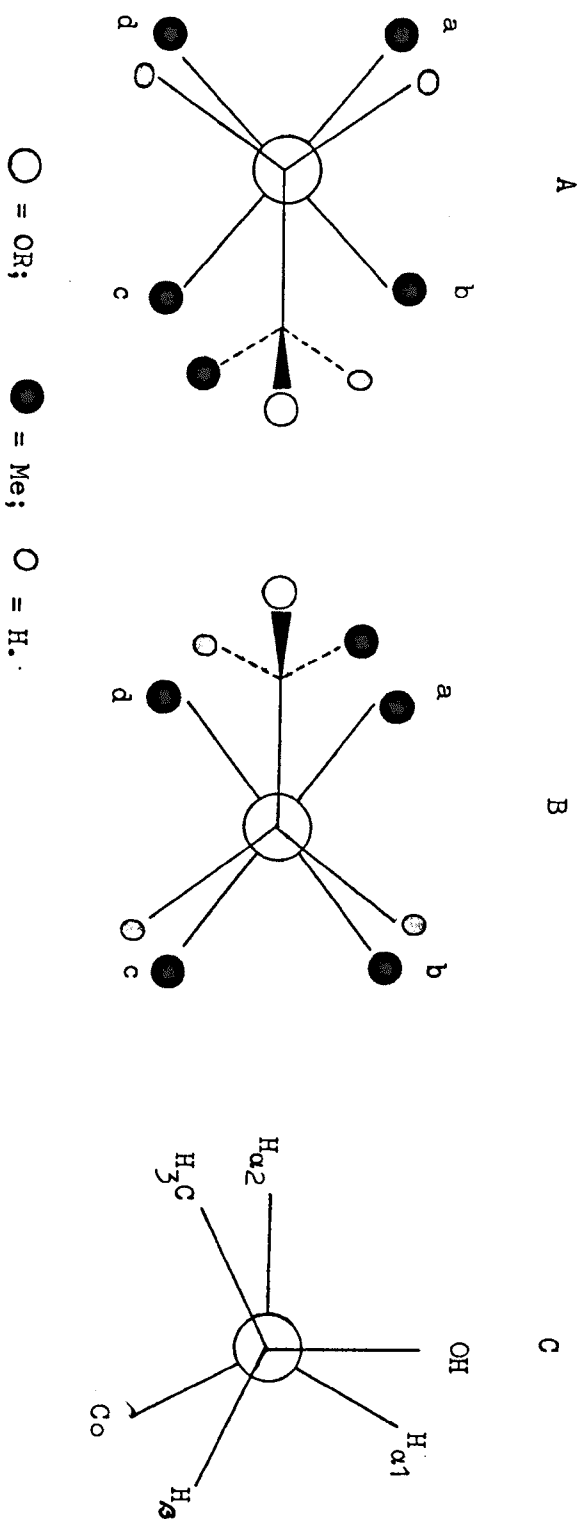
Chemical shifts for the protons in β -substituted propyl(pyridine)cobaloximes.

Cobaloxime	C(1)-H	DMG-CH ₃	C(2)-H	C(3)-H	$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{CH}_3 \end{array}$	$\begin{array}{c} -\text{OCH}_2 \\ \\ 2 \end{array}$	$\begin{array}{c} -\text{CH}_2- \\ \\ \text{CH}_3 \end{array}$	Pyridine		
								α -H	β -H	γ -H
(S) - 	8.82(t) 7.86(d)	7.86(s)	6.79(m)	8.95 (d)	-	-	-	1.41(d)	2.63 (t)	2.21 (t)
(S) - 	8.43(t) 8.88(d)	7.84(d)	5.9 (m)	8.88 (d)	7.96 (s)	-	-	1.36(d)	2.63 (t)	2.2(t)
(S) - 	8.67(t) 7.99(d)	7.99(d)	7.0(m)	8.83 (d)	-	5.7(s)	$\begin{array}{c} \text{-Ph} \\ \\ 2.79 \\ \text{(s)} \end{array}$	1.5(d)	2.78 (t)	2.35 (t)
(RS) - 	8.73(t) 8.99(d)	7.88(s)	7.13 (m)	8.99 (d)	-	6.22 (q)	8.92 (t)	1.39 (d)	2.66 (t)	2.23 (t)

biacetyldioxime units. However, the values for the chemical shifts of the α -methylene protons decrease in the order: (4-dimethylamino pyridine)cobaloxime > (pyridine)cobaloxime > (4-cyanopyridine)cobaloxime. This is the expected order, for on account of the trans-effect the electron-density at the α -carbon atom is directly related to the electron-donating power of the trans-ligand. The chemical shifts of the β -CH₂ protons are also in the same order, although the variation in the actual values is less. This is also to be expected, as the inductive effect, responsible for the trans-effect, diminishes rapidly with distance. As noted in the previous chapter, the chemical shifts of the β -CH₂ protons in the product of an alcoholysis are well distinguished from those in the starting material.

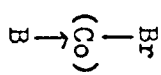
The ¹H n.m.r. spectra of the β -substituted propylcobaloximes are not wholly first order. On comparing these spectra with those of the β -substituted ethylcobaloximes several similarities and dissimilarities become obvious. Protons in similar environments in the two types of cobaloximes show similar chemical shifts. Thus the α , β and γ -protons of the pyridine ligand occur in the same region of the spectrum: between 1.3 and 2.8 τ . The methyl protons of the units of biacetyldioxime also have similar τ -values: 7.8 - 8.0 τ . Here the similarity ends. Although the pyridine protons have chemical shifts in the same range, their actual values show small but definite differences. The positions of the α -protons decrease in the order (53) > (32) > (54) > (52); the β -protons: (53) > (32) > (54) > (52); the γ -protons: (53) > (32) > (54) > (52). All the pyridine protons in (54) and (52) are more deshielded than in (53) or (32). Hence it is not only the trans-effect which is

FIGURE VI



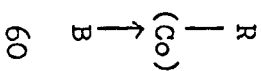
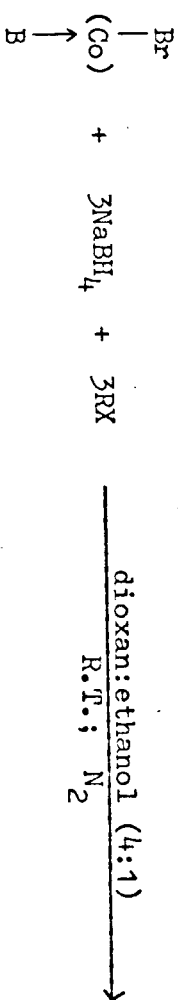
responsible for the electron-density at the pyridine carbon atoms. The observed differences may be due to slight deviations from planarity of the bis (biacetyldioximato) system consequent of the nature of the σ -alkyl group. The biacetyldioxime methyl protons of the β -substituted propyl cobaloximes are not equivalent, for they are seen as a doublet as opposed to the singlet observed in the case of the β -substituted ethyl cobaloximes. In the former case the β -carbon atom is chiral. As the σ -alkyl group rapidly rotates about the Co-C bond, over the biacetyldioxime moiety, it differentiates among the four methyl groups. Figure VI shows a Newman projection looking down the Co-C bond. When the alkyl side-chain is orientated as shown in (A), then the magnetic environment of the methyls (b) and (c) is clearly non-equivalent. The side-chain rotates through 180° to give (B). Here too, the magnetic environment of two methyls, in this case (a) and (d), is different. However, as seen from the figure, by virtue of this rotation (a) and (c) can experience the same environment. Similarly, (b) and (d) become identical. This is true for any position occupied by the alkyl side-chain as it rotates about the Co-C bond and the C(1)-C(2) bond. Thus, on account of the chiral β -carbon atom in the side-chain, and rapid rotations of this side-chain, there are two diastereotopic pairs of diagonal methyl groups which must give rise to a doublet as observed. For similar reasons, a doublet for the biacetyldioxime methyls was observed in the case of alkyl cobaloximes with chiral phosphines as ligands⁸⁶.

The 2 α -CH₂ protons of β -substituted propyl cobaloximes are also diastereotopic and usually exhibit different chemical shifts. They are coupled in different ways to the adjacent β -H. While H α_2 couples with H β and with H α_1 , to give a triplet between 8.4 to 8.8 τ



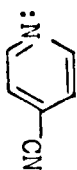
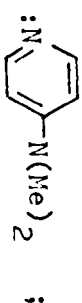
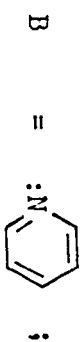
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XXXII



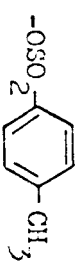
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XXXIII



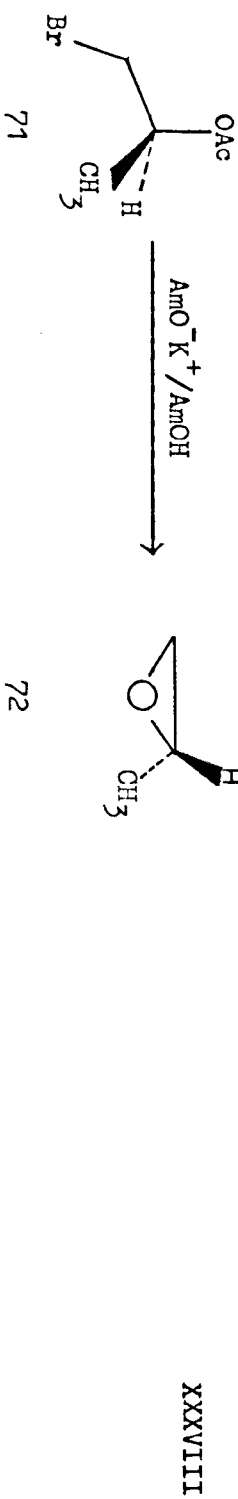
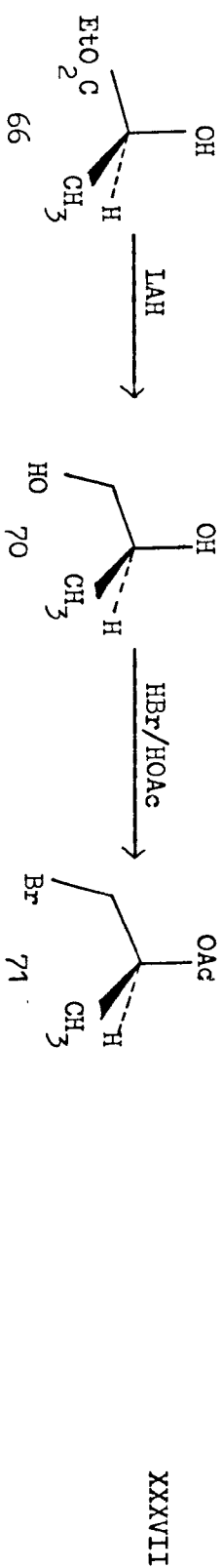
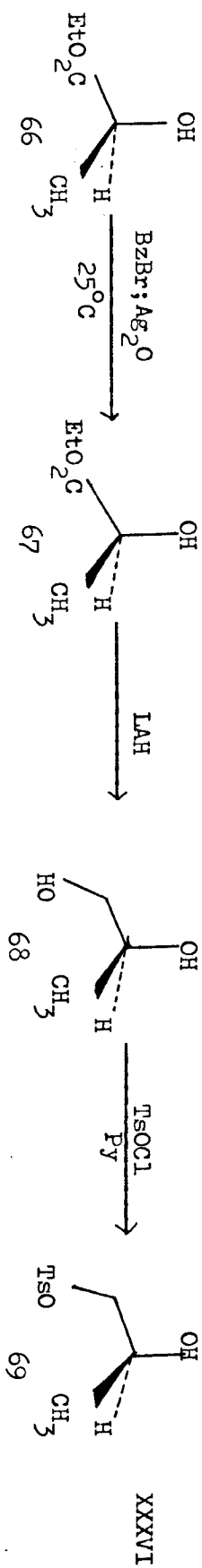
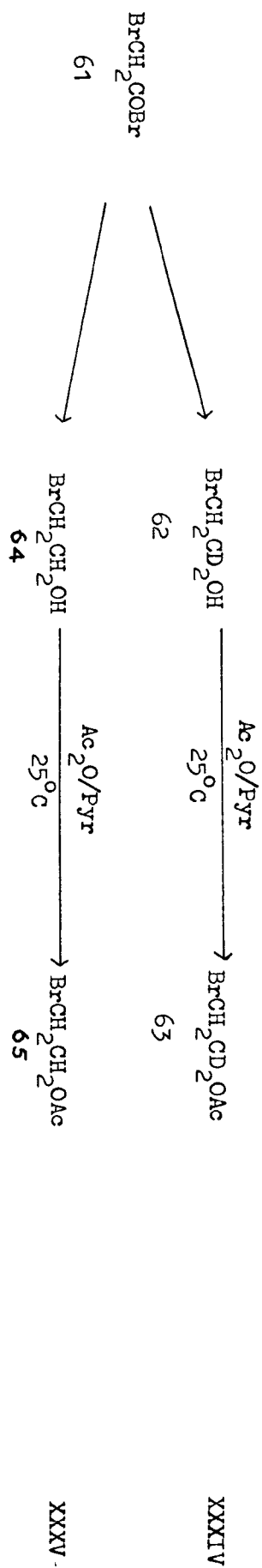
DMG = biacetyldioxime

X = -Br ;



($J = 8\text{Hz}$), H_{α_1} couples only with H_{α_2} and is seen as a doublet. In the case of (53) and (54) this doublet coincides with the doublet of the biacetyldioxime methyl protons. These observations indicate that the alkyl side-chain prefers a conformation shown in figure VI C in which the dihedral angles between H_{α_1} and H_{β} , and H_{α_2} and H_{β} , have the values $\approx 90^\circ$ and $\approx 150^\circ$ respectively. The corresponding coupling constants calculated using the Karplus equation are $J \approx 0$ ($\theta = 90^\circ$) and $J \approx 7$ ($\theta = 150^\circ$), which agree well with the observed values. The C-2 methyl group appears as a simple doublet on account of coupling with $\beta\text{-H}$. The latter is coupled both to H_{α_2} and the C-2 methyl and hence appears as approximately a pentuplet between 6-7 τ . This interpretation of the ^1H n.m.r. spectra is based on spin-decoupling experiments and a study of spectra recorded at various temperatures⁸⁷. Irradiation of the $\beta\text{-H}$ causes the $\alpha\text{-CH}_2$ and $\beta\text{-CH}_3$ peaks to collapse into doublets and a singlet respectively.

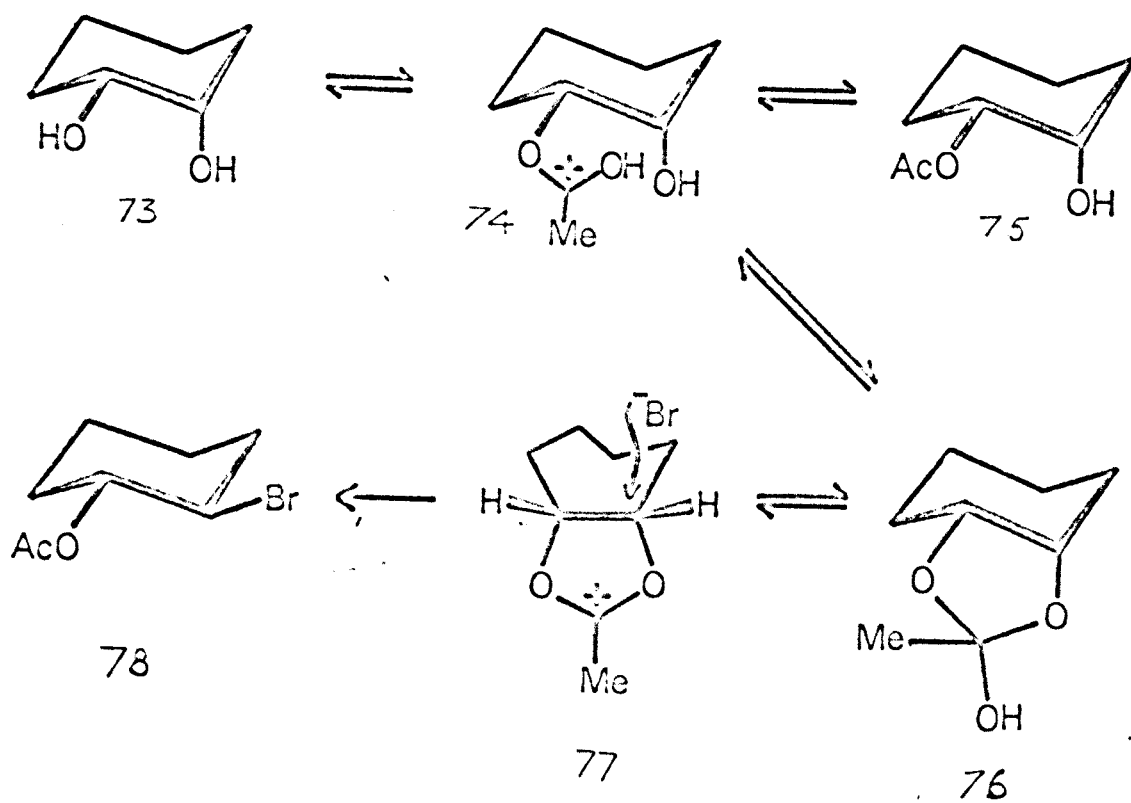
The cobaloximes (49), (52), (53), (54), (55) and (57) were synthesised by the route shown in scheme XXI. Some of the methods described in literature^{88,89} for preparing alkylcobaloximes were utilised for the synthesis of β -acetoxyalkylcobaloximes and the corresponding solvolytic products. These methods did not give the required products in reasonable yields. One procedure involved preparation of sodio-cobaloxime, which is then alkylated by an alkyl halide. This method was tested with benzyl bromide. Low yields of benzylcobaloxime were obtained and the major isolated product was the monobenzyl ether of biacetyldioxime which was identified from its spectroscopic properties⁹⁰. It was decided to use bromocobaloxime as an intermediate which could be alkylated to give alkylcobaloximes. The preparation of the bromocobaloxime has been described else-



where⁹¹. The route indicated in the scheme is a modification of an alkylcobaloxime synthesis described in the literature⁹². In this method absolute ethanol was used as a solvent. Since this might cause alcoholysis of the desired acetoxyalkylcobaloxime, 20% ethanol in dioxan was used as a solvent. This solvent system permitted a balance to be achieved between the need to reduce solvent polarity, but maintain sufficient solubility of starting material and reagents. A suspension of the bromocobaloxime, in this solvent, was prepared in a Schlenk tube connected to a vacuum line. This suspension was deaerated and the reaction carried out under an atmosphere of nitrogen. The deaeration is important for the presence of any oxygen would reduce the yield. After deaeration, sodium borohydride was added, followed by the alkylating agent, under nitrogen. At the conclusion of the reaction the solvent was evaporated off, under high vacuum, at room temperature. The product was rapidly chromatographed on a small silica gel column and recrystallised to give the pure product.

The synthesis of the alkylating agents are outlined in scheme XXII. Optically pure (S)-(-)-ethyl lactate (66) was used as the starting material for the preparation of (S)-1-acetoxy-2-bromopropane (71), (S)-propylene oxide (72) and (S)-2-benzyloxypropan-1-yl-p-toluene sulphonate (69). A method of preparing chiral propylene oxide is described in literature⁹³. This involved bubbling dry hydrogen bromide gas through neat propane-1,2-diol available from enzymic reduction of hydroxyacetone. The resulting bromohydrin was treated with potassium hydroxide, whereupon the epoxide could be distilled off. This method was found to be experimentally cumbersome and gave overall a very low yield of the epoxide. A superior method was discovered which involved treating propane-1,2-diol with

SCHEME XXIII



hydrogen bromide in glacial acetic acid. In the first experiment, one equivalent of HBr/HOAc was added and the reaction mixture was stirred for 18 hours. On working up, the product was identified as a mixture of mainly 2-acetoxy-1-bromopropane accompanied by small amounts of 1-acetoxy-2-bromopropane and 1,2-diacetoxypropane. If the amount of HBr is raised to 3 equivalents then almost a quantitative yield of (71) is obtained. When the (S)-(+)-propane-1,2-diol, obtained easily by reduction of (S)-(-)-ethyl lactate with lithium aluminium hydride, was used as the substrate, 89% of a mixture of (S)-(-)-2-acetoxy-1-bromopropane (94:6 by n.m.r. analysis) was obtained. Treatment of this mixture with 1 mol equivalent of potassium amylate in amyl alcohol at 25°C immediately gave pure (S)-(-)-propylene oxide (72) in 85% yield. Both steps in the synthesis must therefore be stereospecific. The reaction mixture is at all times homogeneous and the yields of propylene oxide are near quantitative. Thus, this method provides a very clean and efficient route for preparing valuable synthetic intermediates.

The mechanism (scheme XXIII) was established by using cis- and trans-cyclohexane-1,2-diols as substrates⁹⁴. The latter gave trans-1,2-diacetoxycyclohexane, while the former gave trans-1-acetoxy-2-bromocyclohexane. When the progress of the reaction was followed by recording ¹H n.m.r. spectra at intervals, a signal was seen to appear at 3.8 ppm downfield from CH₂CO₂H and then to disappear. This signal is consistent⁹⁵ with that of the methine proton of the cis-2-methyl-1,3-dioxolan-2-ylum ion (77). In the presence of bromide ions this is captured by S_N2 attack to give (78). The intermediacy of such a carbonium ion (77) was proposed in the conversion of vicinal diacetates to halohydrins - among other

products - by treatment with hot aqueous hydrohalic acids⁹⁶.

Further evidence for the formation of such an intermediate comes from the observation that whilst trans-1,2-diacetoxycyclohexane is stable to liquid HF, the corresponding cis isomer is converted to (77)⁹⁷. A full discussion of the scope and mechanism of the reaction of vicinal diols with hydrogen bromide in acetic acid is given in reference 94. The synthesis of the p-bromo-benzene sulphonate of 2-benzyloxypropan-1-ol, starting from chiral ethyl lactate, has been reported⁹⁸. A similar procedure was used for the synthesis of the corresponding p-toluene-sulphonate (69).

Although 1-acetoxy-2-bromoethane could be easily prepared by treating ethylene glycol with HBr/HOAc, this method is obviously not applicable to the synthesis of a specifically dideuteriated derivative of this bromoacetate. Consequently an alternative synthesis was sought. It was soon found that 2-bromoacetyl bromide could be reduced by lithium aluminium hydride to 2-bromoethanol, which was easily transformed to 1-acetoxy-2-bromoethane by means of acetic anhydride in pyridine. Repetition of this procedure, but using lithium aluminium deuteride, gave 1-acetoxy-2-bromo-1,1-dideuterioethane in 23% overall yield (from 2-bromoacetyl bromide). A reason for this low yield could be the cyclisation of the initially formed aluminium alkoxide salt of 2-bromo-1,1-dideuterioethanol to ethylene oxide, which is subsequently reduced to ethanol.

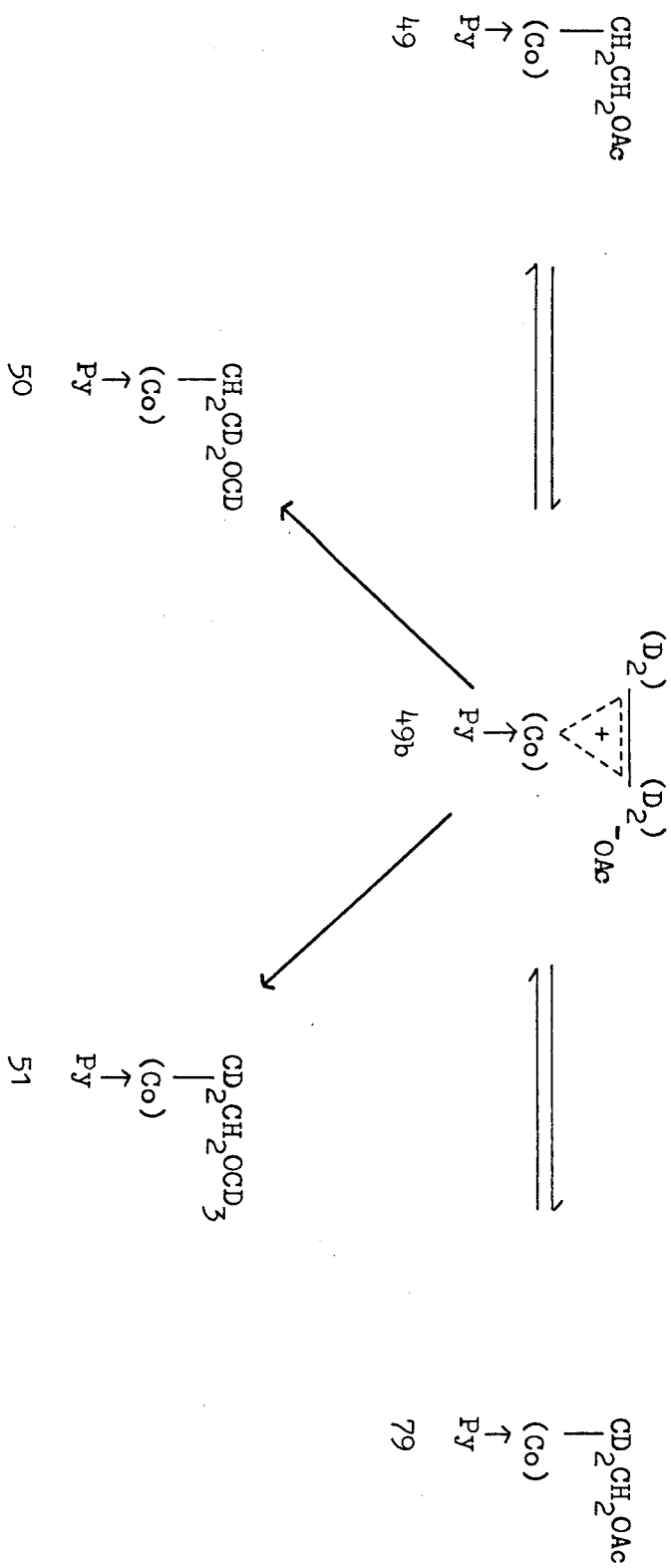
The solvolyses of β,β -dideuterio- β -acetoxyethyl cobaloxime (49) (equation XXVII in scheme XX) provide very strong evidence in favour of the olefinic π -complex (15b) as key intermediate, or at least transition state, in the solvolyses. This reaction yields the

isomeric solvolytic products, (50) and (51), in roughly equal amounts. Since one of the methylene groups, in (49), (50) or (51), is dideuteriated, the remaining methylene protons appear as a singlet. However, this is a broad singlet on account of coupling with ^2H on the adjacent methylene group. The $\alpha\text{-CH}_2$ protons in (49) and (50) have chemical shifts of 8.51 τ and 8.43 τ respectively. The $\beta\text{-CH}_2$ protons in (51) and (79) have chemical shifts of 6.93 τ and 6.29 τ respectively. Thus the presence or absence of these species in the reaction mixture can easily be deduced from the ^1H n.m.r. spectra recorded during the course of the reaction. As mentioned above, there is a complete scrambling of label during the solvolysis. There are two possible routes by which this can occur, as shown in schemes XXIV and XXV. Route 1 involves the formation of a 2-methyl-1,3-dioxolan-2-ylum ion, discussed earlier, which can revert to the starting acetate (49) or (79) by attack either at C-1 or C-2. This would result in complete scrambling in the starting material followed by methanolysis to give the product perhaps in a fashion other than that indicated in scheme XIV (Chapter II) and without scrambling. If this is the path followed by the reaction, then the following points hold:

(a) the scrambling is due entirely to the initial equilibria 5 and 6;

(b) since equal amounts of (50) and (51) are formed, equilibria 5 and 6 must be very much faster than the solvolysis itself;

(c) (49) and (79) undergo another reaction (perhaps an $\text{S}_{\text{N}}2$ reaction) to give the products, in which only the β -carbon atom is



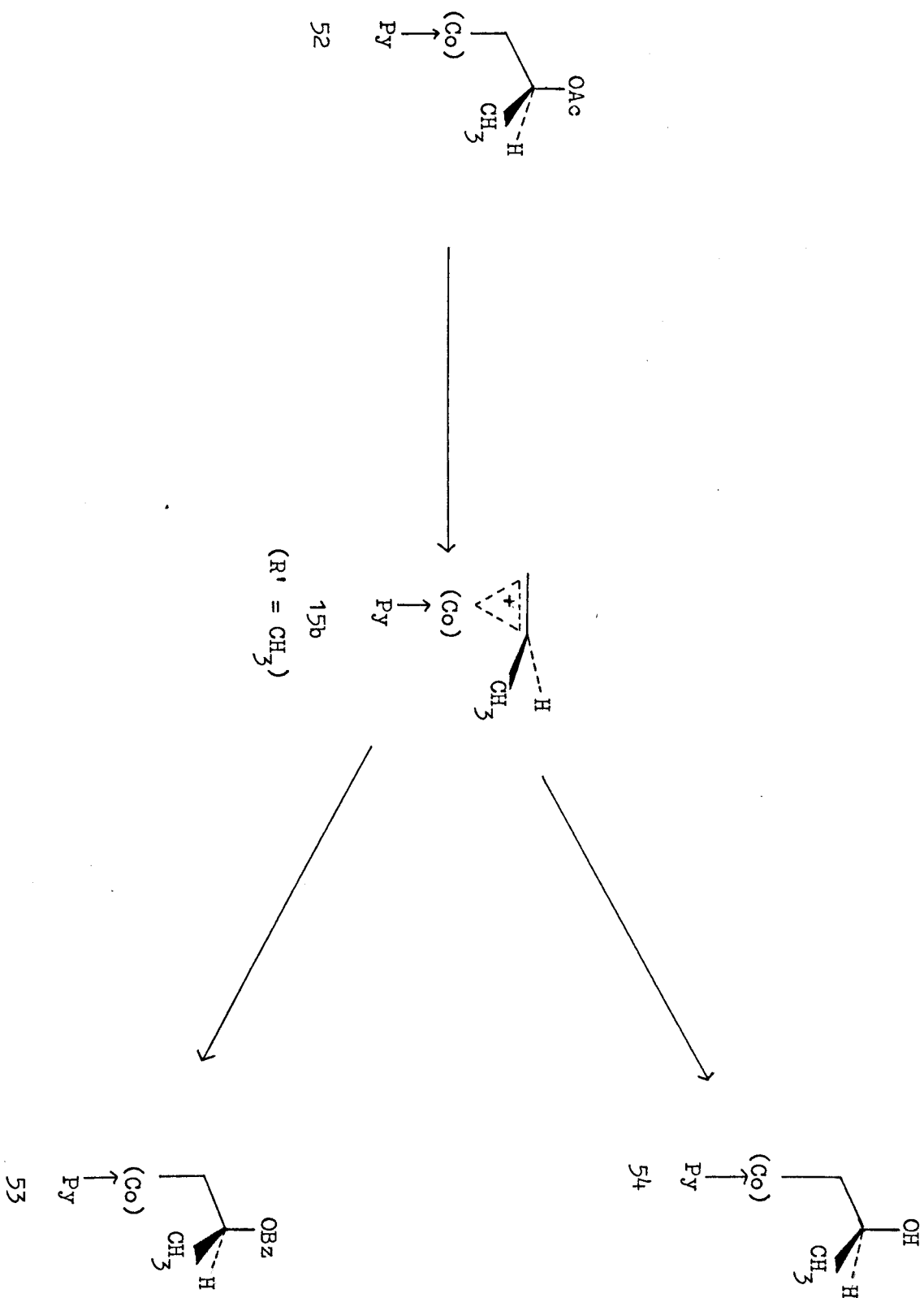
affected and there is no migration of the cobalt ion.

The second route involves the intermediacy of an olefinic π -complex of Co(III). Step 1 is the slow rate-determining step in which the π -complex is formed. The scrambling of the label occurs in this intermediate as represented by the equilibrium between (50a) and (51a). This is then rapidly captured by solvent to give the isomeric products (50) and (51). A further complication in the interpretation of scrambling comes from the possibility of ion-pair return which could equilibrate (49) and (79) via (49b) at a rate competitive with solvent capture of the intermediate.

A study of the ^1H n.m.r. spectra recorded during the solvolysis throws some light on these various possibilities. Assuming that the solvolysis proceeds entirely via the first pathway, then scrambling of the label will be complete prior to solvolysis. In this case a singlet at 6.29 τ , for the β -CH₂ protons, will appear soon after start and will rapidly become equal to the singlet at 8.51 τ . This may also be the case for the pathway involving ion-pair return. On the other hand, if scrambling occurs by the second route - as a direct consequence of solvolysis - then the rate of appearance of the singlet at 6.93 τ will parallel the rate of appearance of the solvolytic product. As a result, the ratio of α -CH₂: β -CH₂, after the first half-life, will be 3:1. As the solvolysis progresses this ratio will decrease and, at the conclusion of the reaction, attain a value of 1:1. Finally, if the actual reaction path is a combination of the pathways discussed above, then no such relationship will be observed but a significant amount of (79) will be seen during the reaction. It was found that while a small amount of

leakage occurs via (49a) or (49b) (less than 10% of (79) is seen throughout the reaction), the major pathway is one that requires the intermediacy of an olefinic π -complex like (50b). Even allowing for the errors involved in measuring the integrals of the appropriate peaks, the ratio of α -CH₂: β -CH₂ is very close to 3:1 after the first half life, and at the end of the reaction has a value of 1:1. This clearly indicates that scrambling is the result of solvolysis and that an olefinic π -complex of Co(III) is a necessary intermediate. This evidence makes route 1 unlikely as a contributor to the solvolytic pathway. It should be noted that the results discussed rule out the occurrence of hydrogen or deuterium 1,2-shifts in the intermediate (50b) since this would result in a cobaloxime (66.7% on a statistical basis ignoring isotope effects) in which the alkyl side-chain becomes -CHDCHDOCD₃. In this case both the α -CH and β -CH protons would appear as doublets and such signals are clearly absent from n.m.r. spectra (cf. fig.XIII). Pertinent to the results discussed is a recent report concerning methanolysis of β -acetoxy ethyl pyridinato cobaloxime in which the β -CH₂ is labeled with ¹³C 99. It was observed that in the solvolytic product the label is equally distributed between the α - and the β -positions. Again, an intermediate like (50b) must be involved. However, in this ¹³C-experiment it is not possible to distinguish among alternative pathways (and none were considered by the authors) for the scrambling. Taken together the ²H- and ¹³C-labeling experiments strongly implicate (50b) as the key intermediate in these solvolyses.

Prior to the solvolysis of the labeled β -acetoxyethylcobaloximes an attempt was made to synthesise β -acetoxy- σ -isopropylcobaloxime. It was felt that the solvolyses of this would yield products identical



to those obtained from the solvolyses of β -acetoxy- σ -n-propyl cobaloximes, thus providing evidence for a 1,2-shift by cobalt. Such evidence would implicate a π -complex as an intermediate in the solvolyses. 2-bromopropan-1-ol was prepared by reduction of 2-bromopropionyl bromide with lithium aluminium hydride and acetylated in the usual way to give 1-acetoxy-2-bromopropane. This was used as a starting material for the β -acetoxy- σ -isopropyl cobaloxime. However, these attempts were not successful.

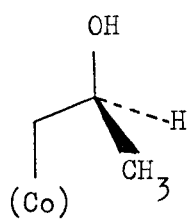
It was mentioned in Chapter II that a high negative value was obtained for the entropy of activation in the ethanolysis of β -acetoxy ethylcobaloxime⁸¹. This indicates a high barrier to rotation about the $\text{CH}_2\text{-CH}_2$ unit in the side-chain. Now, in both the acetate and the solvolytic product, the ethyl ether, there is little restriction to rotation about this bond. Hence, the large negative value for the entropy of activation is further evidence for a species like (50b). In this complex, the C-C bond is perpendicular to the z-axis of the complex. As the positive charge is delocalised over three atoms, the two ethylenic carbon atoms and the cobalt, the olefinic moiety is held so as to prevent a rotation about the C-C axis. In other words, the solvolyses should result in a retention of configuration. This is borne out by the solvolyses of chiral β -acetoxy- σ -n-propylcobaloxime (52). This, and other chiral cobaloximes, were prepared as shown in scheme XXI. The starting materials for these syntheses were prepared according to scheme XXII.

2
2 The benzylolysis of (52) in benzyl alcohol was studied. The solvolytic product was checked by ^1H n.m.r. for purity and its optical rotation measured. For comparison, this product was also synthesised independently as shown in scheme XXI. It was found that

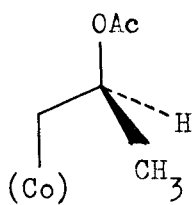
TABLE V

Cobaloxime

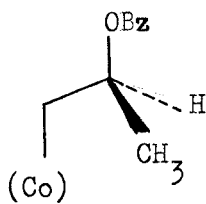
Specific rotation



+ 8.21



+ 2.5



+ 3.72

FIGURE VII

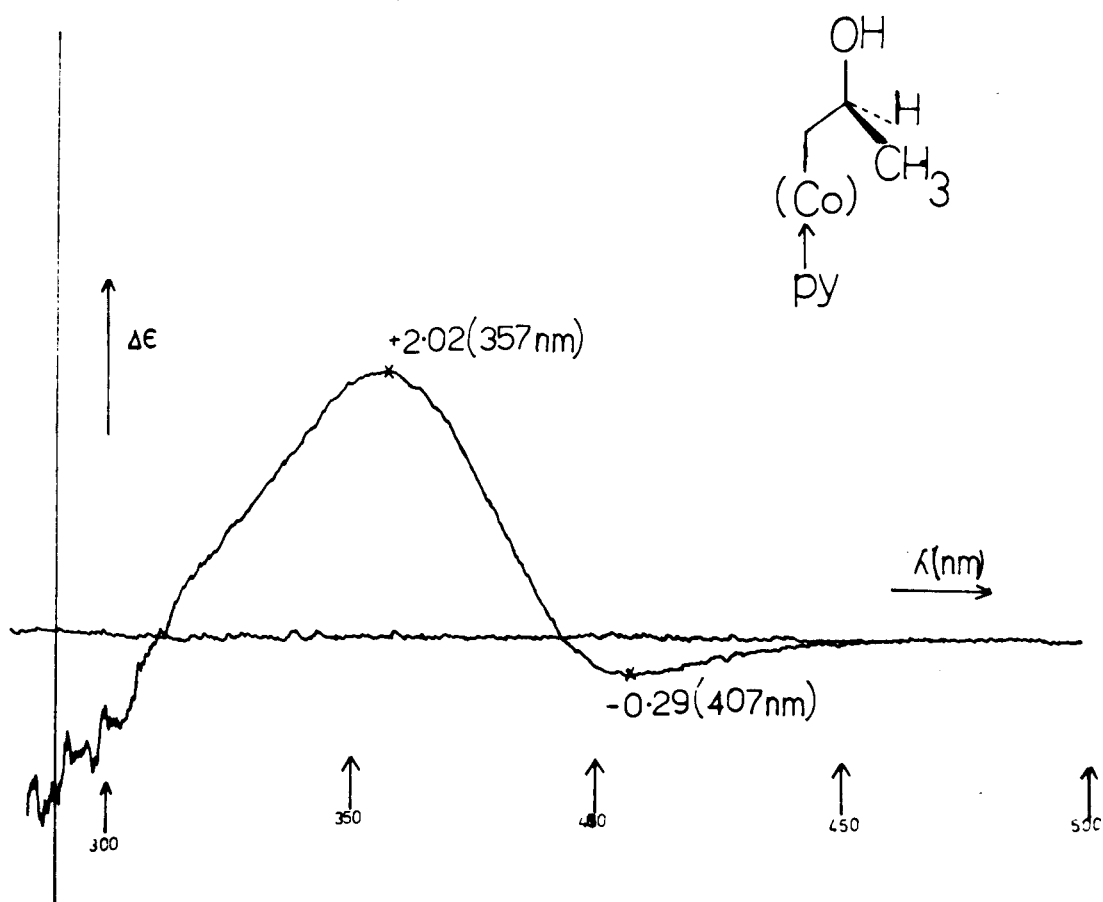
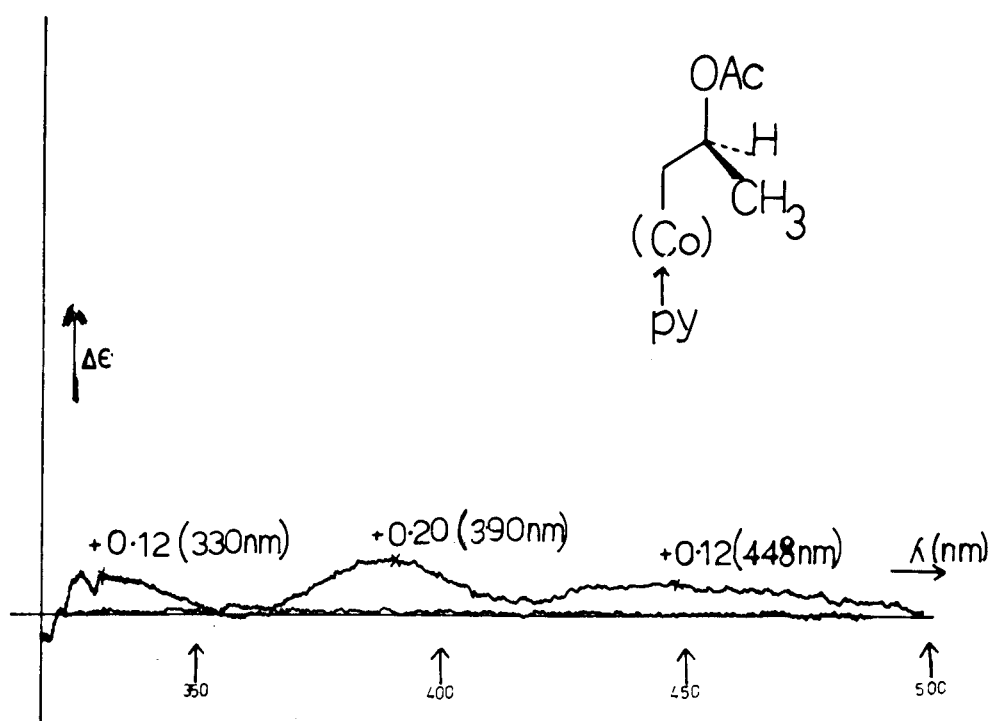
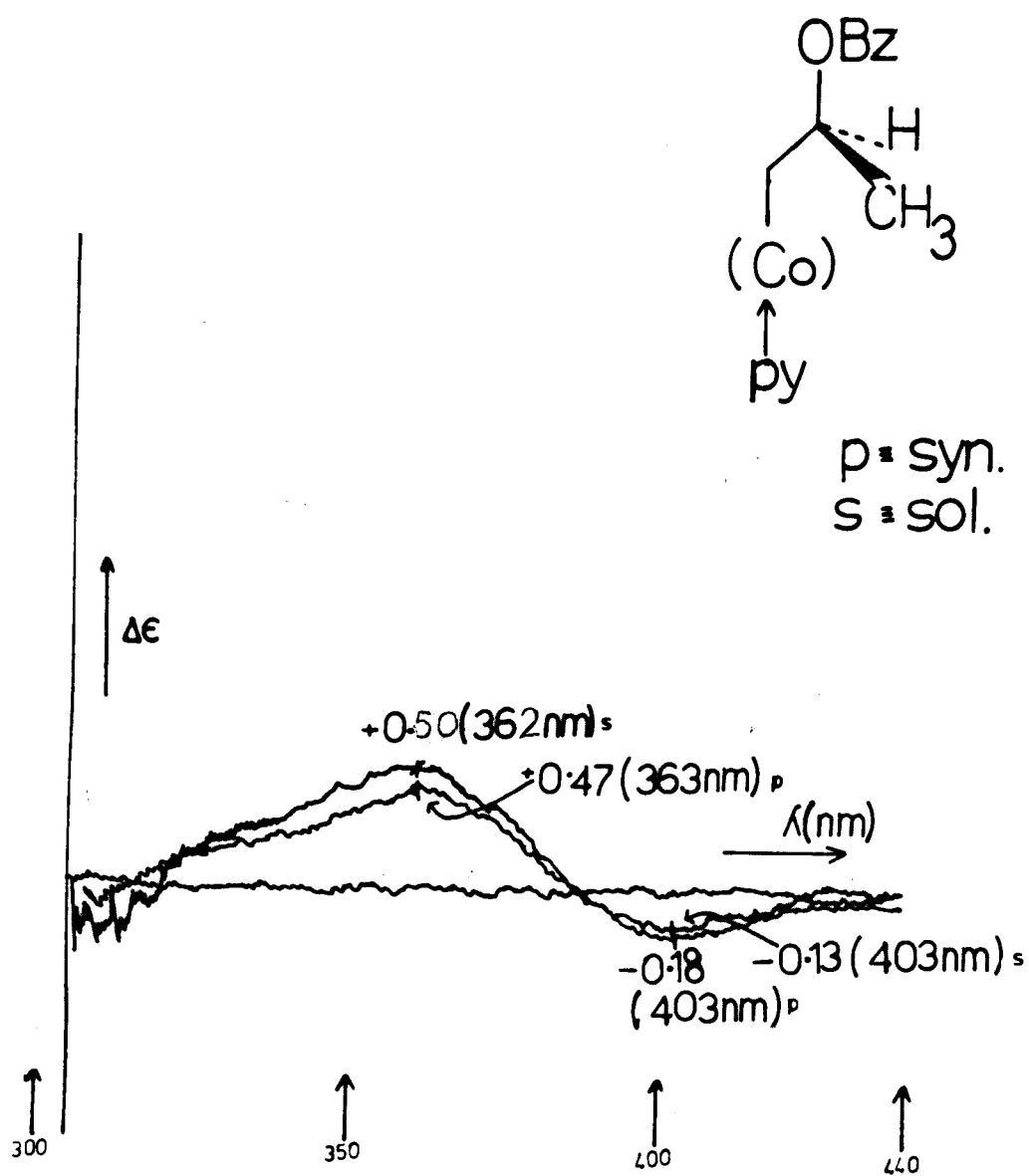
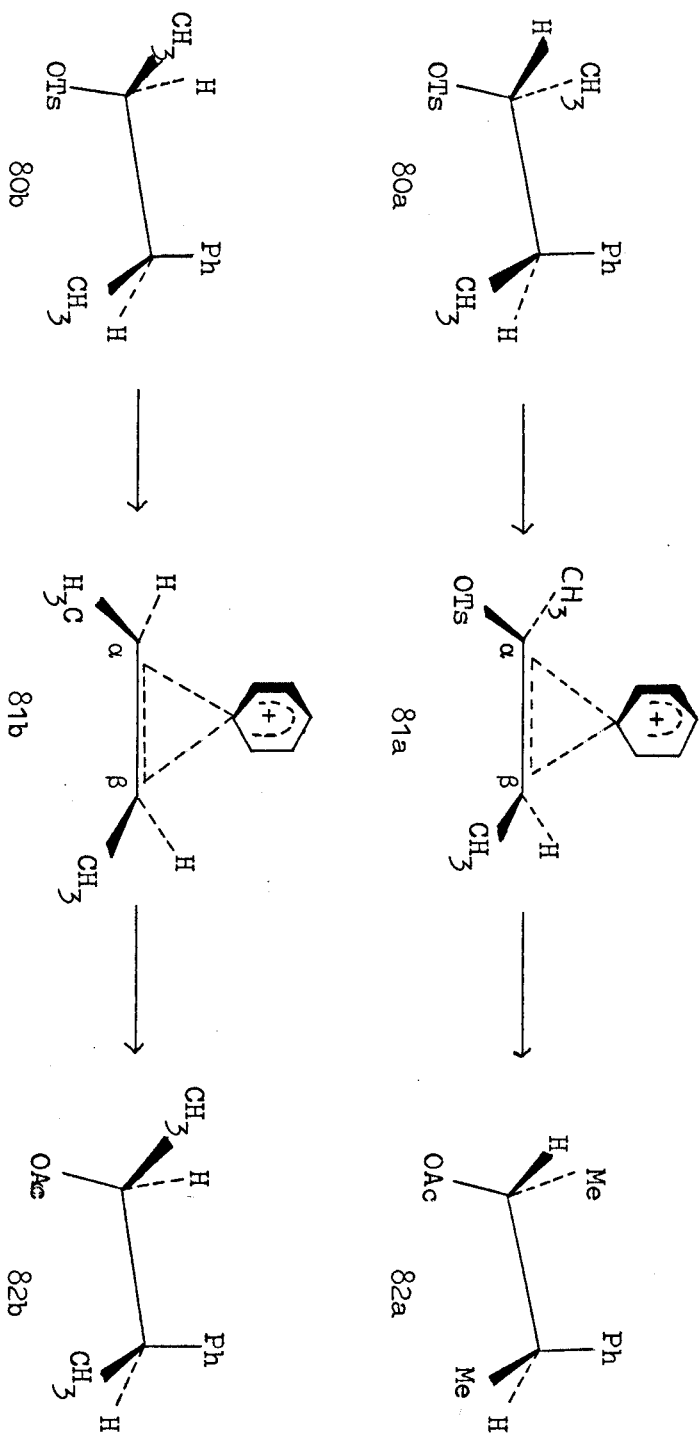


FIGURE VIII



the specific rotation of the solvolytic product was almost identical with that of the synthetic product. The values for specific rotations of (52), (53) and (54) are given in table V. Circular dichroism spectra were recorded for (52) and (54) and are shown in figure VII. Figure VIII shows the C.D. spectra of solvolytic and synthetic (53). It is seen that, within experimental error, the two curves are identical. This is strong evidence that the solvolyses proceed with retention of configuration although the reaction is of an S_N1 type. The retention of configuration suggests that bond breakage must precede bond formation and that the intermediate is attacked on the same side by the solvent. If a simple β -carbonium ion, or some kind of bimolecular displacement, were involved, then attack on the other side would be possible leading to a racemic product in the former case and a probably inverted product in the latter. Also, if there was a small amount of leakage via these two possible routes, a reduction in the specific rotation would be observed. As the optical activity of both the solvolytic and synthetic products is almost identical, these possibilities have to be ruled out. Such a mechanistic scheme, which involves participation by a neighbouring group and results in retention of configuration, has analogy in the proposed 'phenonium ions',¹⁰⁰. It was found that acetolysis of optically active erythro-3-phenyl-2-butyl tosylate (80a) yielded the optically active erythro-acetate (82a) with 96% retention of configuration. Similarly, the optically active threo-isomer (80b) yields almost racemic threo-acetate (82b). In both cases the product is formed by attack either at the α - or the β -carbon atom of the intermediate (81a) or (81b). It is important to note that, conceptually, these intermediates are identical to (15b). The similarity with ferrocenyl cations has been pointed out in Chapter II.



(From: R.W. Alder, R. Baker and J.M. Brown: 'Mechanism in Organic Chemistry', Wiley-Interscience, London, 1971, p 107.)

The methanolyses of a series of cobaloximes with four different base ligands were studied. These are summarised in scheme XX. The extent to which the olefinic π -complex of cobalt can be stabilised depends on the extent to which the positive charge can be delocalised and the extent to which Co(III) can be stabilised in preference to the π -complex. Thus it would be expected that as the electron-donating ability of the ligand is increased the formation of the π -complex is made easier and its reactivity increased. Three pyridines, two of them 4-substituted, were the ligands in the cobaloximes studied. The Lewis basicity of these ligands decreases in the order: 4-dimethylaminopyridine > pyridine > 4-cyanopyridine. The behaviour of β -acetoxyethyl(triphenylphosphine) cobaloxime was also investigated. The rate of disappearance of starting material in the solvolyses of the (pyridine)cobaloximes was found to decrease as the Lewis basicity of the pyridine ligand decreased. When triphenylphosphine is the ligand, little or no solvolytic product is formed, as mentioned in Chapter II. The hypothetical hydrolytic product of the (triphenylphosphine)cobaloxime has been synthesised and is stable under the conditions of solvolysis. It must be admitted that the effect of trans-ligands on the solvolyses is not well understood. However, two possible reasons for the decomposition - rather than solvolyses - observed with (triphenylphosphine)cobaloxime are as follows. The Co-P bond being considerably polarised towards cobalt causes an increase in electron density at cobalt, which may stabilise Co(III) in the intermediate (15b) in preference to a π -complex. In this case, although the π -complex may be formed very easily, it loses ethylene very much faster - relative to its capture by solvent - to give des-alkylcobaloxime(s) as product(s). In this context it is important

TABLE VI

Solvolyses of β -acetoxyethylcobaloximes, with different pyridines as trans-ligands, in $\text{CD}_3\text{OD}:\text{CDCl}_3$ (2:3).

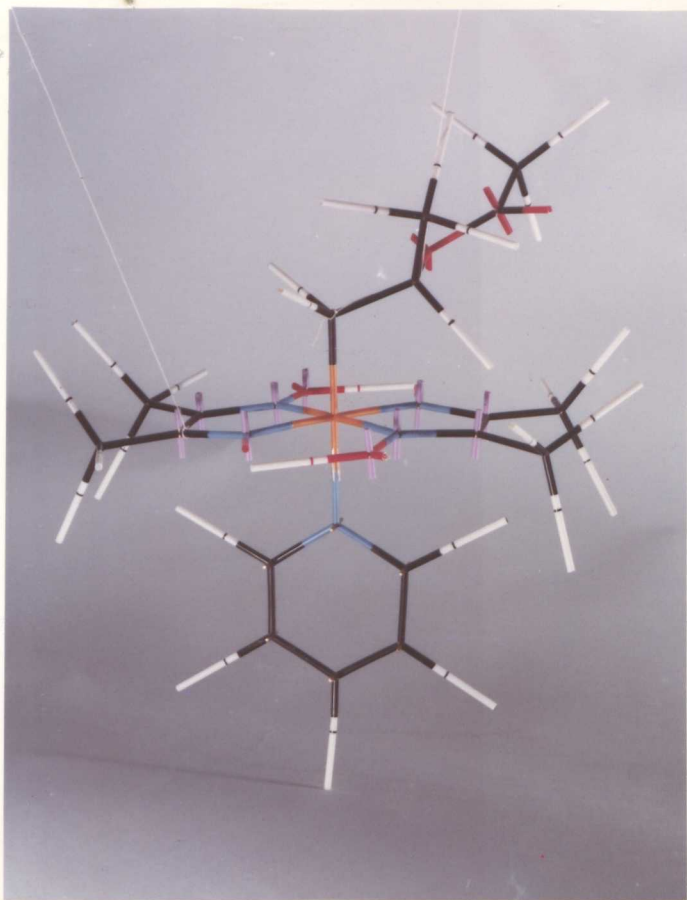
<u>Ligand</u>	<u>k sec⁻¹</u>
4-dimethylamino-pyridine	7.3×10^{-5}
pyridine	8.2×10^{-6}
4-cyano-pyridine	4.86×10^{-6}

to consider the solvolyses of chlorocobaloximes with different trans-ligands. It was found that the rate of aquolysis of chloro(triphenylphosphine)cobaloxime is about 3.5 times greater than that of chloro(pyridine)cobaloxime¹⁰¹. Presumably, this reaction proceeds via a Co(III) intermediate (e.g. (15b)) in which the positive charge on cobalt is stabilised more by triphenylphosphine than by pyridine.

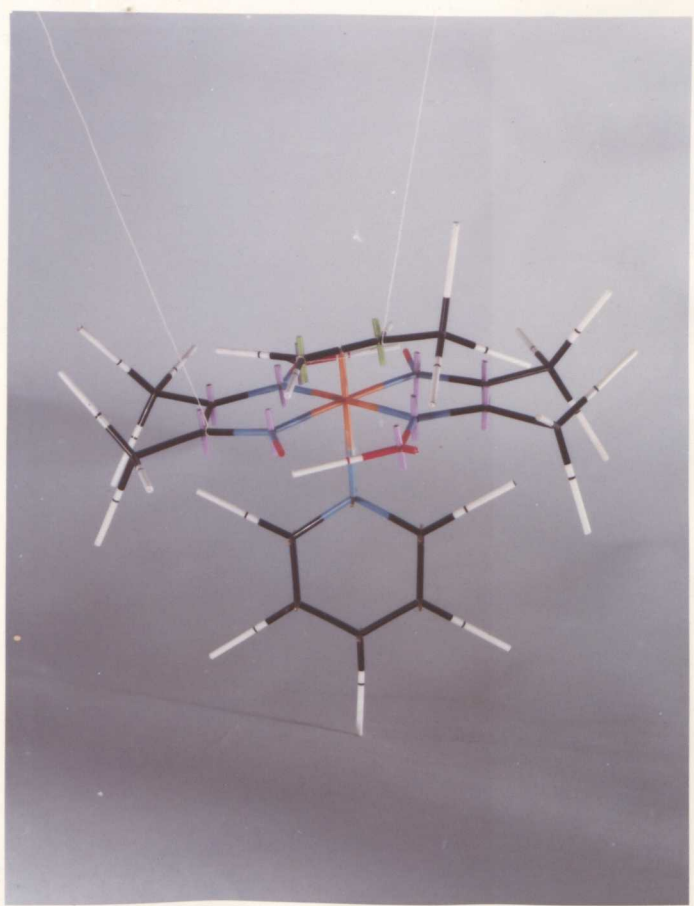
A second reason, for the observed decomposition of (triphenylphosphine)cobaloxime, is that cobalt may form a strong $d\pi-d\pi$ bond with phosphorous, in which case its filled d-orbitals will not be available to form a $d\pi-p\pi$ bond with ethylene and this may be necessary to stabilise the π -complex. Hence no π -complex is formed and decomposition occurs in a concerted fashion to give des-alkylcobaloximes. The decomposition of (triphenylphosphine)cobaloxime, if explained in terms of a Co-P $d\pi-d\pi$ bond, may be interpreted in favour of an olefinic π -complex as an intermediate in the solvolyses of the pyridine complexes. If the solvolyses involved an intermediate carbonium ion stabilised by $\sigma-\pi$ hyperconjugation, then a Co-P $d\pi-d\pi$ bond would not significantly affect the formation and reactivity of this intermediate and (triphenylphosphine)cobaloxime would give solvolytic products analogous to those from solvolyses of (pyridine)cobaloximes. However, it must be noted that $d\pi-d\pi$ bonds between transition metal ions and phosphorous are not beyond dispute.

The solvolyses of cobaloximes with different pyridines as ligands can best be rationalised in terms of an olefinic π -complex. In the cobaloxime with 4-dimethylaminopyridine as a trans-ligand, the

solvolysis is very rapid with a half-life of about three hours. In the (pyridine)cobaloxime the rate is even slower and the half-life of the starting material is about twenty hours. The solvolysis of the (4-cyanopyridine)cobaloxime is the slowest of the three, with a half-life of about eighty hours. It is apparent that the rate of solvolysis increases with the electron-donating ability of the trans-ligand. A stronger electron-donating ligand would cause a higher electron-density about cobalt. This in turn would promote back-donation from the d-orbitals of cobalt into the vacant p-orbitals of the ethylene, leading to a greater stabilisation and hence ease of formation of the π -complex. An electron-withdrawing ligand, on the other hand, would reduce the back-donation necessary to stabilise the π -complex. Thus, the solvolyses of cobaloximes with different pyridines as ligands are in accord with a scheme involving the intermediacy of an olefinic- π -complex as a key intermediate.



a) Model of β -acetoxypropyl(pyridine)cobaloxime



b) π -Complex formed from (a)

CHAPTER IV

The existence of a solvolytic chemistry of β -acetoxyalkylcobaloximes is of considerable interest, at least from the view-point of organometallic chemistry. The solvolyses results range from almost complete solvolysis, as with (pyridine)cobaloximes, to complete decomposition as in the case of (triphenylphosphine)cobaloxime. The different kinds of solvolyses studied, and discussed in Chapters II and III, have made it necessary to invoke a common mechanism for both decomposition and solvolysis. The most important feature of this mechanism is the novel olefinic π -complex of cobalt(III) which is the key intermediate. The two possible alternatives to this, a simple β -carbonium ion and a carbonium ion stabilised by σ - π hyperconjugation, have also been discussed. The experiments with specifically labeled β -acetoxyethylcobaloxime seem rigorously to exclude at least the former of these two possibilities. While the results discussed in previous chapters have been interpreted in terms of a π -complex (15b), the intermediate stabilised by σ - π hyperconjugation (15c) cannot be entirely ruled out. Perhaps both are involved and the cobalt in (15c) migrates from C-1 to C-2 via (15b) as a transition state.

β -Acetoxymercurials undergo mainly decomposition reactions, while analogous substituted ferrocenes exhibit mainly solvolytic reactions - as has been mentioned. A π -complex as an intermediate

in the latter is substantiated by experimental observations and has been rigorously shown to be involved in the former type of reactions. β -acetoxyalkylcobaloximes which undergo both decomposition and solvolysis probably form a good link between deoxymercurations and solvolyses of substituted ferrocenes.

The cis- and trans-effects observed in the case of cobalamins²¹ are also observed with cobaloximes. However, while in cobalamins the observed cis-effect may actually be a manifestation of distortions in the corrin ring consequent of the alkyl ligand rather than transmission of electronic effects through the cobalt ion³⁴, the latter may be true of cobaloximes. This becomes evident from the ¹H n.m.r. spectra where substitution of the alkyl ligand by an electro-negative group results in a down-field shift in the biacetyldioxime methyl protons. The cobalt atom also enhances the reactivity at the β -carbon atom. This is indicated by the rate constants for the solvolyses of β -acetoxyalkylcobaloximes which are comparable in reactivity to trityl acetates. In a recent report, the evidence for cis- and trans-effect in various organometallic derivatives of cobalt chelates has been discussed¹⁰². It was concluded that these two effects could facilitate Co-C bond fission by increasing the electronic charge on the cobalt. The abnormally low value for the C=O stretching frequency (1715 cm^{-1}) in trifluoroacetylcobaloxime, in which the CO is β to cobalt, has already been commented upon.

The formation of the postulated π -complex depends on the strength of the $d\pi - p\pi$ bond between cobalt and the ethylenic moiety. The solvolyses of cobaloximes with different trans ligands are discussed in Chapter III. This discussion includes a certain amount of

speculation about the possibility of competition for the d-electrons of cobalt from the trans ligand. This competition could involve a $d\pi-d\pi$ bond with phosphorous in the case of triphenylphosphine as a trans ligand or a $d\pi-p\pi$ bond with the pyridine ligand. Evidence for at least the $d\pi-p\pi$ bond comes from ligand exchange studies on various cobaloximes. It was found¹⁰³ that methyalaquocobaloxime loses the water ligand approximately eight times faster than the corresponding phenylcobaloxime in acetone containing 1% water, subsequently liganding with imidazole. The n-propyalaquocobaloxime reacts 200 times faster. While the alkyl ligands increase the electron-density around cobalt the phenyl group does the opposite on account of its mesomeric effect and possibly $d\pi-p\pi$ bond formation. In the reactions of thiols with methyalaquocobaloxime it was found that neutral thiols reacted faster than thiolate anions and both of them faster than substituted pyridines. The reason for this was suggested to be greater π -bonding in the ground state between Co and S atoms¹⁰⁴. Thus, the trans ligand could make strong demands on the d-electrons of cobalt, thereby affecting the solvolysis in the alkyl side chain.

The similarity between cobaloximes and cobalamins has been discussed in Chapter I. The object of this research was, initially, to obtain evidence for a mechanism for the catalytic action of coenzyme B₁₂. When it was realised that this scheme was rather unlikely, it was decided that solvolyses of β -acetoxyalkylcobaloximes would provide a chemistry relevant to that of cobalamins. The postulated π -complex could also be a valid intermediate in the reactions catalysed by coenzyme B₁₂. According to a recent proposal for diol-dehydrase action¹⁰⁵, in the intermediate the substrate is attached to the cobalt. It is in this species that the cobalt undergoes

a 1,2-shift giving rise to the rearranged product. There is very strong evidence that the first step involves a homolytic fission of the Co-C bond in coenzyme-B₁₂ and subsequently the substrate attaches itself to cobalt forming the intermediate. Consequently, unlike the π -complex, this is not a charged species. However, when the cobalt undergoes a 1,2-shift to give the product, as proposed, it may do so via an intermediate or a transition state which is analogous to the olefinic π -complex invoked in the solvolyses of cobaloximes. Similar solvolytic studies of β -acetoxyalkylcobalamins are therefore necessary. If analogous results are obtained then it would be plausible to propose the formation of such intermediates in the coenzyme-B₁₂ catalysed reactions.

EXPERIMENTAL

Melting points (m.p.) :-

The m.p.s were taken on a Reichert heated microscope stage and are uncorrected.

Infra-Red Spectra (I.R.) :-

I.R. spectra were recorded with Perkin Elmer 257 and 457 grating machines. Spectra were run in 0.25 m.m. NaCl cells, for the former, and 0.2 m.m. KBr cells for the latter, using dichloromethane or chloroform as solvent unless otherwise stated. The maxima are designated as w (weak), m (medium) or s (strong). Broad peaks are indicated by 'b' before the appropriate designation.

Ultra-Violet Spectra (U.V.) :-

U.V. spectra were recorded with a Unicam SP-800, using quartz cells and methanolic solutions. They are given as the maximum in nanometres followed by the molar extinction coefficient.

Nuclear Magnetic Resonance Spectra (N.M.R.) :-

N.M.R. spectra were recorded with a Perkin Elmer R12 (60 MHz). Tetramethylsilane (T.M.S.), $\tau=10$, was used as an internal reference and deuteriochloroform solutions were used unless otherwise stated. The peaks are designated by the chemical shifts (τ) in p.p.m. followed in brackets by the multiplicity: s (singlet),

d (doublet), t (triplet), q (quartet), m (multiplet); and the integration (H). 100 MHz spectra were run by the Physico Chemical Measurements Unit (P.C.M.U.), Harwell, on a Varian HA-100.

Specific Rotations :-

The specific rotations of the chiral cobaloximes were measured on a Bendix-NPL Automatic Polarimeter using ethanol-free chloroform as solvent.

Circular Dichroism Spectra (C.D.) :-

The C.D. spectra were recorded by Dr. P.M. Scopes at the Westfield College, Hampstead, London, N.W.3.

Mass Spectra :-

Mass spectra were run by the University of Hull service and by P.C.M.U. They are designated by the mass peak with its percentage intensity relative to the base peak, in brackets.

Gas Liquid Chromatography (G.L.C.) :-

G.L.C. were run on a Honeywell F & M. The columns, and column temperatures, are specified.

Thin Layer Chromatography (T.L.C.) :-

Qualitative T.L.C. were taken using 5 x 20 cm glass plates coated with silica gel PF 254 (Merck, U.V. sensitive), eluting with ethyl acetate containing 1% pyridine unless otherwise stated.

Preparative T.L.C. was carried out using 100 x 20 cm plates with 0.5 mm silica gel PF 254 and a Burkard SA 100 applicator.

Elemental Analysis :-

This was carried out by Alfred Bernhardt (W. Germany) and Dr. F.B. Strauss (Oxford) microanalytical services.

Starting Materials :-

Starting materials were used as commercially supplied, with the following exceptions:

Pyridine was dried by refluxing over KOH, followed by distillation, and was stored over KOH pellets.

Benzyl alcohol, benzyl bromide, chloroform, dichloromethane, diethylether, dioxan, ethylacetate, methanol and sodium borohydride were purified by methods described in literature¹⁰⁶.

p-Toluenesulphonylchloride was crystallised according to a literature description¹⁰⁷.

Preparation of Starting Materials :-

Some of the starting materials were not readily available commercially and were prepared as follows:

1-Acetoxy-2-bromoethane -

3.82 g. of ethylene glycol (0.06M) were added, dropwise and with stirring, to 39 g. (0.18M, 3.00 eq) of HBr/HOAc (45% w/v HBr in HOAc, 4.2 m.eq HBr/g. solution by titration for halide ion,

supplied by Hopkin and Williams). The mixture was stirred for 2 h. and then quenched with water (200 mls.). It was neutralised by Na_2CO_3 and the product extracted into CHCl_3 (50 ml. x 3). The CHCl_3 extracts were washed with water, dried over Na_2SO_4 and concentrated on a rotary evaporator (Buchi). The product was then purified by trap-to-trap distillation (0.005 mm Hg/bath temperature 40°C) giving 10 g. (98.5%) of material pure by G.L.C. (lit. b.p. $162-3^\circ\text{C}^{108}$).

N.M.R.	:	7.91 τ (s, 3H)	$-\text{OCOCH}_3$
		6.50 τ (t, 2H)	$-\text{CH}_2\text{O}-$
		5.63 τ (t, 2H)	$\text{Br}-\text{CH}_2-$

IR	:	3000 (m), 1740 (b.s), 1475 (m), 1450 (m),
(DMS Index)		1425 (s), 1415 (s), 1365 (s), 1290 (b.s),
cm^{-1}		1150 (very b.s), 1030 (s), 950 (m),
		895 (w), 875 (w).

IR	:	3000 (m), 1742 (b.s), 1473 (m), 1447 (m),
cm^{-1}		1428 (s), 1415 (s), 1364 (s), 1293 (b.s),
		1150 (very b.s), 1032 (s), 949 (m),
		895 (w), 872 (w).

Analysis %	:	C	H
		Found	29.49 4.50
		Calc. for $\text{C}_4\text{H}_7\text{BrO}_2$	28.98 4.27

2-Bromo-1,1-dideuteroethanol -

10.1 g. (0.05M) bromoacetyl bromide (B.D.H.) in 250 ml.s dry diethylether (ether) was added dropwise and with stirring to a cooled suspension (-5°C) of 1.155 g. (0.028mM) of lithium aluminium deuteride

(L.A.D. supplied by C.I.B.A.) in 60 ml.s dry ether. The reaction mixture was stirred at -5°C for 2h. Excess L.A.D. was destroyed by careful addition of water and the solution was filtered. The aqueous layer was saturated with Na_2SO_4 and extracted with ether. The ether extracts were collected, dried over Na_2SO_4 and concentrated on the Buchi. The crude product was distilled under reduced pressure ($45-46^{\circ}\text{C}/13$ mm Hg) giving 3.27 g. (51.5%) of material pure by G.L.C. B.p. $20^{\circ}/3\text{mm}$.

N.M.R.	:	7.74 τ (broad s, 1H)	-OH
		6.46 τ (" s, 2H)	-CD ₂ -CH ₂
I.R.	:	3622 (m), 3587 (m), 3457 (b.m.), 2965 (m),	
(cm ⁻¹)		2212 (w), 2097 (w), 1427 (m), 1297 (b.s),	
(CCl ₄)		1241 (m), 1199 (s), 1137 (m), 1094 (m),	
		1071 (m), 971 (b.m), 897 (b.w).	
M.S.	:	28 (43.7), 32 (13.2), 43 (100), 47 (13.2),	
		75 (13.2), 89 (29.1), 108 (13.8),	
		109 (13.2), 110 (30.05).	
Accurate mass	:	127.9631	
Calculated for		$\text{C}_2\text{H}_3\text{D}_2\text{O}^{81}\text{Br}$: 127.9630

1-Acetoxy-2-bromo-1,1-dideuterioethane -

2.54 g. (0.02M) of $\text{BrCH}_2\text{CD}_2\text{OH}$ were dissolved in 10 ml. of dry pyridine. 5.7 ml. (0.06M) of acetic anhydride were added dropwise and with stirring. The reaction was allowed to go on for 2 h. and was then quenched with water (25 ml.). The product was extracted into ether (25 ml. x 3), dried over Na_2SO_4 and purified

by trap-to-trap distillation (0.005 mm Hg; bath temperature 35°C) giving 2.1g (48%) of the product pure by G.L.C. B.p. 20°/1.8 mm.

N.M.R.	:	7.89τ (s, 3H)	$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{CH}_3 \\ \underline{\quad 3} \end{array}$
	:	6.49τ (broad s, 2H)	$-\text{CD}_2-\text{CH}_2-$ $\underline{\quad 2}$
I.R. cm ⁻¹ (CCl ₄)	:	2941 (m), 2157 (w), 1742 (b.s), 1430 (s),	
	:	1374 (s), 1252 (b.s), 1188 (s), 1165 (s),	
	:	1146 (s), 1062 (s), 1037 (s), 960 (m).	
Analysis %	:		C H
	:	Found	28.43 2.98
	:	C ₄ H ₅ D ₂ BrO ₂ requires	28.53 2.51

(S)-(+)-Propane-1,2-diol —

33g (0.28M) of (S)-(-)-ethyl lactate (Fluka A.G., $[\alpha]_D^{26}$ -13.9° (neat)) in 150 ml dry ether was added to a stirred suspension of 10.8g (0.284M) lithium aluminium hydride (L.A.H., supplied by Fisons) in 200 ml ether under nitrogen. The addition was carried out at a rate necessary to maintain a steady reflux (approximately over 0.5h). The mixture was stirred at 25°C for 3h. Excess L.A.H. was destroyed by careful addition of 25 ml water (slight excess) and stirring for further 1.5h. The mixture was filtered and the residue was washed with ether and dichloromethane, giving 5g (23%) product. The solid was dissolved in 2N H₂SO₄ and continuously extracted with dichloromethane giving a combined yield of 17.2g (81%) pure by G.L.C. B.p. 93°/18 mm (lit. b.p. 96-8°C/ 21 mm).

$[\alpha]_D^{25}$ -16.28° (neat)

Highest literature value $[\alpha]_D^{26} -15.9^\circ$ (neat) for (R)-(-)-isomer obtained from yeast reductase reduction of hydroxyacetone⁹³.

N.M.R. : 8.83 τ (d, 3H) -CH-CH_3
 8.38 τ (m, 3H) $\text{-CH}_2\text{-CH}$
 5.11 τ (s, 2H) -CH-OH
 $\text{-CH}_2\text{-OH}$

I.R. : 3500 (very b.s), 2950 (s), 1462 (s), 1421 (b.s),
 1888 (s), 1343 (s), 1297 (m), 1231 (m),
 1144 (s), 1048 (s), 998 (s), 950 (m), 935 (s),
 837 (s), 865 (w).

(S)-(-)-2-Acetoxy-1-bromopropane —

71g. (0.3M) of HBr/HOAc was added rapidly with stirring to 7.6g (0.1M) (S)-(+)-propane-1,2-diol cooled in an ice bath. The reaction mixture was stirred for 0.5h at 25°C and then was quenched with water. After neutralising this mixture with solid Na₂CO₃, the product was extracted into ether. The extracts were dried over K₂CO₃ and concentrated on the Buchi. This product was found to be a mixture (94:6 by n.m.r.) of 2-acetoxy-1-bromopropane and 1-acetoxy-2-bromopropane. Distillation gave 16g (89%) of the former pure by G.L.C. B.p. 57°/11 mm.

$[\alpha]_D^{26} -9.46$ (neat)

$[\alpha]_D^{23} -13.55$ (CHCl₃, c 5.8)

N.M.R. : 8.67 (d, 3H) -CH-CH_3
 (neat) (s, 3H) $\begin{array}{c} \text{O} \\ \parallel \\ \text{-C-CH}_3 \end{array}$

6.47 τ (d, 2H)	Br- <u>CH₂</u> -CH -
4.91 τ (m, 1H)	- <u>CH</u> -

I.R. (film) : 2994 (m), 1741 (b.s), 1430 (m), 1375 (s),
neat, cm⁻¹ 1245 (b.s), 1133 (m), 1034 (b.s), 958 (m).

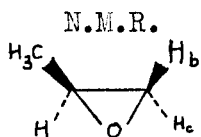
(S)-(-)-Propylene oxide —

58.1 ml (0.86M) potassium amylate was added dropwise to 9.05g (0.08M) bromoacetate mixture (crude product from the ether extract in the previous preparation) in 20 ml amyl alcohol with stirring at room temperature. Potassium bromide was precipitated soon after start of the reaction. When addition was complete, the mixture was warmed to 100°C and the propylene oxide distilled out, through a 10 cm vigreux column with efficiently cooled condenser and receiver, giving 2.47g (85%). B.p. 35°C.

$$[\alpha]_D^{22} -8.21 \quad (\text{CHCl}_3, c \ 5.04)$$

$$\text{lit. value } [\alpha]_D^{20} +8.5 \quad (\text{CHCl}_3, c \ 5.0)$$

for (R)-(+)-isomer¹⁰⁹



: 8.68 τ (d, 3H)	-CH-CH ₃
7.58 τ (q, 1H)	-CH _b H _c -
7.28 τ (t, 1H)	-CH _b H _c -
7.02 τ (m, 1H)	- <u>CH</u> -

I.R. : 3040 (b.s), 2965 (m), 1465 (b.s), 1437 (b.s.),
cm⁻¹ 1429 (b.s.), 1404 (b.s), 1276 (s), 1261 (s),
1135 (b.s), 1112 (b.s), 1030 (s), 1017 (s),
962 (s), 947 (s), 836 (very b.s), 770 (s),
757 (s).

(S)-(+)-2-Benzyloxypropan-1-yl-toluene-p-sulphonate —

(S)-(+)-Benzyloxypropane-1-ol was prepared as described in literature⁹⁸. This consisted in synthesis of (S)-(+)-2-benzyloxy ethyl lactate, from (S)-(-) ethyl lactate, followed by reduction with L.A.H. This was used as a starting material in the synthesis. 1.66g (0.01M) of $\text{CH}_3\text{CH}(\text{OCH}_2\text{Ph})\text{CH}_2\text{OH}$ was dissolved in 15ml of pyridine. 3.8132g (0.02M) of toluene-p-sulphonylchloride was added to the solution, which was then left standing overnight at 0°C. The mixture was poured over ice-water and the precipitate thus formed was collected by filtration. The aqueous layer was extracted with ether (100ml x 2). The extracts were washed with 1N HCl (100ml x 2), water (100ml x 1), dried over Na_2SO_4 and evaporated to dryness on the Buchi. This was purified by trap-to-trap distillation (0.02mm Hg, bath temperature 40°C) giving 2.94g (90%) of the product pure by T.L.C. (silica gel PF 254, 20% ethyl acetate in benzene).

N.M.R.	:	8.83 τ (d, 3H)	$\text{CH}_3\text{-CH}$
		7.57 τ (s, 3H)	-Ph-CH_3
		6.20 τ (m, 1H)	-CH-
		6.01 τ (d, 2H)	$\text{-CH-CH}_2\text{-}$
		5.44 τ (d, 2H)	$\text{-OCH}_2\text{-}$
		2.64 τ (d, 5H)	Ph-
		2.68 τ , 2.18 τ (d,d, 4H)	-Ph-CH_3
I.R.	:	3089 (m), 3067 (s), 3025 (s), 2977 (s),	
(CCl_4)		2937 (s), 2871 (s), 1922 (w), 1807 (w),	
cm^{-1}		1725 (m), 1600 (m), 1497 (m), 1455 (s),	
		1355 (very b.s), 1313 (s), 1277 (s), 1178 (b.s),	
		1097 (b.s), 1055 (b.s), 967 (b.s), 917 (b.s).	

M.S. : 17 (40.6), 18 (100), 27 (25.2), 28 (44.8),
 38 (18.2), 39 (88.2), 41 (21.0), 48 (15.4),
 50 (37.8), 51 (63.0), 52 (21.0), 62 (22.4),
 63 (61.5), 64 (18.2), 65 (100), 77 (58.7),
 78 (18.2), 79 (39.2), 89 (40.6), 90 (21.0),
 91 (98.0), 92 (99.5), 105 (16.8), 107 (18.2),
 155 (64.4).

Analysis	:	C	H
Found		63.2	6.25
$C_{17}H_{20}O_4S$ requires		63.7	6.30

Some of the β -substituted alkylcobaloximes were initially prepared by reported synthetic routes⁸⁸. One of these, which was used more than the others, was as follows. Cobaltous chloride, two equivalents of biacetyldioxime (DMG), two equivalents of sodium hydroxide and one equivalent of pyridine (or any other base to be used as the trans-ligand) were mixed together with stirring in methanol under N_2 . The reaction mixture was cooled to $-70^\circ C$. At this temperature a quarter equivalent of sodium borohydride was added with stirring and under nitrogen, followed by one equivalent (or excess as required in some cases) of the alkylating agent. This was stirred at $-70^\circ C$ for about 1h and then allowed to warm up to room temperature over 3h. The reaction mixture was freed of insoluble material by filtering and washing with methanol. The filtrates were then worked up to give the alkylcobaloxime. β -Hydroxyethylcobaloxime, prepared via this method by using ethylene oxide as the alkylating agent, was acetylated with acetic anhydride in pyridine to give the β -acetoxyethylcobaloxime. However, it was necessary to evolve different synthetic routes to the specifically labelled and chiral cobaloximes,

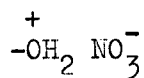
as the one described above is not suitable for this purpose. These procedures are described later.

Hydroxobis(biacetyldioximato)pyridinatocobalt(III) —

(a) Hydroxoquo-cobaloxime required for this synthesis was prepared as follows⁹². 11.9g (0.04M) $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and 11.6g (0.1M) of biacetyldioxime were mixed in 75ml of water. 15ml of 30% H_2O_2 was added gradually with heating and vigorous stirring. After stirring for 1h excess conc. HCl was added giving a dark green precipitate. This was filtered, washed with dilute HCl, alcohol and ether. The chlorohydrochlorocobaloxime thus obtained was treated with boiling water and stirred for 1h. The product was filtered and washed with water, alcohol and ether. The grey-green product (the chloroquo-cobaloxime) was treated with 1eq. of cold conc. K_2CO_3 and stirred vigorously. After 10-15 min. the mixture was filtered and washed with acetone giving 16.1g (50%) of the brownish-yellow hydroxoquo-cobaloxime.

1.25g (0.0387M) of this cobaloxime in 10ml water was treated with 1.93ml (0.0387eq) of 2N HNO_3 . 3.068g (1eq) of pyridine was added and the solution stirred for 2h⁹⁵. This was then evaporated to dryness giving 733mg (42.2%) of the dark brown nitrate salt of the hydroxocobaloxime. 448mg (1 mM) of this salt were treated with 165mg (1 mM) of K_2CO_3 in 5ml water. The reaction mixture was stirred for 2h and the product was extracted into dichloromethane (5ml x 2). The extracts were collected, dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in 10ml anhydrous pyridine and some molecular sieves (type 4A) were added. The solution was then stirred overnight,

evaporated to dryness and the product extracted in dichloromethane. Stirring with pyridine was necessary to replace the pyridine which might have been substituted by water during the reaction with K_2CO_3 . The product was rapidly chromatographed over a small silica gel column. CH_2Cl_2 , EtOAc and EtOAc:MeOH (1:1) were successively used as eluents and three fractions were collected. T.L.C. indicated that the first two fractions were identical. They were combined and recrystallised from methanol-ethylacetate giving 177mg (46.1%) of the product pure by N.M.R. and T.L.C. However, as mentioned in Chapter II, the elemental analysis was not satisfactory.



I.R. : ≈ 3000 (very broad), 2124 (b,w), 1750 (b.w),
(nujol) 1636 (m), 1608 (m), 1548 (b,m), 1488 (m),
 cm^{-1} 1242 (m), 1197 (w), 1092 (w), 1038 (w),
981 (w), 908 (w), 812 (w), 750 (m), 679 (m).

-OH

N.M.R. : 7.58 τ (s, 12H) DMG methyls
2.77 τ (t, 2H) pyridine β -H
2.26 τ (t, 1H) pyridine γ -H
1.70 τ (d, 2H) pyridine α -H

I.R. : 3029 (w), 2913 (w), 1613 (m), 1570 (b.s),
 cm^{-1} 1500 (w), 1455 (m), 1374 (m), 1239 (s),
1093 (s), 1073 (s), 982 (m), 614 (m), 512 (s),
432 (w), 384 (m).

U.V. : 225 nm/ 1.3×10^4

(b) 600 mg (1.32 mM) of β -acetoxylethyl(pyridine)cobaloxime were dissolved in 150 ml of dioxan:water (1:1) and thermostatted in a water-bath at 40°C for 3 days. The solution was evaporated to dryness, re-dissolved in dry CH_2Cl_2 (5 ml) and rapidly chromatographed on a small silica gel column (MN - silica gel N supplied by Macherey, Nagel and Co.). Ethylacetate:methanol (1:1) was used as an eluent. The first fraction was collected and re-crystallised from dry CH_2Cl_2 giving 182 mg (19.5%) of the hydroxocobaloxime.

N.M.R.	:	7.56 τ (s, 12H)	DMG methyls
		2.78 τ (t, 2H)	pyridine β -H
		2.25 τ (t, 1H)	pyridine γ -H
		1.72 τ (d, 2H)	pyridine α -H
I.R.	:	3030 (b.w), 2912 (b.w), 1611 (m), 1560 (m),	
cm^{-1}		1498 (w), 1452 (m), 1375 (w), 1231 (m),	
		1090 (b,s), 980 (w), 611 (s), 509 (m), 423 (w).	

Trifluoroacetoxybis(biacetyldioximato)pyridinatocobalt(III) —

500 mg (1.21 mM) of the β -hydroxyethylcobaloxime was dissolved in 15 ml of CH_2Cl_2 . 102.4 ml (1.33 mM, 1.1 eq) of trifluoroacetic acid was added with stirring. There was an immediate effervescence due to ethylene evolution. The reaction mixture was stirred for an hour and evaporated to dryness. The product was re-crystallised from dichloromethane-ethylacetate giving 495 mg (95%).

N.M.R.	:	7.56 τ (s, 12H)	DMG methyls
		2.73 τ (t, 2H)	pyridine β -H
		2.22 τ (t, 1H)	pyridine γ -H
		1.75 τ (d, 2H)	pyridine α -H

I.R. : 3035 (b.w), 2910 (w), 1714 (s), 1610 (s),
 cm⁻¹ 1563 (s), 1495 (m), 1453 (s), 1396 (s),
 1368 (m), 1236 (s), 1182 (b.s), 1141 (s),
 1091 (s), 1073 (s), 979 (s), 837 (m), 519 (s),
 430 (m).

U.V. : 242 nm/1.65 x 10⁵

Analysis %	:	C	H
Found		37.8	4.02
C ₁₅ H ₁₉ CoF ₃ N ₆ O ₅ requires		37.45	4.44

The methods reported in literature for the syntheses of cobaloximes⁸⁸ are not suitable for making chiral and specifically labeled cobaloximes. The use of sodio-cobaloxime was suggested in a personal communication⁸⁹. This cobaloxime was prepared by treating a suspension of chlorocobaloxime in dry and distilled tetrahydrofuran with sodium and refluxing until all sodium dissolved. Evaporating this solution to dryness gave the sodiocobaloxime. However, when this was treated with benzyl bromide (2 eq), the anticipated benzylcobaloxime was obtained in low yields (15%). It was decided to use lithiocobaloxime (prepared analogously to sodiocobaloxime) as an intermediate. The preparation was carried out as follows. 1.715 g (4 mM) of chlorocobaloxime were suspended in 50 ml dry and distilled tetrahydrofuran. 27.8 mg (4 mM) of Li was added and the solution was refluxed for 24 hours. 0.95 ml (8 mM) of benzyl bromide was added and the solution stirred for 2 hours. It was evaporated to dryness and the product extracted into CH₂Cl₂. This was rapidly chromatographed on a small silica gel column using ethylacetate as an eluent. Three fractions were collected. The first fraction (about 40% of

the total collected) was a white compound which was purified by sublimation. It was identified from its m.p. 87°C (lit. value $85 - 86^{\circ}\text{C}$) and its spectroscopic properties⁹⁰ —

N.M.R.	:	7.74 τ (s, 6H)	DMG methyls
		4.57 τ (s, 2H)	$-\text{O}-\text{CH}_2-\text{Ph}$
		2.40 τ (s, 5H)	$\text{Ph}-\text{CH}_2$
I.R.	:	3580 (m), 3310 (very b.m), 3000 (m), 2935 (m),	
cm^{-1}		1735 (w), 1673 (w), 1642 (m), 1565 (m),	
		1498 (w), 1456 (s), 1370 (b.s), 1222 (m),	
		1091 (m), 1015 (s), 980 (s), 910 (s), 823 (m).	

Fractions 2 and 3 contained the benzylcobaloxime contaminated with a large amount of des-alkylcobaloxime(s). After the failure of this method it was decided to use bromocobaloxime⁹¹ as an intermediate in a modification of a method described in literature⁹². β -Acetoxy- β, β -dideuterio-ethyl(pyridine)cobaloxime, β -acetoxyethyl(4-dimethylaminopyridine)cobaloxime, β -acetoxyethyl(4-cyanopyridine)cobaloxime, (S)-(+)- β -acetoxypropyl(pyridine)cobaloxime, (S)-(+)- β -hydroxypropyl(pyridine)cobaloxime and (S)-(+)- β -benzyloxypropyl(pyridine)-cobaloxime were prepared by this method - which is described for the β -acetoxyethyl(4-cyanopyridine)cobaloxime - using the appropriate alkylating agents and bromocobaloximes. Bromo(4-cyanopyridine)-cobaloxime and bromo(4-dimethylaminopyridine)cobaloxime were prepared by a method analogous to that described for bromo(pyridine)cobaloxime⁹¹. According to this method, cobaltous acetate and 2 eq of DMG were stirred in hot 95% ethanol, under nitrogen. 2 eq of the appropriate pyridine was added and the solution cooled down to room temperature. 1 eq NaBr was added and air was bubbled through the reaction mixture

for about 0.5h. This was then allowed to stand when the cobaloxime crystallised out. It was filtered, washed and dried. The yields of the two new bromocobaloximes and their spectroscopic and analytical data are as follows:

Bromo(4-cyanopyridine) —

Yield : 75%

N.M.R. : 7.61 τ (s, 12H) DMG methyls
 2.53 τ (d, 2H) pyridine C(2)-H
 1.50 τ (d, 2H) pyridine C(3)-H

I.R. : 3419 (b.w), 2919 (m), 2229 (w), 1675 (s),
 cm⁻¹ 1617 (s), 1561 (b.s), 1505 (m), 1365 (s), 1219 (m),
 1078 (b.s), 980 (m), 842 (m).

Analysis %	:	C	H
Found		34.5	4.51
C ₁₄ H ₁₈ BrCoN ₆ O ₄ requires		35.6	3.84
C ₁₄ H ₁₈ BrCoN ₆ O ₆ .H ₂ O requires		34.69	4.07

Bromo(4-dimethylaminopyridine)cobaloxime) —

Yield : 69%

N.M.R. : 7.64 τ (s, 12H) DMG methyls
 7.06 τ (s, 6H) N(CH₃)₂
 3.72 τ (d, 2H) pyridine C(3)-H
 2.42 τ (d, 2H) pyridine C(2)-H

I.R. : 2920 (m), 2580 (w), 2365 (b.w), 1785 (b.w),
 cm⁻¹ 1625 (s), 1555 (b.s), 1375 (b.m.), 1189 (b.m),
 1068 (b.s), 981 (m), 815 (m).

Analysis %	:		C	H
Found			35.66	5.32
B ₁₅ H ₂₄ BrCoN ₆ O ₄ requires			36.70	4.93
C ₁₅ H ₂₄ BrCoN ₆ O ₄ .H ₂ O requires			35.40	5.28

β-Acetoxyethylbis(biacetyldioximato)-4-cyanopyridinato-
 cobalt(III) —

A suspension of 473.2 mg (1 mM) of bromo(4-cyanopyridine)-cobaloxime in 10 ml dioxan:water (4:1) was prepared in a Schlenk tube attached to a vacuum line. This suspension was degassed and flushed with oxygen-free nitrogen. 114 mg (3mM) of NaBH₄ were added with stirring (under N₂) followed by 501 mg (3mM) of BrCH₂CH₂OAc also under N₂. The reaction mixture was stirred under N₂ for 4h. It was evaporated to dryness, extracted in CH₂Cl₂ and filtered. The filtrate was concentrated and rapidly chromatographed on silica gel using ethyl acetate-dichloromethane as follows. A saturated solution of the cobaloxime was prepared in ethyl acetate using minimum amount of CH₂Cl₂ to increase solubility. The solution was evaporated on the Buchi. When crystallisation commenced, on account of the evaporation of CH₂Cl₂, the flask was removed from the Buchi, stoppered and allowed to stand at 0°C to complete crystallisation. The crystals were filtered, washed with ethyl acetate and dried at room temperature under high vacuum giving 150 mg (30.6%) of the product.

N.M.R.	:	8.43 τ (t, 2H)	Co- <u>CH₂</u> -
		8.06 τ (s, 3H)	$\begin{array}{c} \text{O} \\ \parallel \\ \text{-C-CH}_3 \\ \text{---} \end{array}$
		7.86 τ (s, 12H)	DMG methyls
		6.32 τ (t, 2H)	<u>CH₂</u> -OAc
		2.45 τ (d, 2H)	pyridine C(2)-H
		1.21 τ (d, 2H)	pyridine C(3)-H

I.R.	:	2907 (b.w), 2232 (w), 1727 (s), 1613 (m),
cm ⁻¹		1561 (s), 1502 (w), 1378 (s), 1230 (s), 1089 (s),
		1069 (s), 1018 (s), 977 (m), 954 (m), 835 (s),
		524 (m), 452 (m).

Analysis %	:	C	H
Found		44.78	5.42
C ₁₈ H ₂₅ CoN ₆ O ₆ requires		45.50	5.30

The yields for spectroscopic and analytical data for the β - acetoxylethyl(4-dimethylaminopyridine)cobaloxime, the correspondingly deuteromethyl ethers of this and the cobaloxime described above, and the β -benzyloxypropyl(pyridine)cobaloxime are as follows:

β -Acetoxylethylbis(biacetyldioximato)-4-dimethylamino-pyridinatocobalt(III) —

Yield : 33%

N.M.R.	:	8.61 τ (t, 2H)	Co- <u>CH₂</u> -
		7.86 τ (s, 12H)	DMG methyls
		7.01 τ (s, 6H)	-N-(<u>CH₃</u>) ₂
		6.24 τ (t, 2H)	<u>CH₂</u> -OAc
		3.57 τ (d, 2H)	pyridine C(3)-H
		1.94 τ (d, 2H)	pyridine C(2)-H

I.R. : 2907 (b.m), 1725 (s), 1622 (s), 1538 (b.s),
 cm^{-1} 1432 (b.m), 1379 (s), 1228 (s), 1089 (s), 1080 (s),
 1016 (s), 952 (s), 816 (s), 525 (m), 450 (m)

Analysis %	:	C	H
Found		45.79	6.60
$\text{C}_{19}\text{H}_{31}\text{CoN}_6\text{O}_6$ requires		45.30	6.34

β -Benzyloxybis(biacetyldioximato)pyridinatocobalt(III):

(a) synthetic —

Yield : 79.5%

N.M.R.	:	8.67 τ (t, 2H)	Co-CH <u>2</u>
		8.83 τ (d, 3H)	-CH-CH <u>3</u>
		7.99 τ (d, 13H)	DMG methyls and Co-CH <u>1</u>
		7.0 τ (m, 1H)	-CH-CH <u>3</u>
		5.7 τ (s, 2H)	-O-CH <u>2</u> -Ph
		2.79 τ (s, 5H)	-Ph
		2.78 τ (t, 2H)	pyridine β -H
		2.35 τ (t, 1H)	pyridine γ -H
		1.50 τ (d, 2H)	pyridine α -H

I.R. : 3655 (w), 2993 (b.s), 2455 (b.w), 1609 (m),
 cm^{-1} 1565 (s), 1497 (m), 1454 (s), 1379 (m),
 1238 (b.s), 1157 (m), 1125 (m), 1090 (very b.s),
 695 (m), 633 (m), 588 (w), 516 (s), 460 (m),
 437 (m).

U.V. : 234.5 nm (2.63×10^4)

$$[\alpha]_D^{22} + 3.72 \quad (\text{CHCl}_3, c 1.938)$$

$$\text{C.D.} \quad : \quad \Delta\epsilon + 0.50 \quad (362 \text{ nm})$$

$$\Delta\epsilon - 0.13 \quad (403 \text{ nm})$$

Analysis %	:	C	H
Found		52.78	6.19
$\text{C}_{23}\text{H}_{32}\text{CoN}_5\text{O}_5$ requires		54.00	6.50
$\text{C}_{23}\text{H}_{32}\text{CoN}_5\text{O}_5 \cdot \text{H}_2\text{O}$ requires		52.10	6.45

(b) from solvolysis —

300 mg (0.64 mM) β -acetoxypropylcobaloxime was dissolved in 5 ml benzyl alcohol and stirred at room temperature for 3 days. The solution was chromatographed on a small silica gel column using ether as an eluent. The product, seen as a pale orange band, was isolated and further purified by preparative T.L.C. (silica gel 0.5 mm; ethyl acetate). The band was scraped off and extracted in ethyl acetate. The extracts were evaporated to dryness giving 122.9 mg (37.4%) of the product pure by N.M.R.

N.M.R.	:	8.66 τ (t, 1H)	Co- <u>CH</u> _{α2}
		8.83 τ (d, 3H)	- <u>CH</u> - <u>CH</u> ₃
		7.99 τ (d, 13H)	DMG methyls and Co- <u>CH</u> _{α1}
		7.01 τ (m, 1H)	- <u>CH</u> -
		5.68 τ (s, 2H)	- <u>CH</u> ₂ -Ph
		2.77 τ (s, 5H)	<u>Ph</u> -
		2.78 τ (t, 2H)	pyridine β -H
		2.37 τ (t, 1H)	pyridine γ -H
		1.52 τ (d, 2H)	pyridine α -H

I.R. : 3667 (w), 2992 (b.s), 2452 (b.w), 1606 (m),
 cm^{-1} 1562 (s), 1495 (m), 1452 (s), 1377 (m),
 1232 (b.s), 1154 (w), 1122 (m), 1062 (very
 b.s), 907 (w), 692 (w), 630 (w), 586 (w),
 514 (w), 458 (w), 434 (m).

U.V. : 234.5 nm/ 2.63×10^4

$[\alpha]_D^{22} + 3.72$ (CHCl_3 , c 1.702)

C.D. : $\Delta\epsilon + 0.47$ (363 nm)
 $\Delta\epsilon - 0.18$ (403 nm)

The spectroscopic data for the corresponding chiral acetoxy-
 and hydroxy-propylcobaloximes is given below.

(a) (S)-(+)- β -Acetoxypropylbis(biacetyldioximato)pyridinato-
 cobalt(III) —

N.M.R.	:	8.88 τ (d, 3H)	$-\text{CH}-\text{CH}_3$
		8.88 τ (d, 1H)	$\text{Co}-\text{CH}_{\alpha 1}-$
		8.43 τ (t, 1H)	$\text{Co}-\text{CH}_{\alpha 2}-$
		7.96 τ (s, 3H)	$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{CH}_3 \end{array}$
		7.84 τ (s, 12H)	DMG methyls
		7.13 τ (m, 1H)	$-\text{CH}-\text{CH}_3$
		2.63 τ (t, 2H)	pyridine β -H
		2.22 τ (t, 1H)	pyridine γ -H
		1.36 τ (d, 2H)	pyridine α -H

U.V. : 241.8 (2.795×10^4)

$$[\alpha]_D^{25} + 2.5 \text{ (CHCl}_3, c \text{ 3.87)}$$

$$\begin{aligned} \text{C.D.} & : \Delta\epsilon + 0.12 \text{ (330 nm)} \\ & \Delta\epsilon + 0.20 \text{ (390 nm)} \\ & \Delta\epsilon + 0.12 \text{ (448 nm)} \end{aligned}$$

(b) (S)-(+)- β -Hydroxypropylbis(biacetyldioximato)pyridinato-cobalt(III) —

N.M.R.	: 8.95 τ (d, 3H)	-CH-CH $\underline{\text{CH}_3}$
	8.82 τ (t, 1H)	Co-CH $\underline{\text{CH}_{\alpha 2}}$ -
	7.86 τ (s, 12H)	DMG methyls
	7.86 τ (d, 1H)	Co-CH $\underline{\text{CH}_{\alpha 1}}$ -
	6.79 τ (m, 1H)	-CH-CH $\underline{\text{CH}_3}$
	2.63 τ (t, 2H)	pyridine β -H
	2.21 τ (t, 1H)	pyridine γ -H
	1.41 τ (d, 2H)	pyridine α -H

$$\text{U.V.} : 239.5 \text{ (} 2.09 \times 10^4 \text{)}$$

$$[\alpha]_D^{22} + 8.21 \text{ (CHCl}_3, c \text{ 1.67)}$$

$$\begin{aligned} \text{C.D.} & : \Delta\epsilon + 2.02 \text{ (357 nm)} \\ & \Delta\epsilon - 0.29 \text{ (407 nm)} \end{aligned}$$

V Solvolyses of β -acetoxyalkylcobaloximes :

(a) Hydrolysis —

600 mg (1.32 mM) of β -acetoxyethyl(pyridine)cobaloxime were dissolved in 150 ml dioxan:water (65:35). The solution was thermostatted, in a water bath, at 25°C. Aliquots were withdrawn at

regular intervals and evaporated to dryness on the freeze-drier. The residue was dissolved in CDCl_3 in order to assay the progress of the reaction by N.M.R. spectroscopy. After 59h from start, 64.0% of β -hydroxyethylcobaloxime, the hydrolytic product, had been formed. The last reading recorded 420h from start (approximately after 12 half-lives) indicated 81.5% of the hydrolytic product.

N.M.R.	: 8.32 τ (t, 2H)	Co- <u>CH₂</u> -CH ₂ -
	7.86 τ (s, 12H)	DMG methyls
	6.96 τ (t, 2H)	-CH ₂ - <u>CH₂</u> -OH

The hydrolysis was repeated using dioxan:water (1:1) at 25°C and 40°C, and (4:1) at 40°C. The progress of the reaction was assayed as described above.

(b) Methanolysis —

50 mg (0.11 mM) of β -acetoxyethyl(pyridine)cobaloxime were dissolved in 0.5 ml $\text{CDCl}_3:\text{CD}_3\text{OD}$ (3:2) in an N.M.R. tube. T.M.S. was used as an internal reference. This was immersed in a bath at 35.9°C - the temperature of the probe. The reaction was followed by recording spectra at intervals. According to the N.M.R. spectrum recorded 60h from start (i.e. nearly after 12 half-lives), 77% of the deuteromethylether had been formed.

N.M.R.	: 8.43 τ (t, 2H)	Co- <u>CH₂</u> -CH ₂ -
	7.86 τ (s, 12H)	DMG methyls
	6.93 τ (t, 2H)	-CH ₂ - <u>CH₂</u> -OCD ₃

The methanolysis was repeated using (1:1) and (2:3) $\text{CD}_3\text{OD}:\text{CDCl}_3$. An apparent increase in the rate was observed as the proportion of deuteromethanol in the solvent increased.

The deuteromethanolyses of β -acetoxyethyl(pyridine)cobaloxime, β -acetoxyethyl(triphenylphosphine), β -acetoxyethyl(4-cyanopyridine)-cobaloxime and β -acetoxyethyl(4-dimethylaminopyridine)cobaloxime were performed in the manner described above. 0.15 mM of each cobaloxime were dissolved in 0.5 ml $\text{CD}_3\text{OD}:\text{CDCl}_3$ (2:3) and the reaction was followed by N.M.R. spectroscopy. This was repeated using 0.075 mM of each cobaloxime in 0.5 ml of the same solvent system. No significant difference in rates in the two cases was found for any of the cobaloximes mentioned above. The products obtained from the deuteromethanolysis of β -acetoxyethyl(4-cyanopyridine)cobaloxime and β -acetoxyethyl(4-dimethylaminopyridine)-cobaloxime were isolated. This was achieved, in each case, by evaporating the reaction mixture to dryness, rapidly chromatographing over silica gel using ethyl acetate as an eluent and recrystallising from ethyl acetate-dichloromethane. Their spectroscopic and analytical data are as follows:

β -($^2\text{H}_3$)methoxyethylbis(biacetyldioximato)-4-cyanopyridinato-cobalt(III) —

N.M.R.	:	8.35 τ (t, 2H)	Co- CH_2 - CH_2
		7.86 τ (s, 12H)	DMG methyls
		6.99 τ (t, 2H)	- CH_2 - CH_2 - OCD_3
		2.41 τ (d, 2H)	pyridine C(2)-H
		1.20 τ (d, 2H)	pyridine C(3)-H

I.R.	:	3675 (w), 2920 (b.w), 2220 (w), 1612 (w),
cm^{-1}		1559 (s), 1370 (b.m), 1215 (b.m), 1085(b.s),
		975 (w), 837 (m).

Analysis %	:	C	H
Found		45.04	5.16
$C_{17}H_{22}CoD_3N_6O_5$ requires		45.4	4.92

β -(2H_3)methanoxyethylbis(biacetyldioximato)-4-dimethyl-aminopyridinatocobalt(III) —

N.M.R.	:	8.59 τ (t, 2H)	Co- <u>CH₂</u> -CH ₂ -
		7.90 τ (s, 12H)	DMG methyls
		7.02 τ (s, 6H)	N-(<u>CH₃</u>) ₂
		7.02 τ (t, 2H)	-CH ₂ - <u>CH₂</u> -OCD ₃
		3.63 τ (d, 2H)	pyridine C(3)-H
		2.03 τ (d, 2H)	pyridine C(2)-H
I.R.	:	3665 (m), 3590 (m), 3415 (very b.m), 2916	
cm ⁻¹		(b.s), 2815 (m), 1729 (b.w), 1623 (s),	
		1535 (very b.s), 1375 (b.m), 1185 (very b.w),	
		1075 (b.s), 1010 (w), 975 (w), 955 (w).	

Analysis %	:	C	H
Found		45.69	6.46
$C_{18}H_{28}CoD_3N_6O_5$ requires		46.20	6.03

Deuteromethanolysis of β -acetoxy- β,β -dideuterioethyl-(pyridine)cobaloxime —

120 mg (0.263mM) of this cobaloxime were dissolved in 1.1 ml $CD_3OD:CDCl_3$ (3:2) in an N.M.R. tube and thermostatted at 37.8°C. Spectra were recorded every hour for the first four hours and then after 8h and 26h. After 40h the reaction mixture was evaporated to dryness and the residue was recrystallised from ethyl acetate-

dichloromethane giving 73.9 mg (65%) of the product pure by N.M.R.

N.M.R.	:	8.41 τ	(broad s, $\frac{1}{2}$ 2H)	Co- <u>CH₂</u> -CD ₂ -
		7.89 τ	(s, 12H)	DMG methyls
		6.94 τ	(broad s, $\frac{1}{2}$ 2H)	Co-CD ₂ - <u>CH₂</u> -
		2.68 τ	(t, 2H)	pyridine β -H
		2.24 τ	(t, 1H)	pyridine γ -H
		1.41 τ	(d, 2H)	pyridine α -H

FIGURE IX

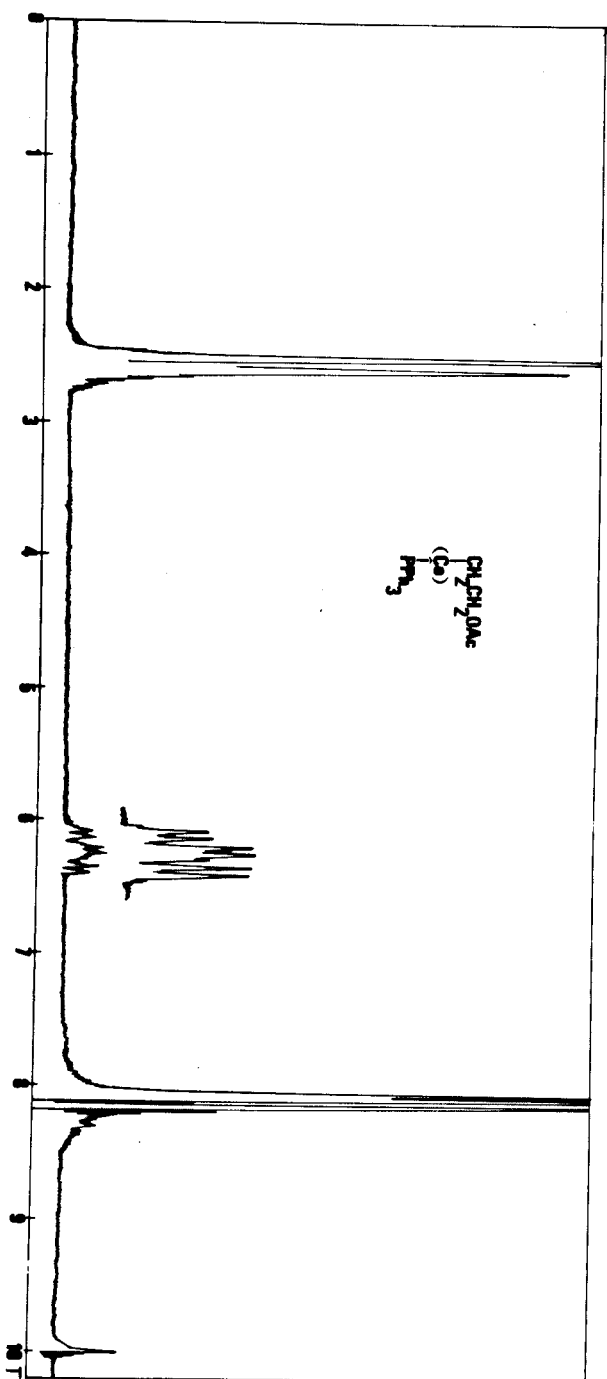
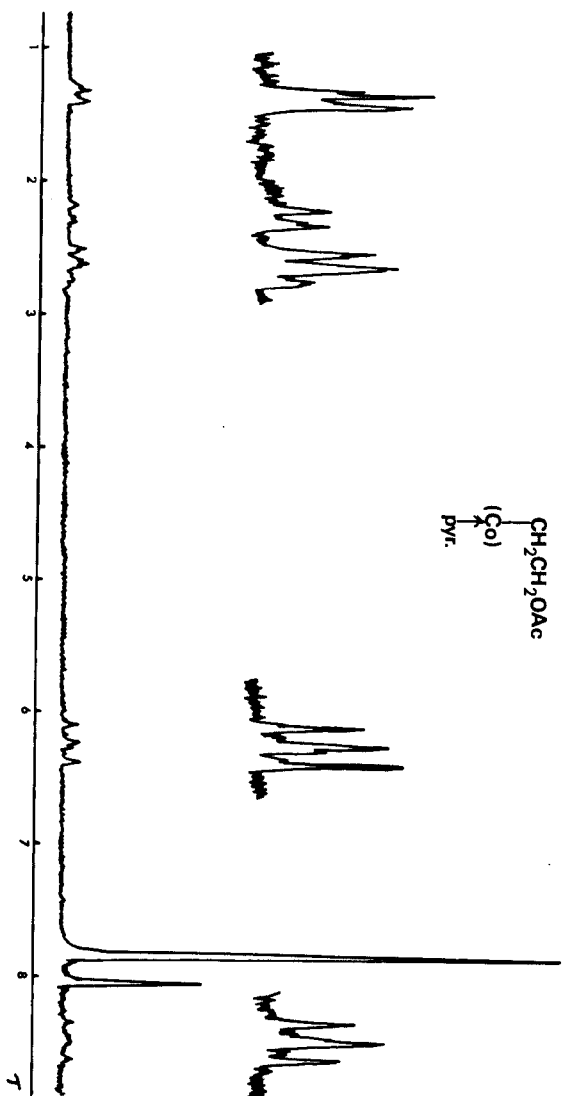


FIGURE X

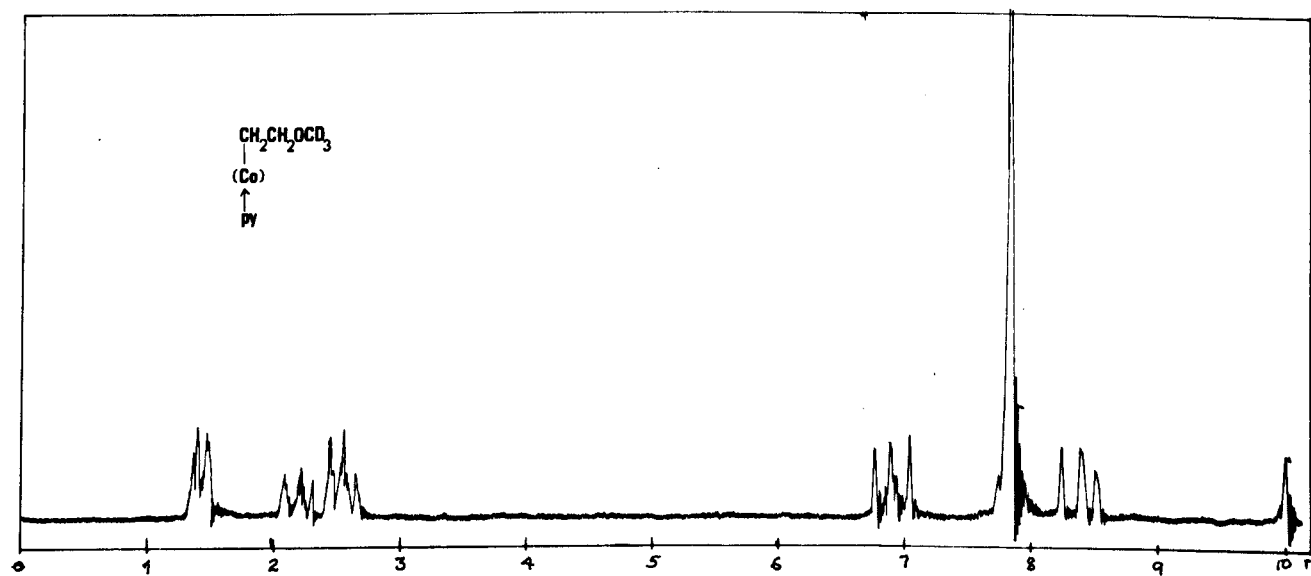
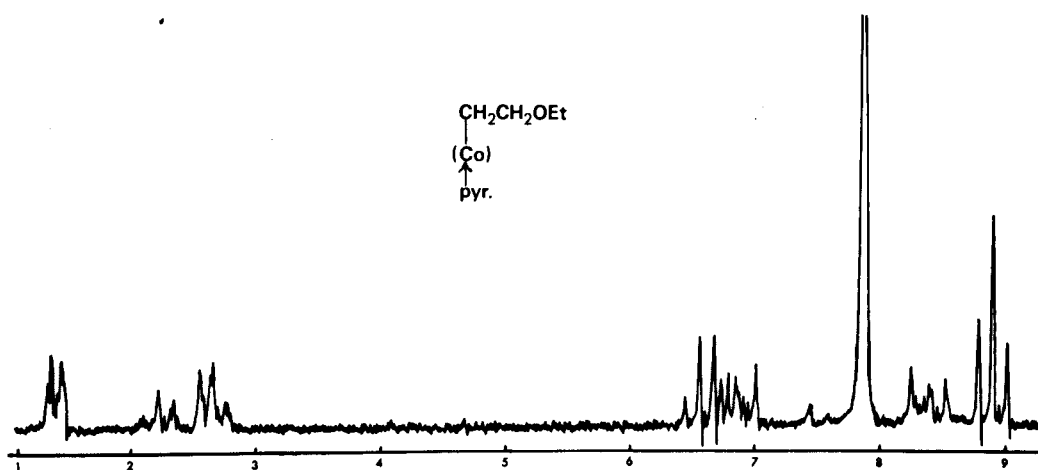
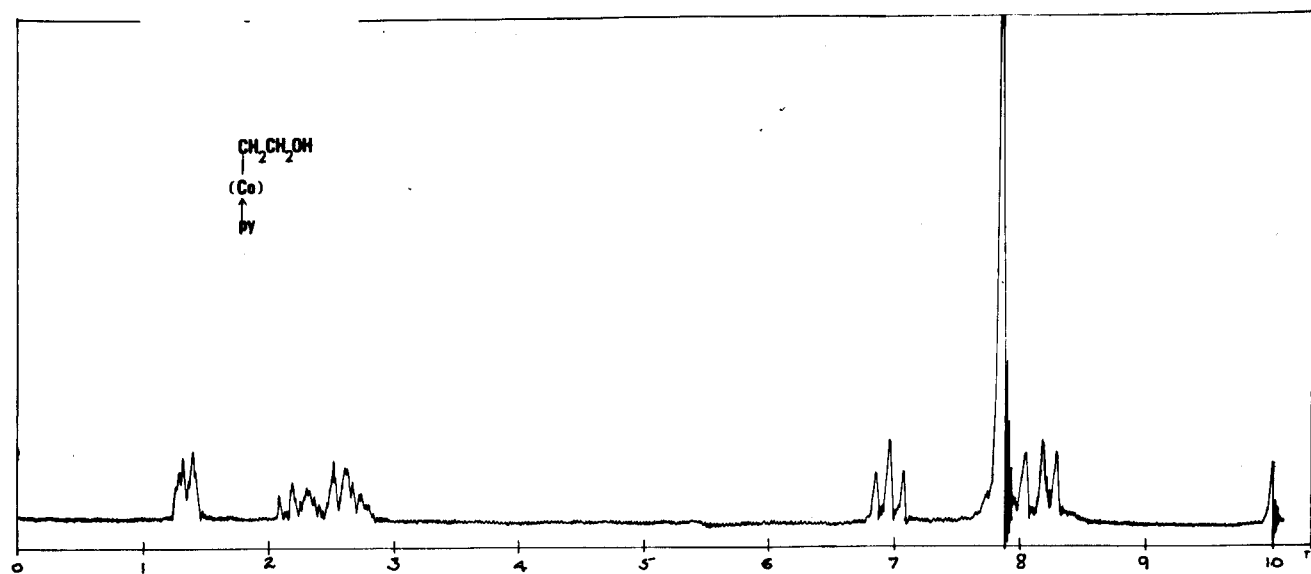


FIGURE XI

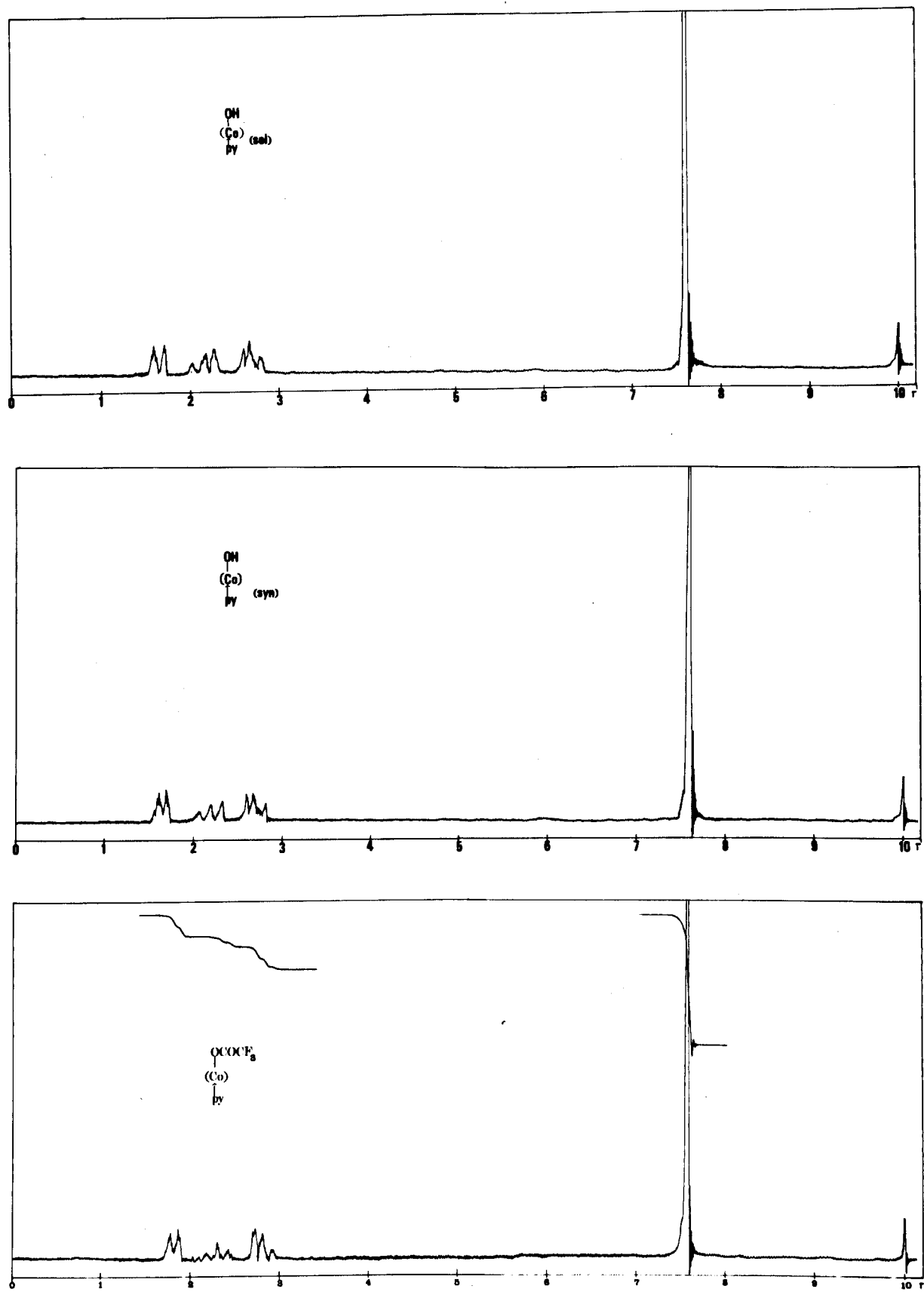
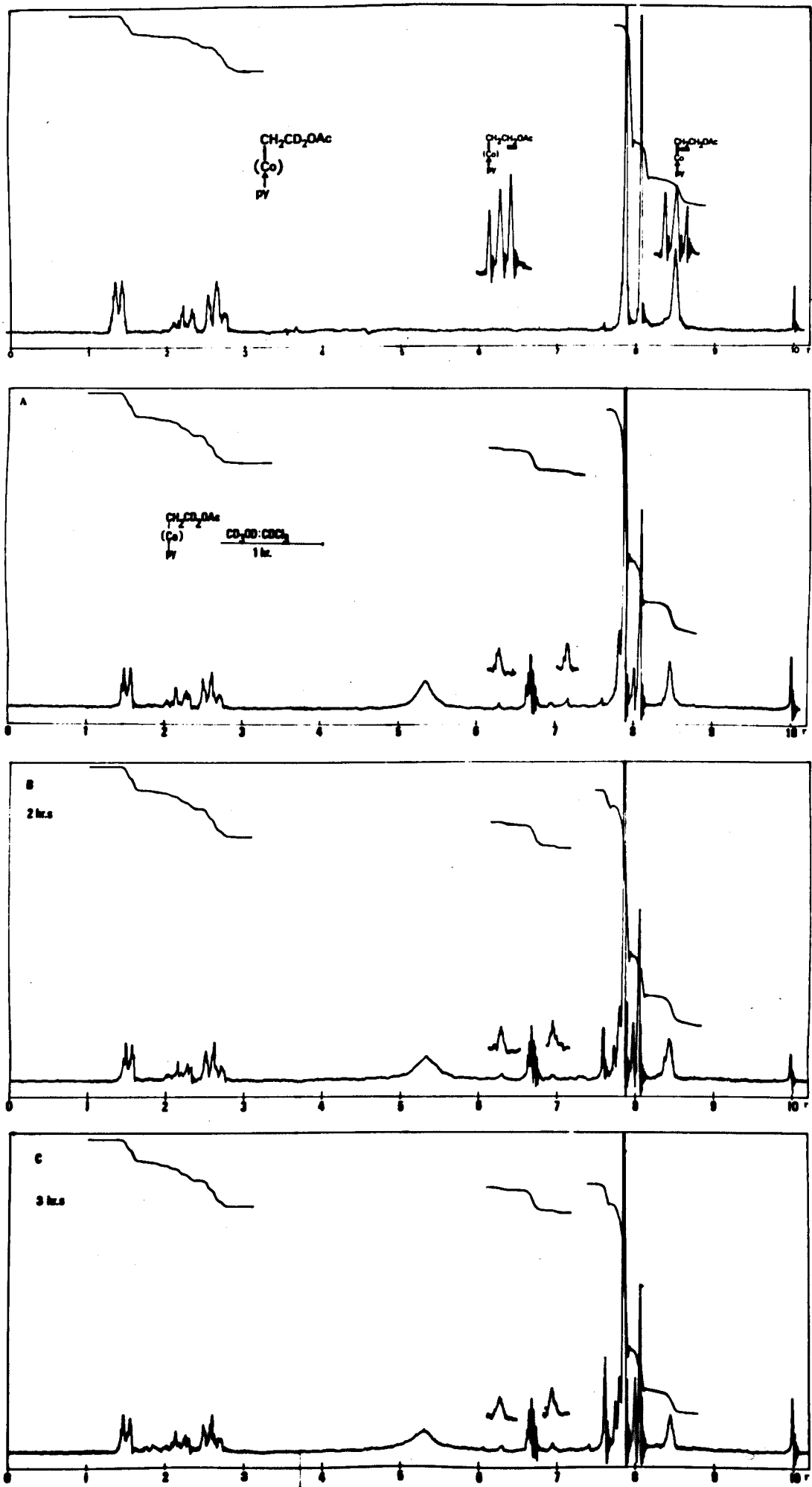


FIGURE XII



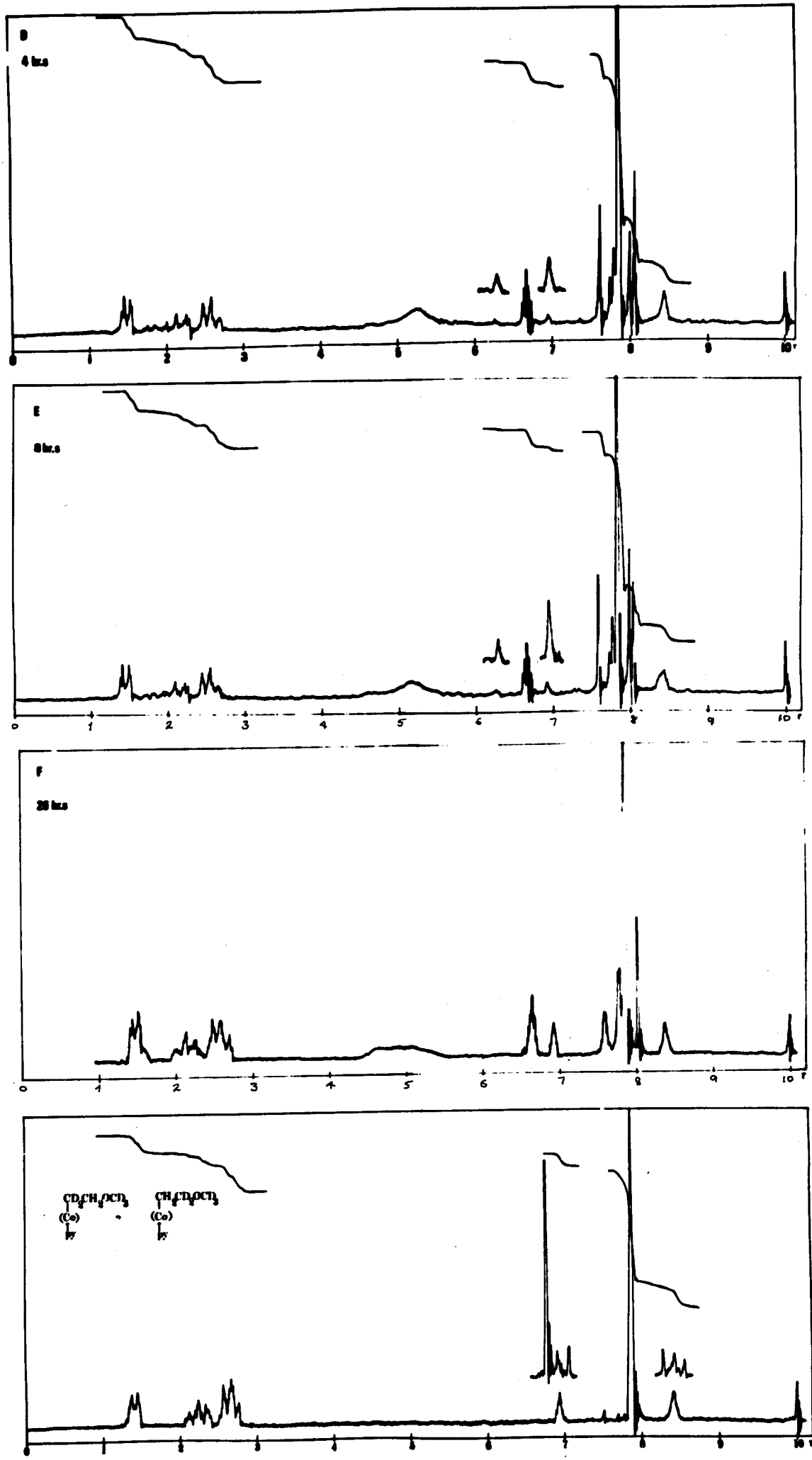


FIGURE XIV

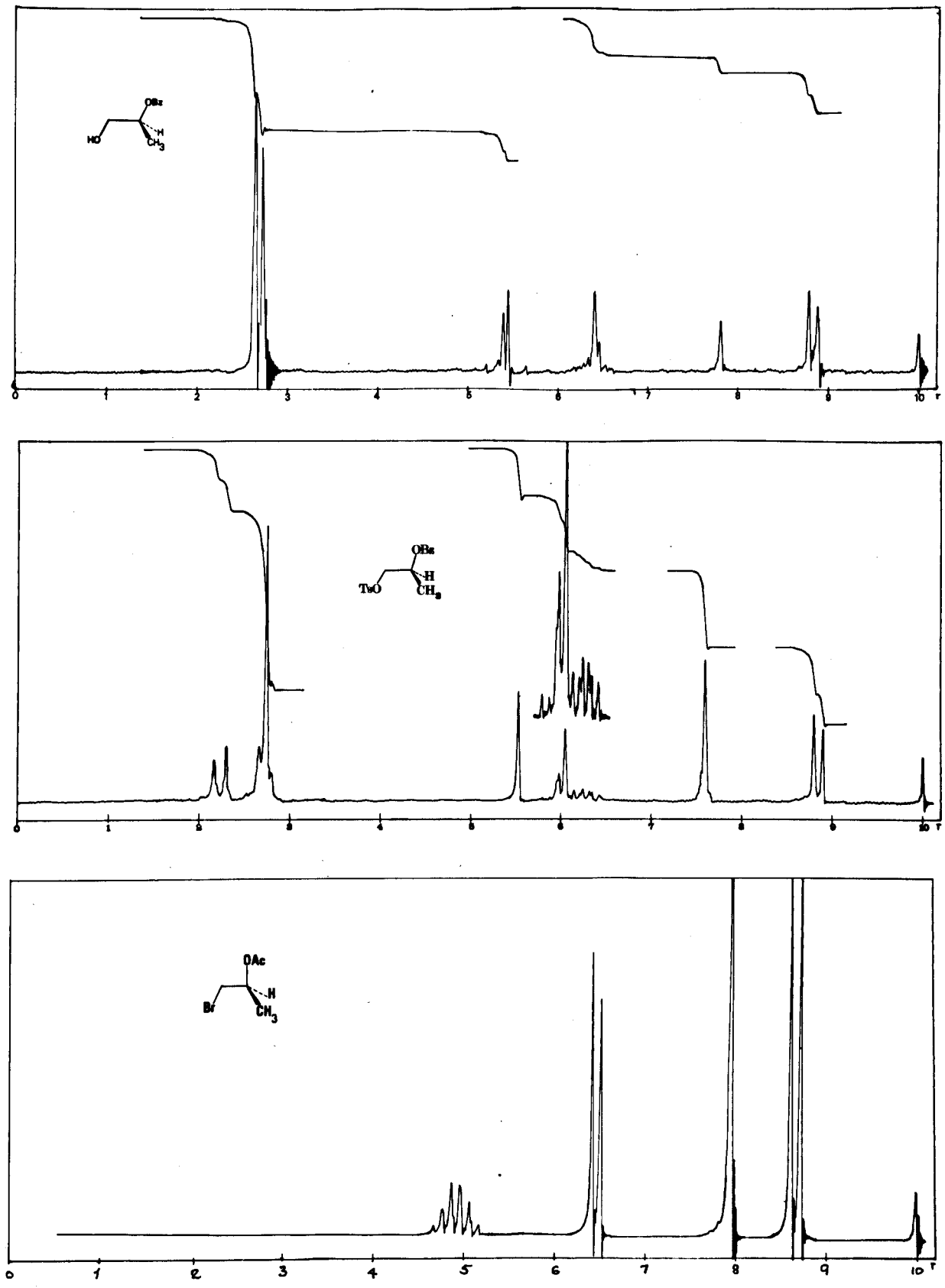


FIGURE XV

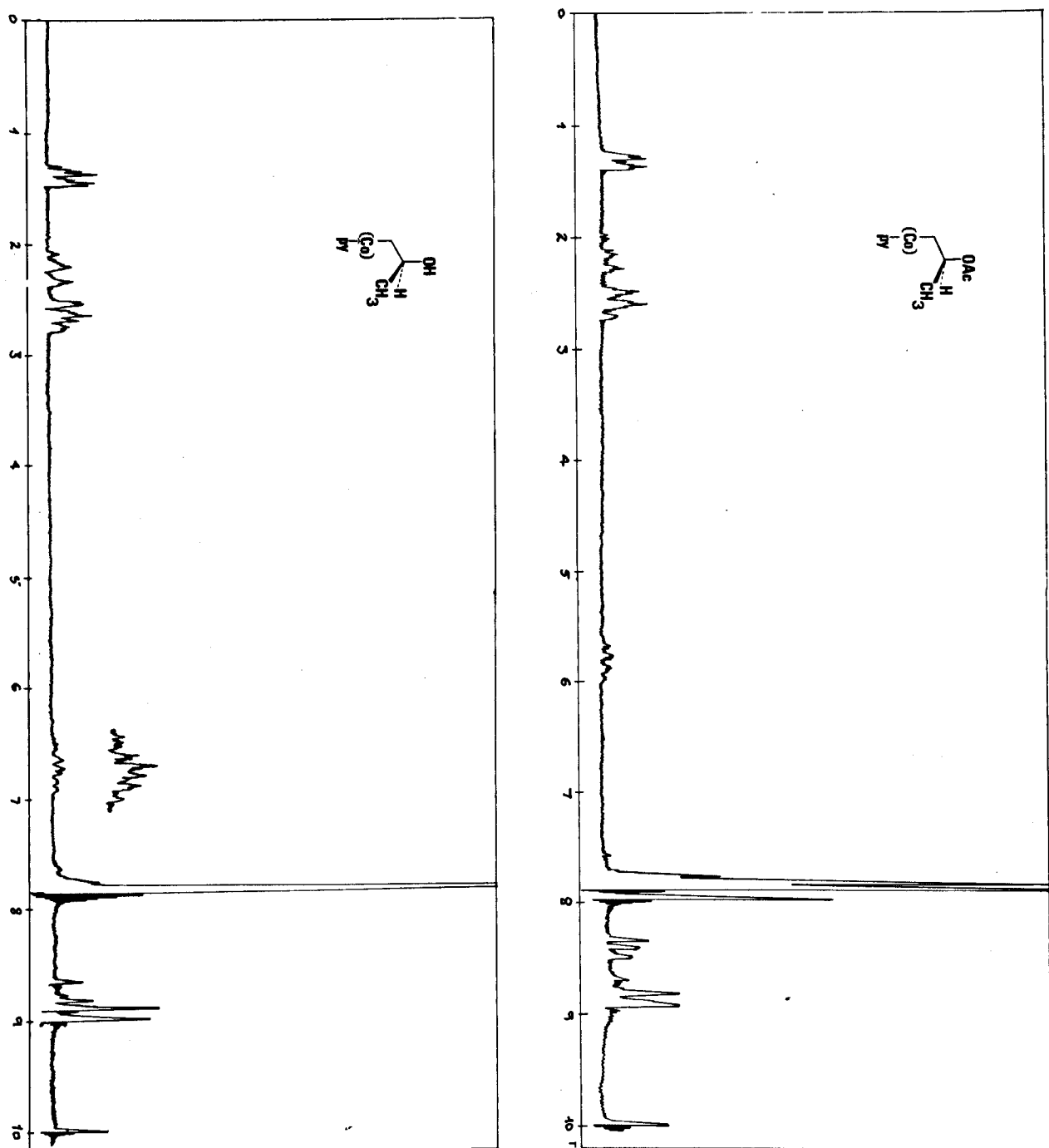


FIGURE XVI

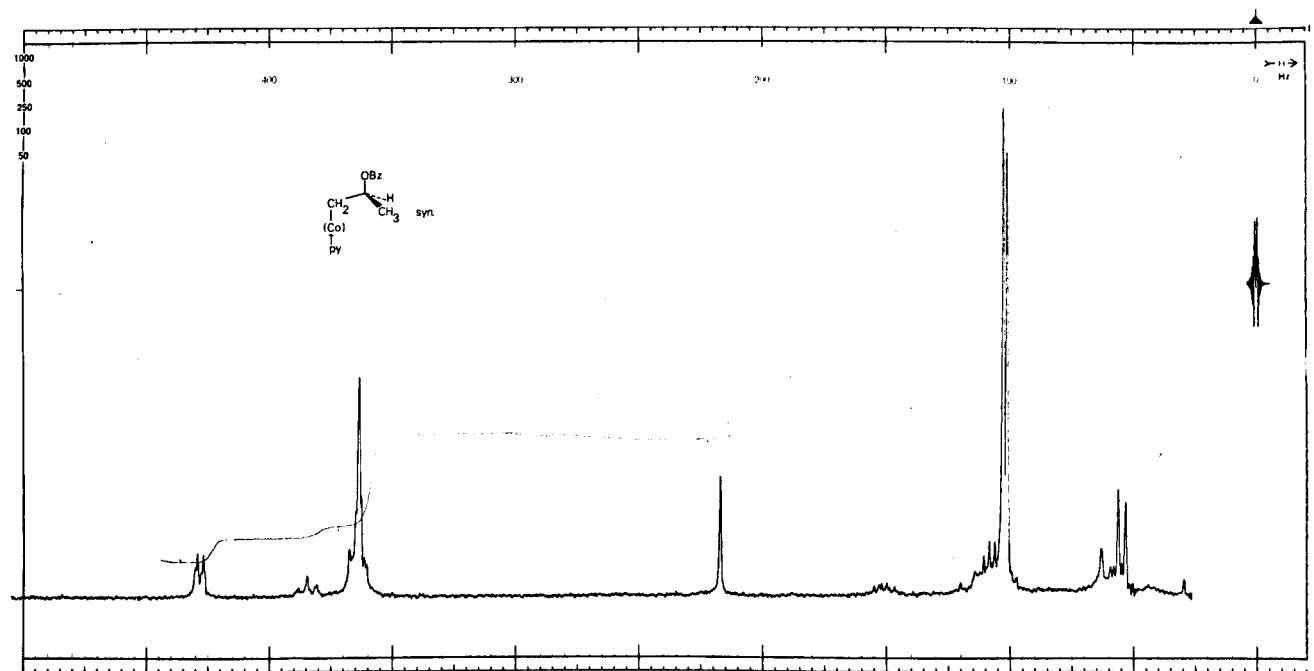
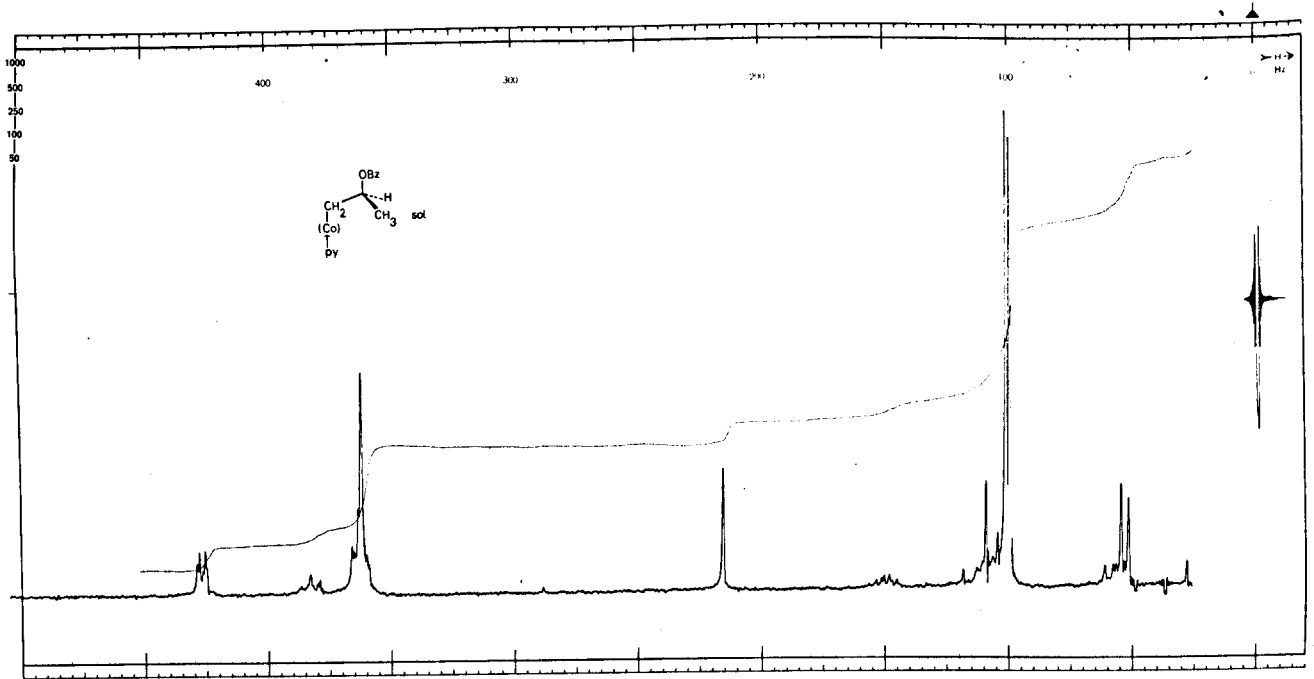
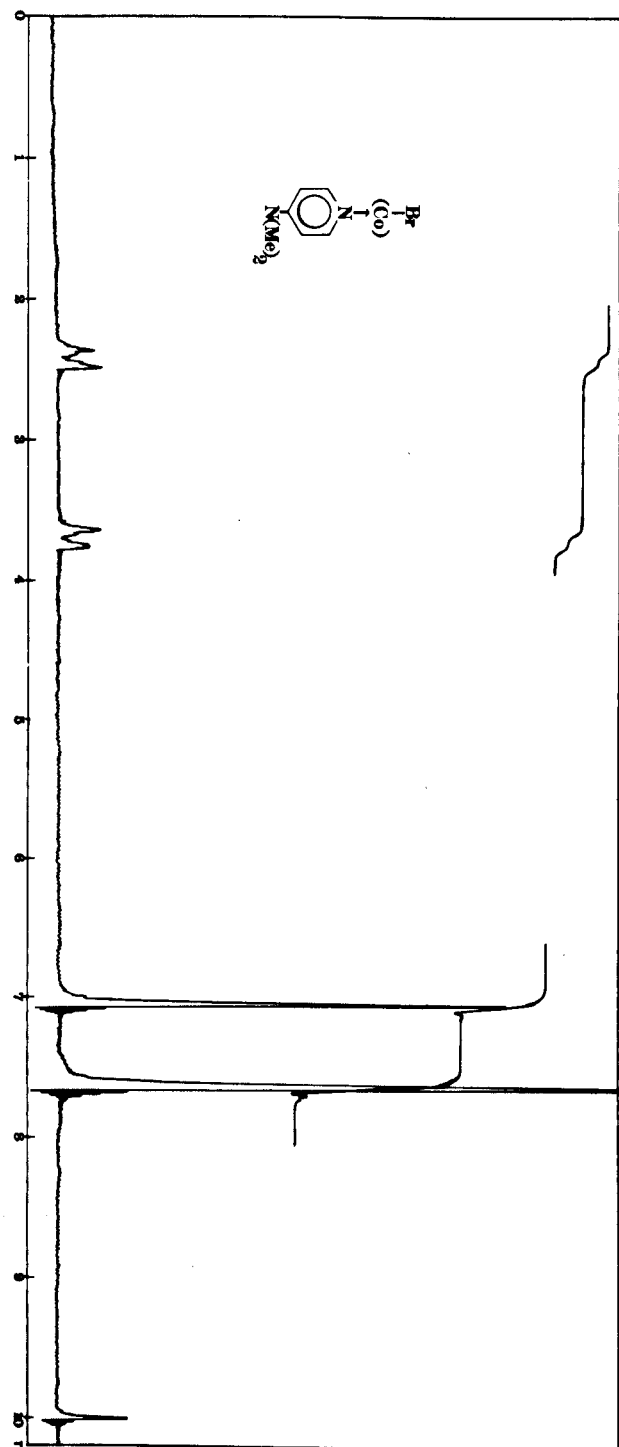


FIGURE XVII



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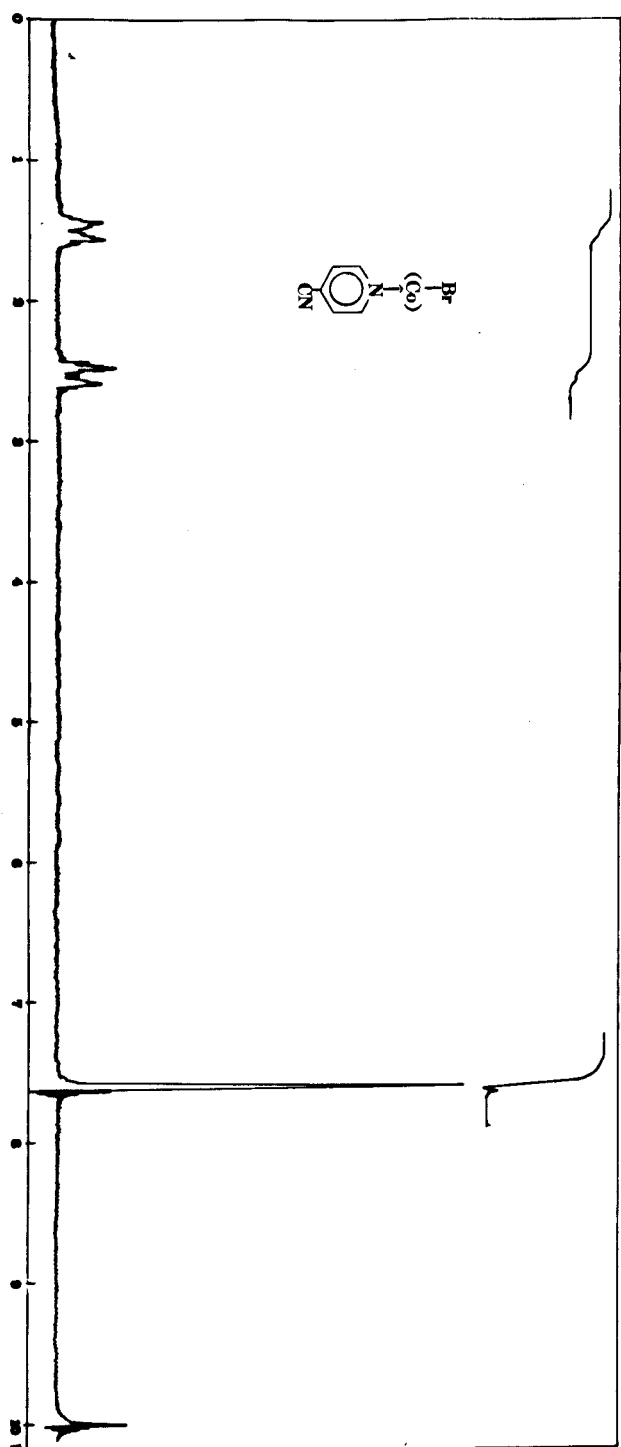


FIGURE XVIII

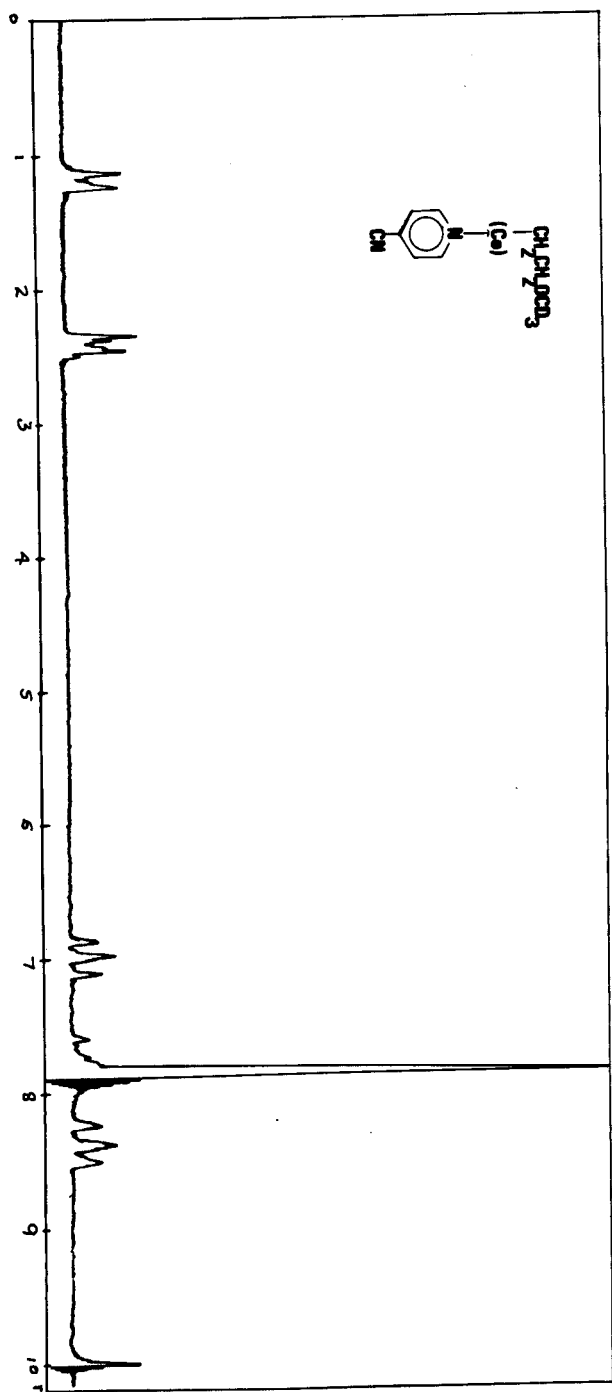
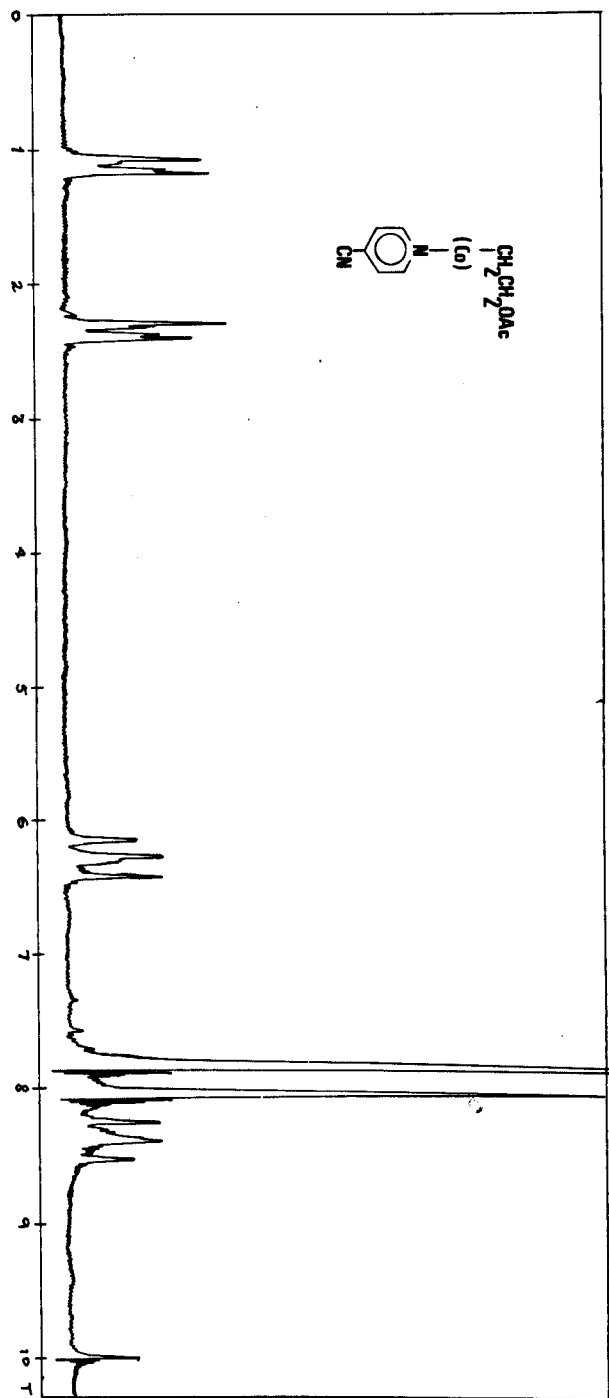


FIGURE XIX

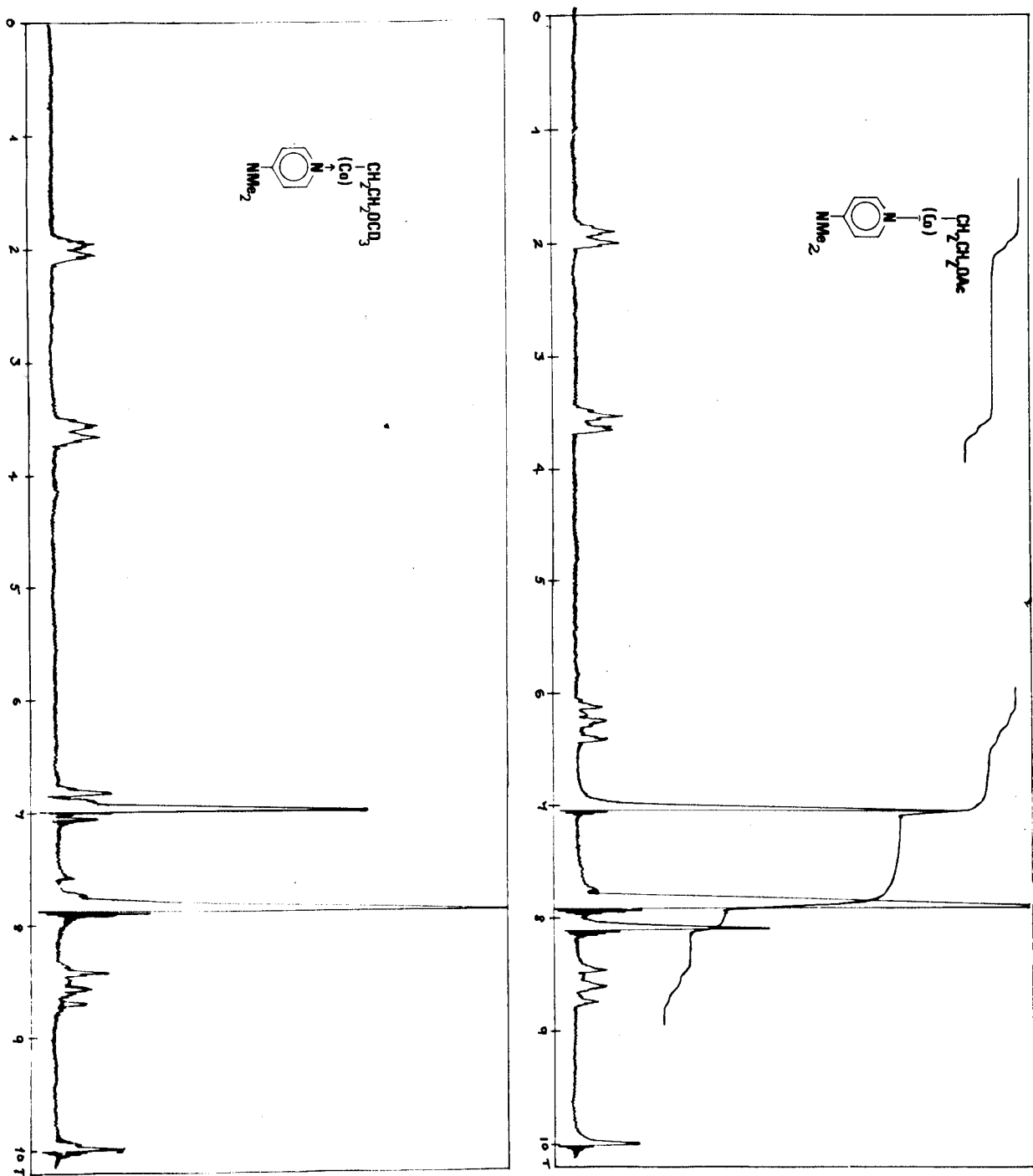


FIGURE XX

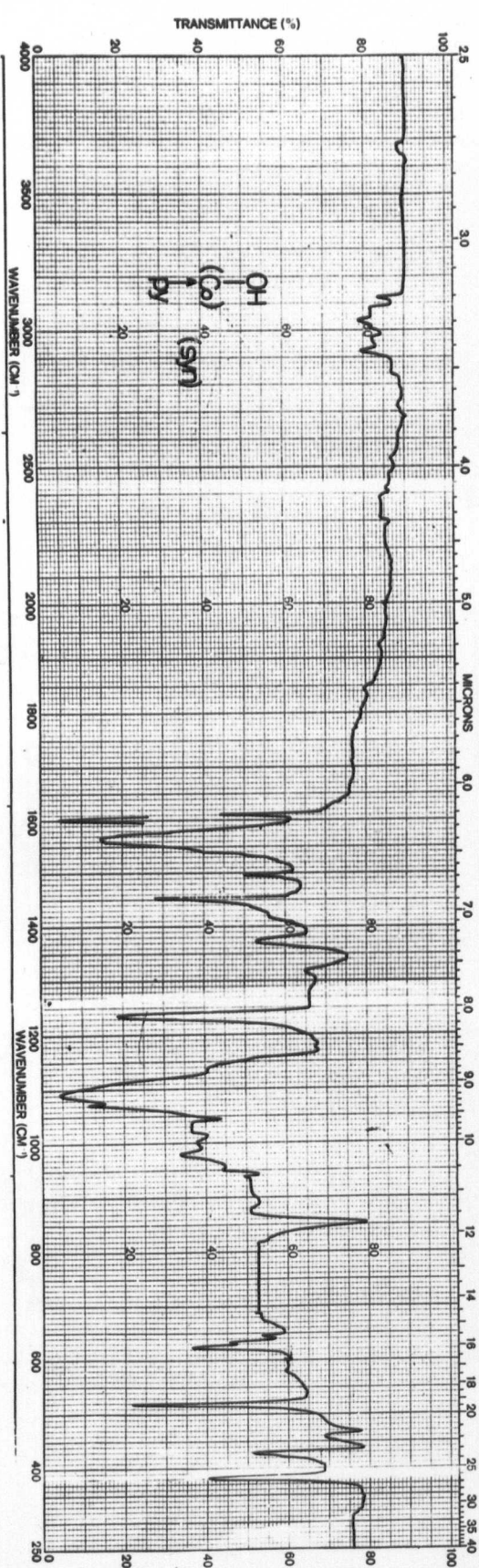
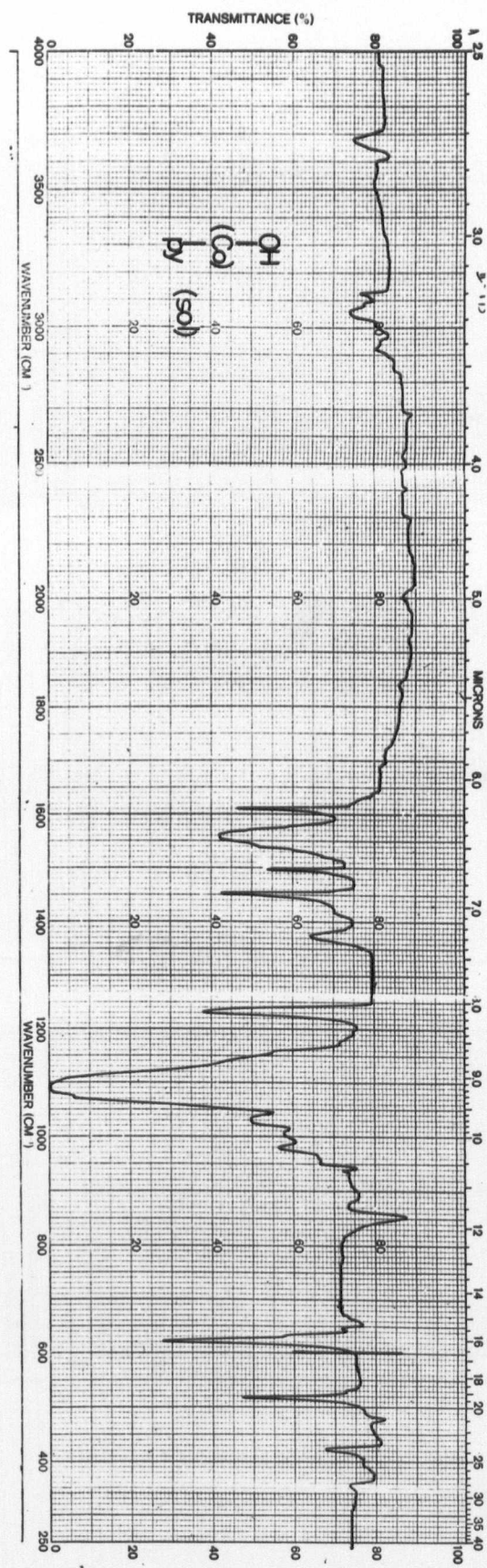


FIGURE XX1

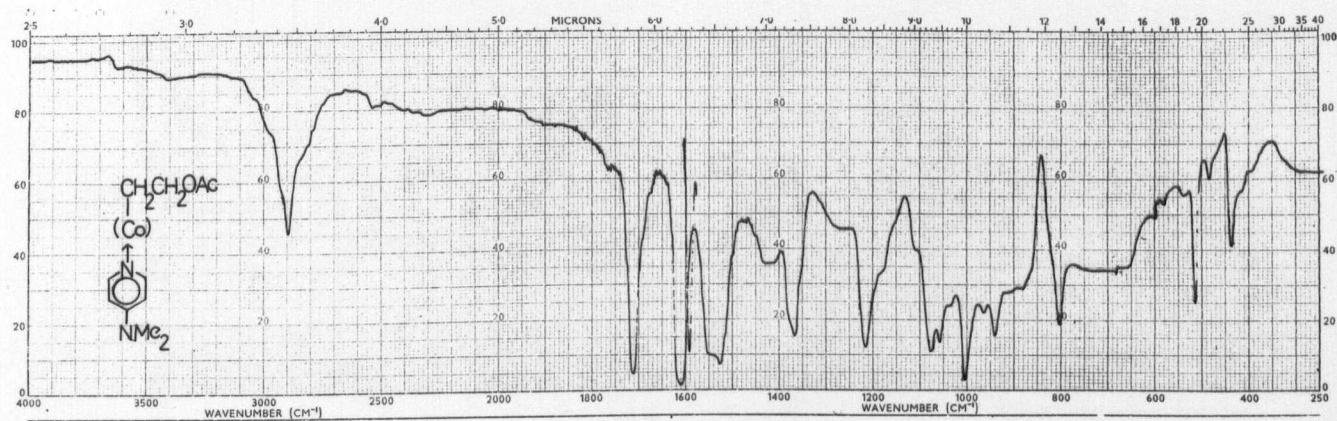
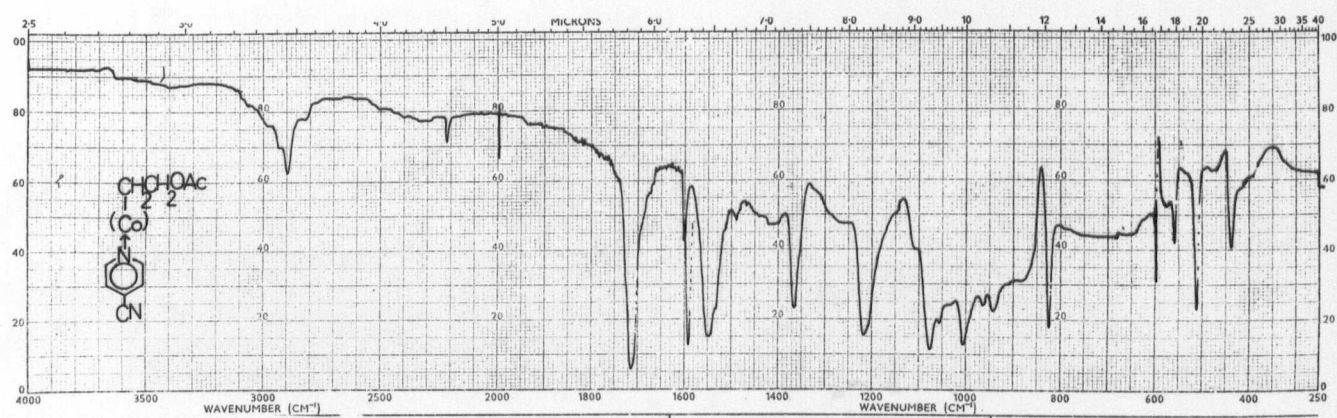
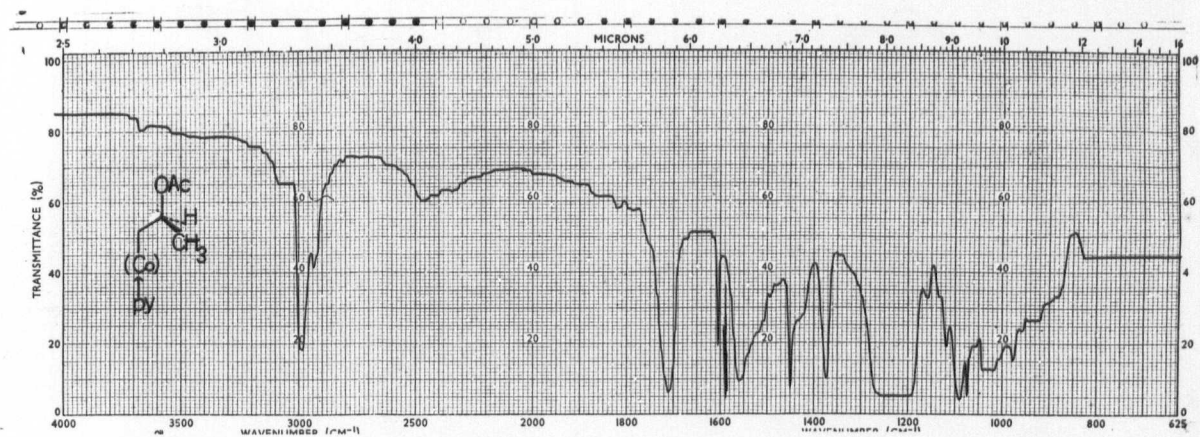


FIGURE XII

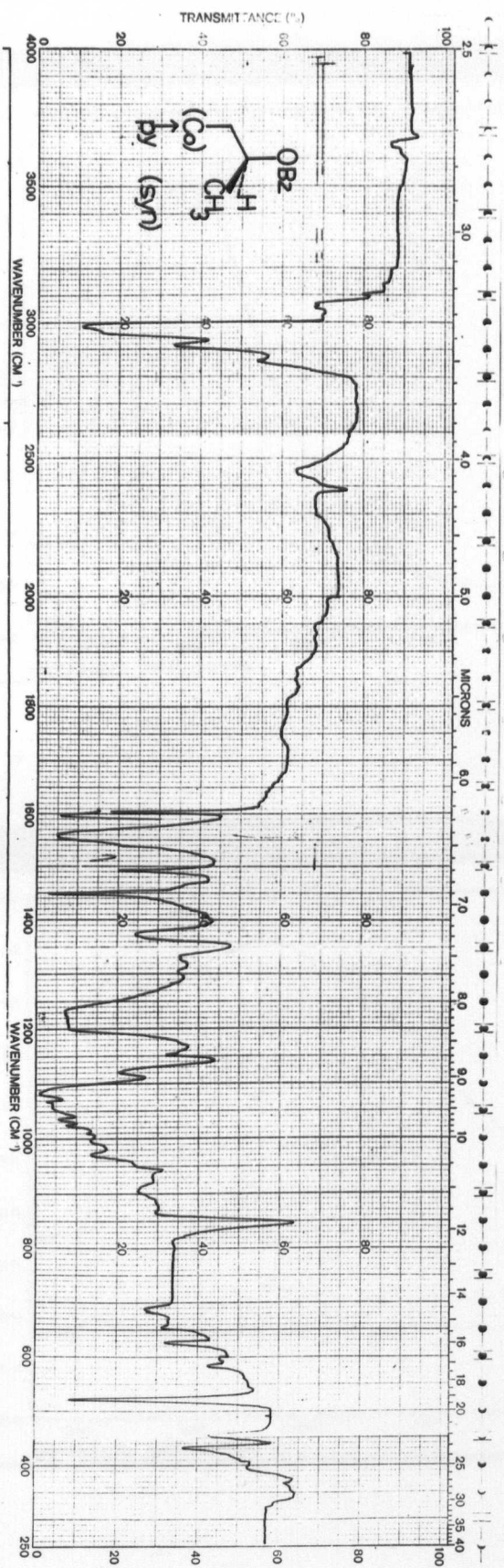
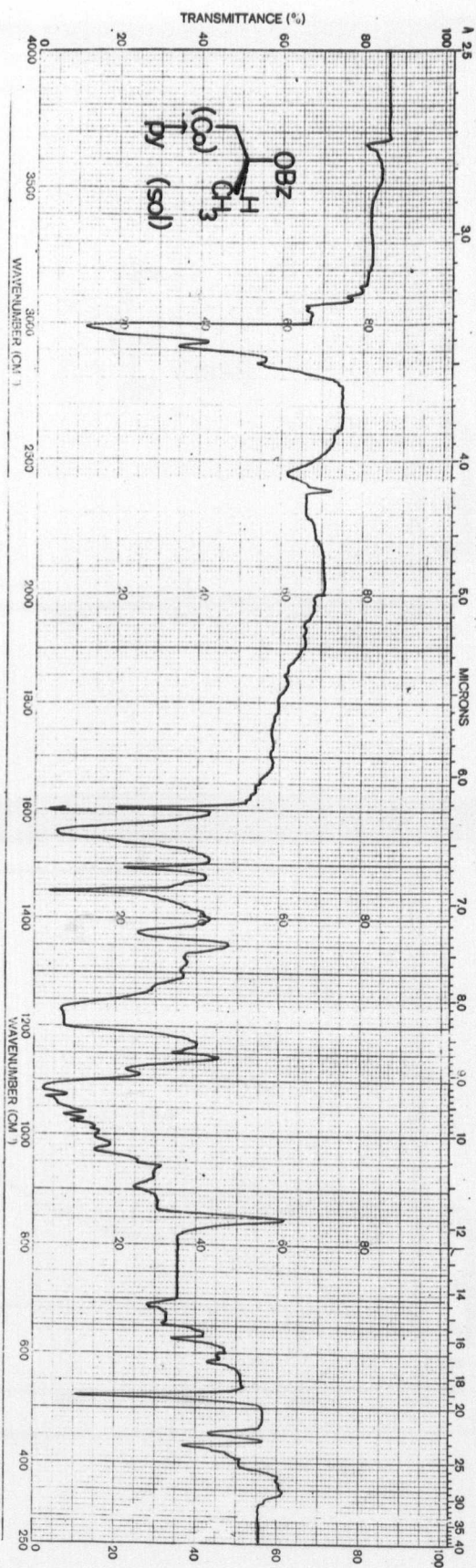


FIGURE XXIII

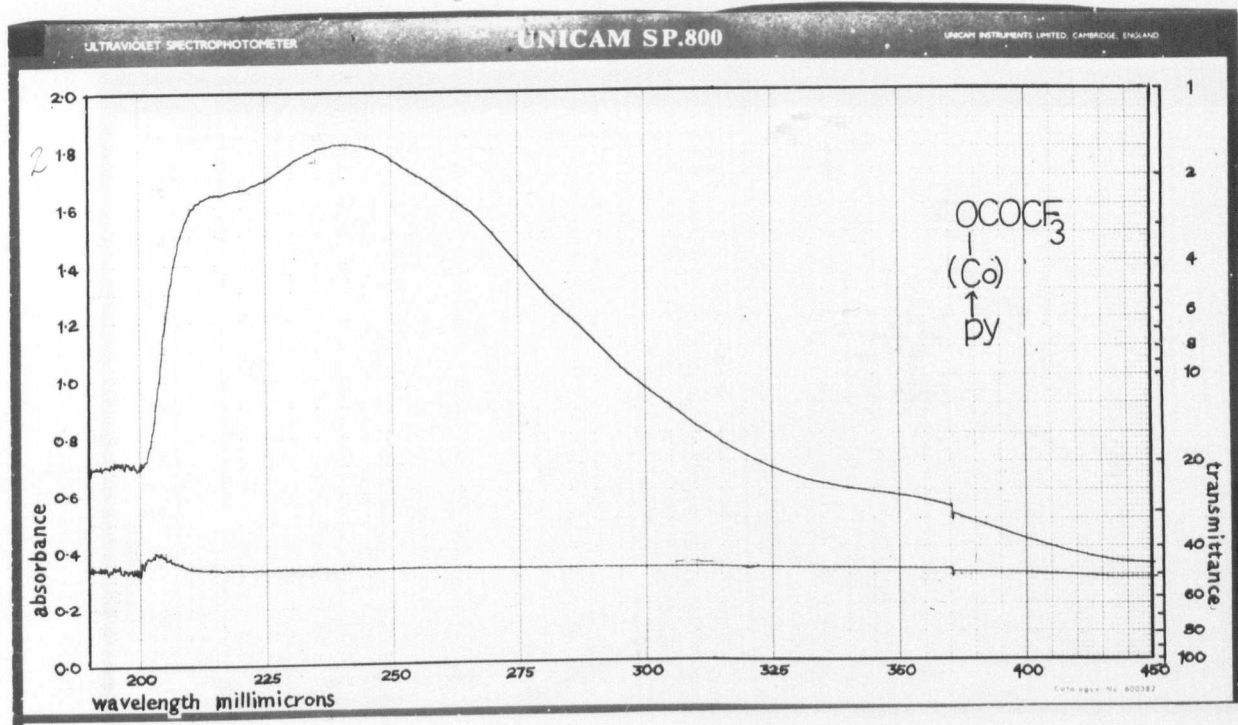
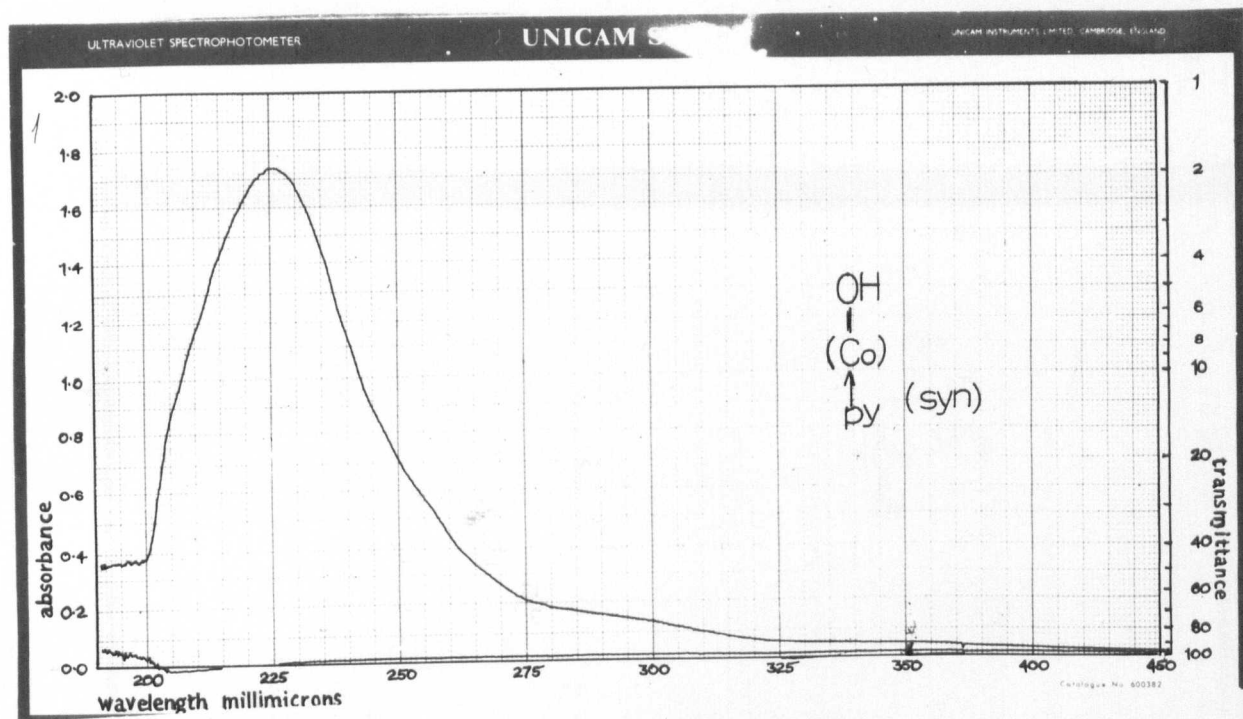


FIGURE XXIV

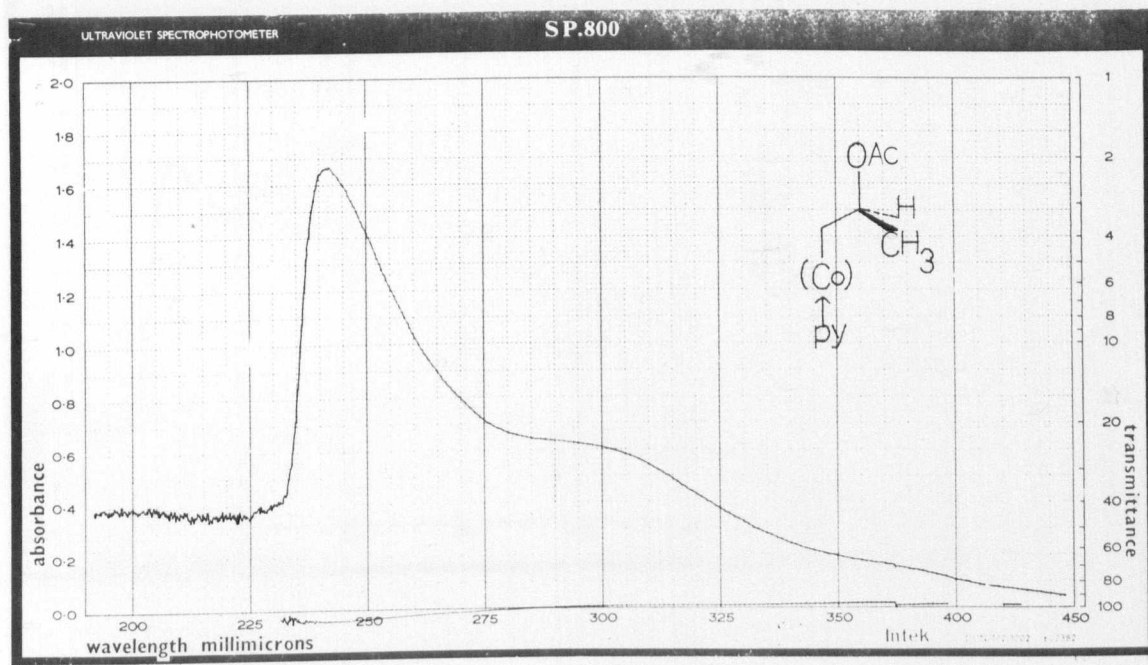
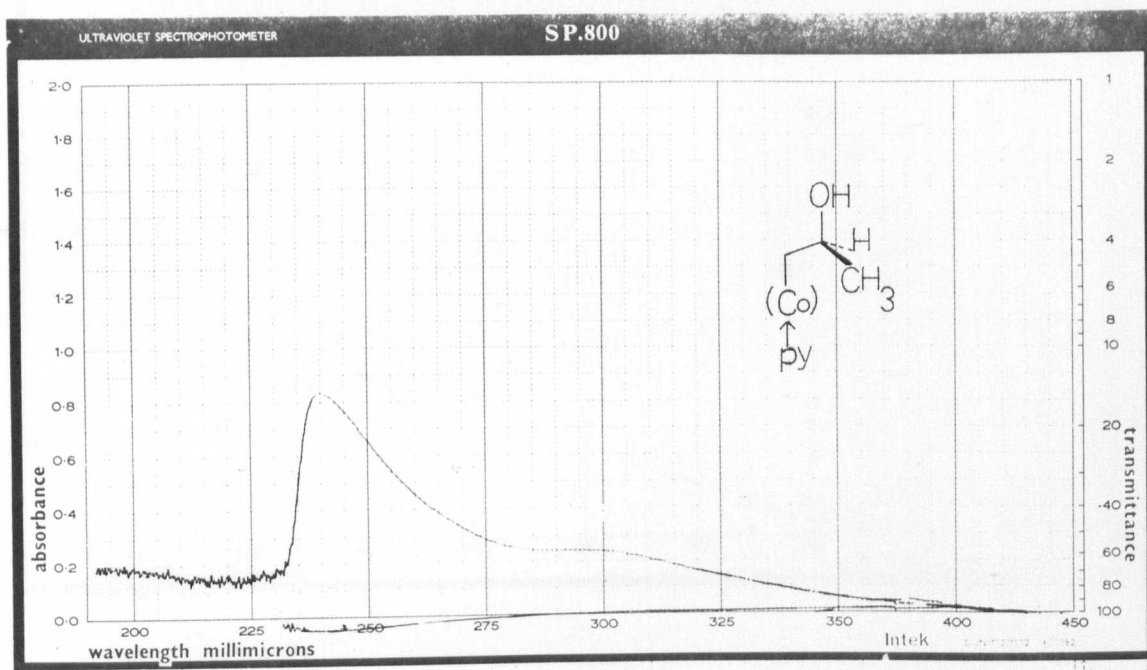
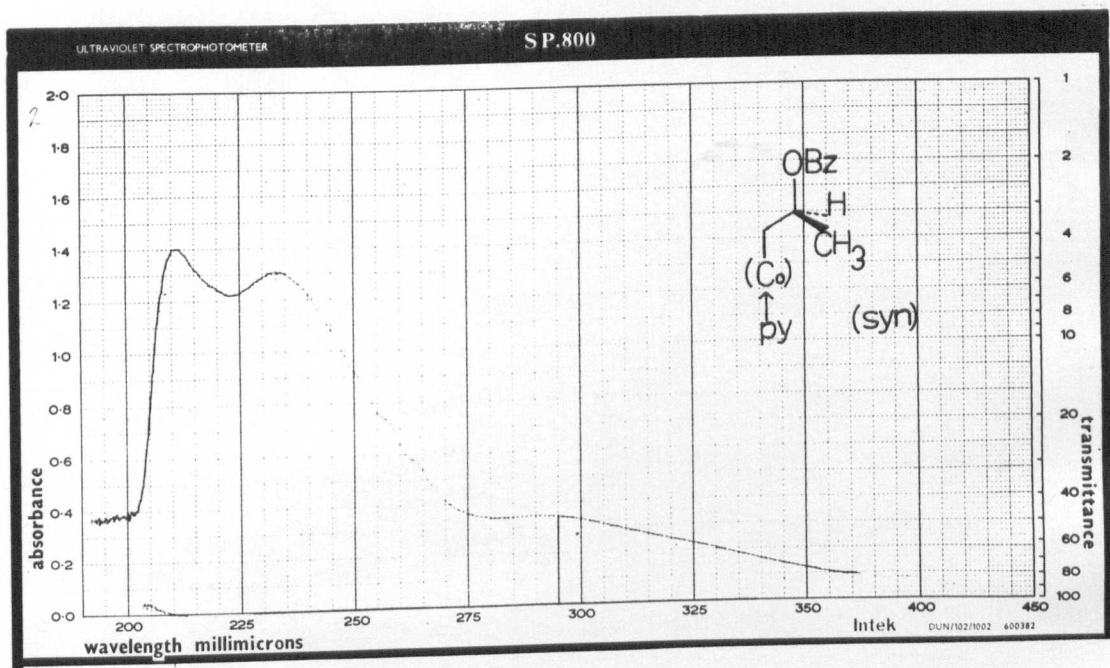
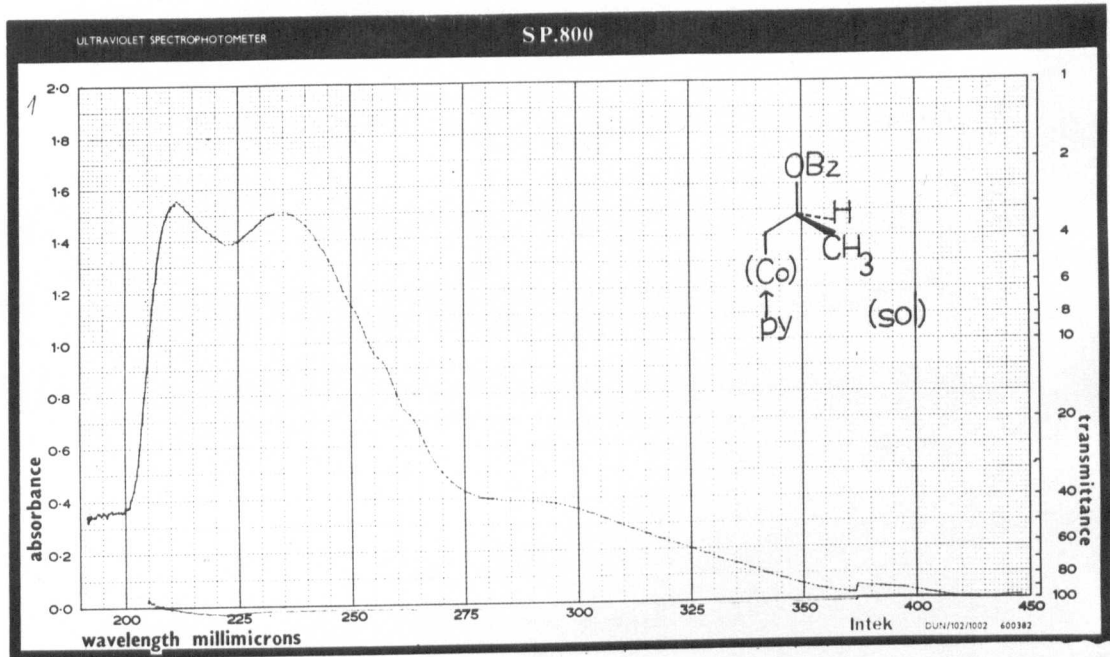


FIGURE XXV



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