ASPECTS OF A POSSIBLE SYNTHETIC ROUTE TO VITAMIN B_{12}

by

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Thanks are also due to Mrs. J. McConnell who painstakingly typed the script and who corrected many errors.

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CONTENTS

SUMMARY

A possible synthetic route to vitamin B_{12}, proposed by J. W. Cornforth, is discussed in the Introduction, which also briefly gives the present status of other synthetic routes to corrins and to vitamin B_{12}. In Cornforth's approach, precursors of ring A and ring D of vitamin B_{12} are to be linked together directly by an adaptation of a bromo-nitro coupling reaction and the work described in Chapters 1, 2, 3 and 4 deals with attempts to achieve this coupling and related work.

A new synthetic route to Hagemann's ester (4-carbethoxy-3-methyl-cyclohex-2-ene-1-one), which makes available the t-butyl ester as well as the methyl and ethyl ester in improved yield, has been discovered and is discussed in Chapter 1 with some mechanistic detail. The t-butyl ester adds nitroethane (as do the other esters) in the presence of a Triton base to give a nitro-ester which can be readily hydrolysed to the nitro-acid.

The nitro-ester, derived by addition of nitroethane to ethyl-Hagemann's ester, is shown (Chapter 2) to consist of the two epimers of trans-4-carbethoxy-3(methyl, 2-nitroethyl)-cyclohexanone by a degradative sequence involving a Nef reaction followed by a hypobromite oxidation. The product is then related to the known trans-4-carbomethoxy-3(methyl, carbomethoxy)-cyclohexanone. The nitro-adducts thus have the correct ring stereochemistry for further development into vitamin B_{12}. This degradation can also be used for correlation of the enantiomers of the nitro-acid after resolution.

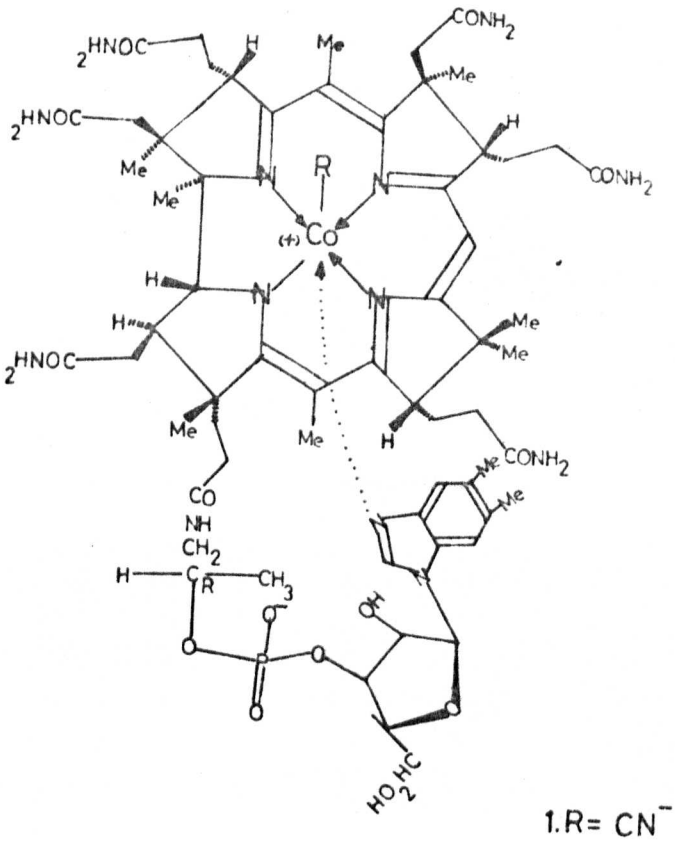
The nitro-ethyl ester epimers are converted (Chapter 3) into a single bromo-isomer (trans-4-carbethoxy-3(methyl, 2,2-bromonitro-ethyl)-cyclohexanone and a coupling reaction with a primary nitro-anion is described. The failure of this reaction to give coupled products leads to the protection of the ketone in the nitro-ethyl ester with an ethylene-ketal followed by conversion into a single bromo-isomer. This compound also failed in the coupling reaction. The production of a single bromo-isomer from two epimers has important implications and hence a series of acid quenching

of nitroanions is studied. These show remarkable stereoselectivity and several novel mechanistic features are discussed.

The stereochemistry of a possible ring D precursor had not been determined in its entirety and Chapter 4 shows how the problems can be resolved although only the initial stages have been achieved.

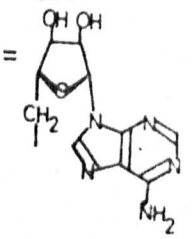
ABBREVIATIONS

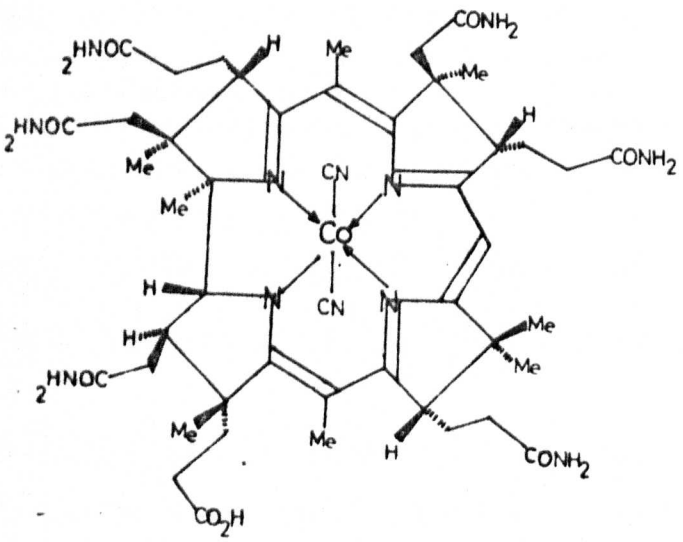
I.R.	:	Infra-red spectrum (s = strong, m = medium, w = weak)
U.V.	:	Ultra-violet spectrum (followed in the text by the wave-length maximum and the molar extinction coefficient)
nm	:	Nanometres
N.M.R.	:	Nuclear Magnetic Resonance spectrum [followed in the text by τ values and in brackets, the multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), the coupling constant J in c.p.s. and the integration]
c.p.s.	:	cycles per second
H	:	proton
M.S.	:	Mass spectrum (m = molecular ion).
m/e	:	Mass divided by ionic charge
G.L.C.	:	Gas, liquid chromatography
T.L.C.	:	Thin layer chromatography
D.M.S.O.	:	Dimethylsulphoxide
O.R.D.	:	Optical rotatory dispersion
D.M.F.	:	Dimethylformamide
H.C.B.D.	:	Hexachlorobutadiene



1. R= CN^-

2. R=





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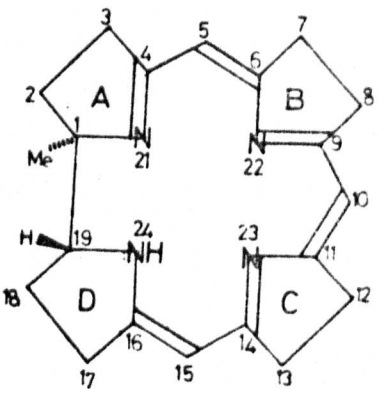

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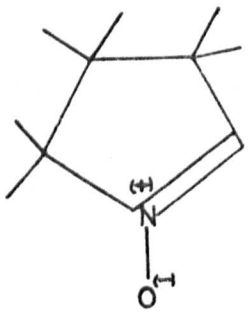

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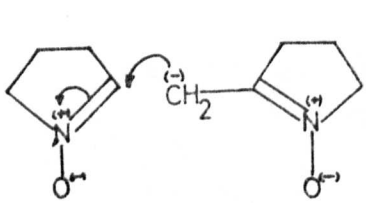

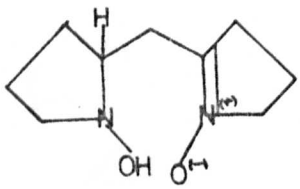

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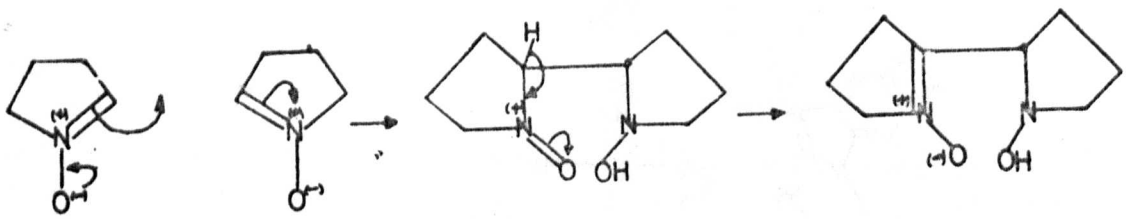
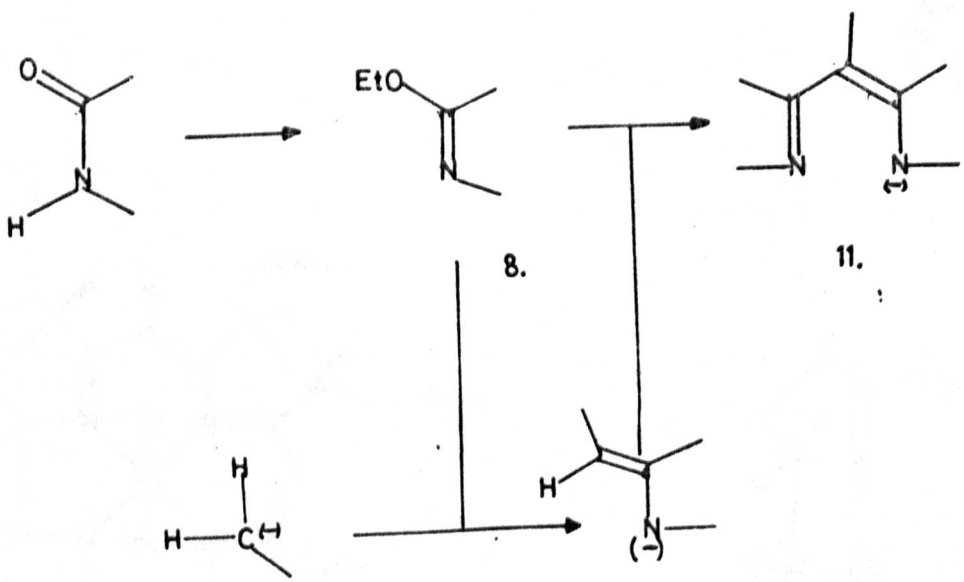


7.

SCHEME I



8.

9.

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11.

INTRODUCTION

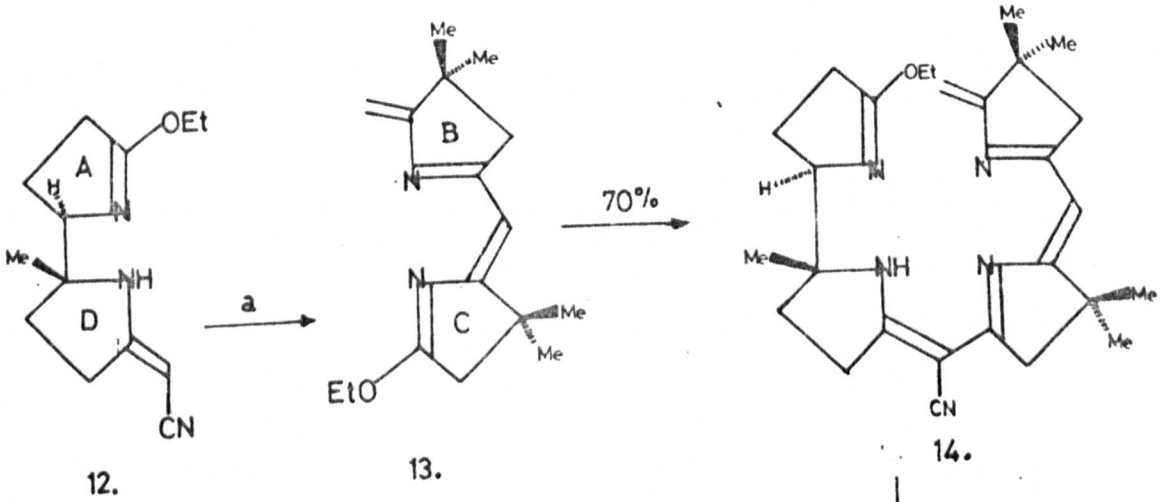
Vitamin B_{12} (cyanocobalamin) was first isolated[1] in 1948 and after much chemical investigation, its complete stereo-structure was shown[2] (1956, by X-ray analysis) to be (1). In 1958 a group of related compounds, the B_{12} co-enzymes, were discovered[3] and their structures shown to be based on (2) by X-ray analysis[4] and by partial synthesis[5] from cyanocobalamin.

The structure of vitamin B_{12} consists of a Co(III) atom surrounded by a near planar quadridentate nitrogen macrocycle related to the trans-corrin structure (3). One of the axial ligands is cyanide whilst the other is the N1 atom of a dimethyl-benzimidazole molecule. This molecule is connected to the side chain at C17 of the corrin nucleus by a 3'-ribose phosphate, D-1-methyl-ethanolamine chain. The nucleus with this chain removed and replaced by cyanide is called cobyric acid (4). The naturally occurring compound has been reconstituted[6] into vitamin B_{12} and thus a total synthesis of cobyric acid (4) achieves total synthesis of vitamin B_{12} (and the B_{12} coenzymes). For the sake of discussion, approaches to this synthesis will be divided, firstly into synthetic routes to the corrin ring (3) and secondly, into routes to cobyric acid (4), although the two should be planned together.

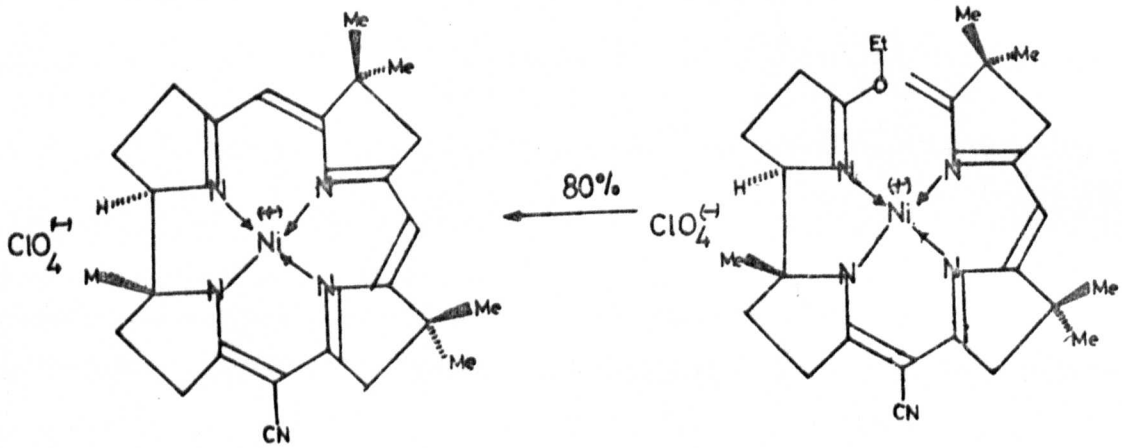
Corrin Synthesis

An early approach[7] to the corrin ring utilised the reactive 1-pyrroline-N-oxides (nitrones), e.g. (5), which could either be coupled to give a methylene bridge, e.g. (6), or to give a direct linkage, e.g. (7). Some initial success was obtained but was never followed up. This method has the advantage of using reduced pyrrole rings but has disadvantages in that development of (6) and (7) for further coupling is difficult and removal of the N-oxide function after cyclisation might be difficult.

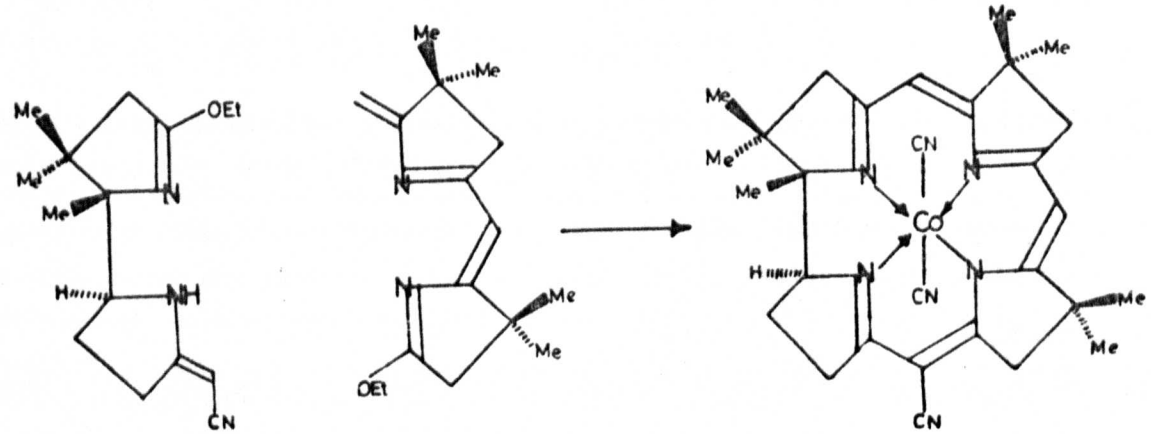
Eschenmoser et al in 1964 published[8] a synthesis of the nickel corrin (16). The basic concept[9] (Scheme I) depends upon the electrophilic nature of imino-esters (8) [prepared by the action of Meerwein's reagent on amides] and their reaction with carbanions (e.g. 9) or enamines (e.g. 10) to form the



12. 13. 14.



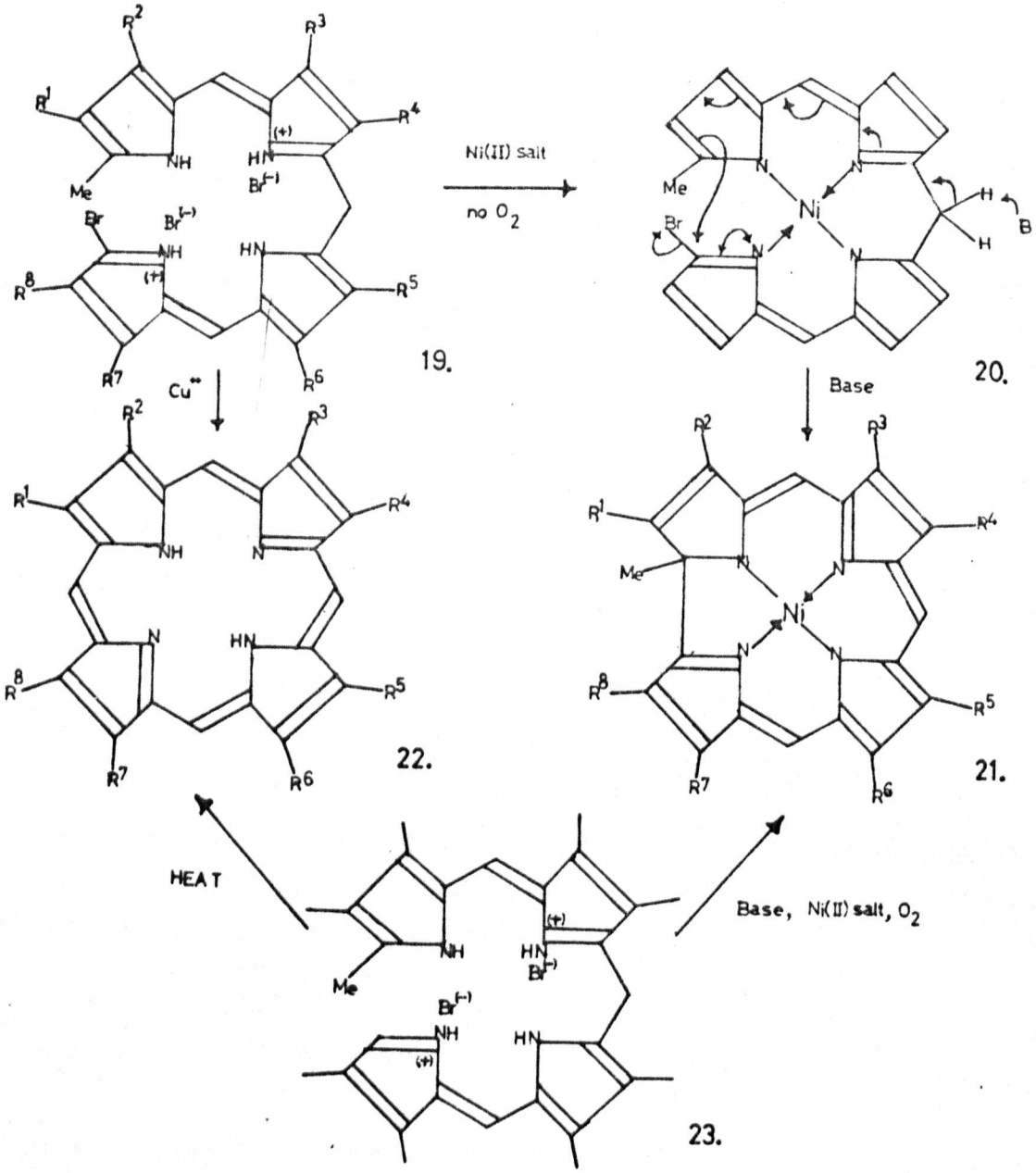
16. 15.



17. 13. 18.

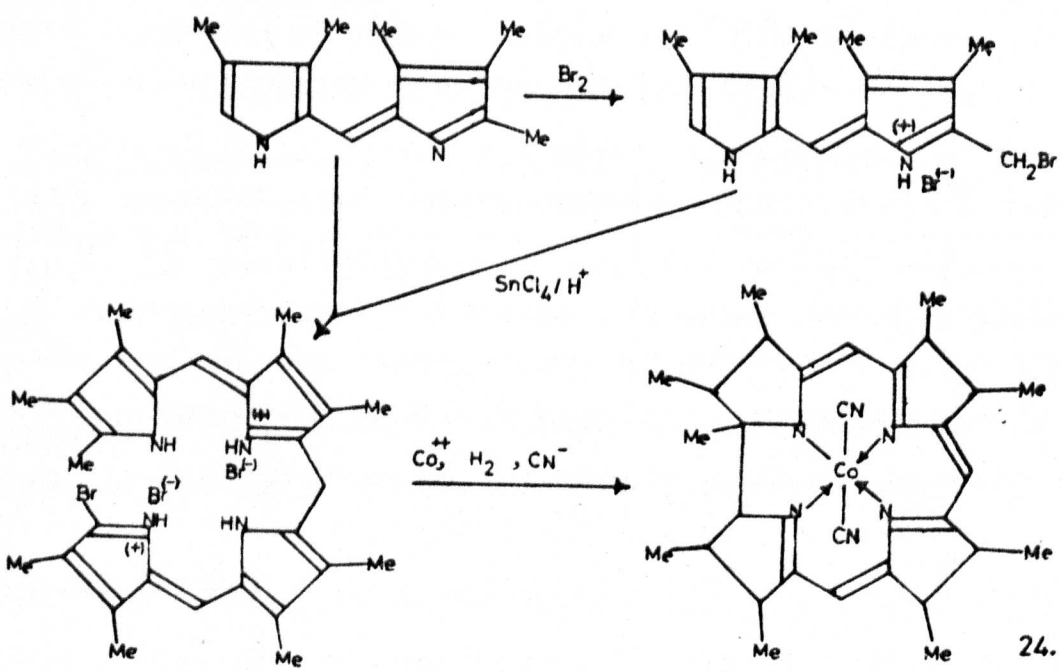
vinylogous amidine chromophore (11). The final stages in the synthesis consisted of combining components (12) and (13) by two successive imino-ester condensations. The fact that each component contained one imino-ester group ensured a specific orientation and the danger of self-condensation was lowered, as the more reactive (conjugated) imino-ester was in the component (13) with the less reactive enamine centre. The route to these precursors was long and will not be discussed here. The first condensation (a) was carried out by treating (12) with an equivalent of sodium ethoxide followed by addition of an equivalent amount of (13) to yield the crystalline sodium salt of (14). The use of a transition metal ion should aid the final ring closure in three ways. Firstly, it removes the proton of the secondary amine; secondly, it enhances the electrophilic reactivity of the imino-ester by complex bonding and thirdly, it fixes the two condensation centres close to each other. The nickel (II) perchlorate complex (15) was used as some initial problems arose with the cobalt complex. Heating (15) did not give ring closure because of the low nucleophilicity of the exocyclic methylene group. This problem was solved by treatment with potassium t-butoxide in boiling t-butanol when the corrin (16) was obtained. It seems that removal of one of the allylic protons by the strong base increases the nucleophilicity of the exocyclic methylene group. The corresponding cobalt corrin has now been prepared,[9] as has[10] the corrin (18) from the more simply prepared precursor (17) and component (13).

A successful synthesis of corrins has been developed[11] which utilises linear tetrapyrrole compounds[11,15] as precursors followed by cyclisation and hydrogenation of the tetradehydro-corrins (21) obtained. Two types of precursor were employed. Firstly, 1-bromo-1,19-dideoxy-19-methylbiladiene-ac dihydrobromides, e.g. (19), were cyclised when heated[12] in methanolic solution in the presence of a base and nickel acetate (no oxygen) to the neutral nickel complexes of 1-methyl-tetradehydro-corrins (21) by the mechanism shown in (20). Treatment with cupric ions led to porphyrins (22). Secondly, 1,19-dideoxy-1-methylbiladiene-ac dihydrobromides, e.g. (23), cyclised to (21) under the same conditions, except that mild aerial oxidation was necessary. Heating (23) gave porphyrins (22). Variation of precursors and



19. 20. 21. 22. 23.

SCHEME II



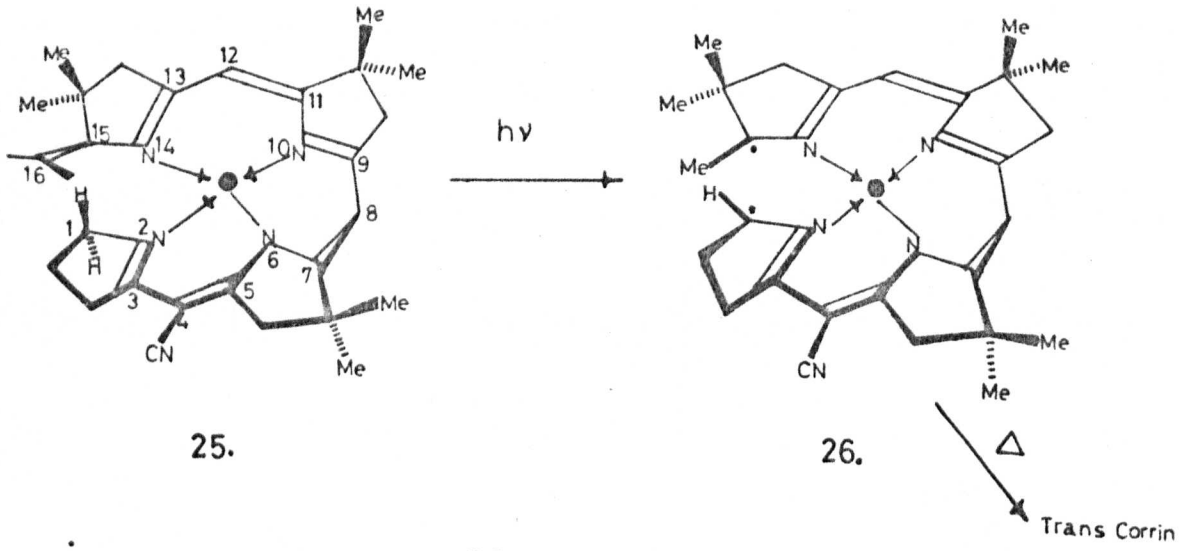
24.

conditions gave 1,19-substituted compounds,[13] 1,19-unsubstituted compounds[14] and metal-free corroles.[15] Use of cobalt (II) salts in place of nickel (II) allowed the preparation[13] of pure 1,19-substituted tetradehydro corrins, but the 1-methyl compounds were unstable and could not be obtained in pure form. The latter could, however, be hydrogenated[13] under pressure at 100°C (Raney nickel) to give the corresponding corrin. This was an amorphous powder identified as a mixture of corrins by the similarity of some of its spectra to those of known corrins. Hydrogenation produces eight new asymmetric centres so a mixture of stereo-isomers could only be expected. This lack of specificity should be compared to the previous method of Eschenmoser which allows more steric control. A route to corrins, e.g. (24) (Scheme II) was thus available.

This method shows some similarities to a proposed scheme for the biosynthesis[16] of corrins and porphyrins. It is thought that linear tetrapyrroles are the in vivo precursors of these compounds but they have not been isolated as yet from natural systems. It should also be pointed out that the precursors (19) and (23) are in a different oxidation state to the natural precursors as they yield porphyrins or tetradehydro corrins directly, whereas an important isolable intermediate in the biosynthesis is a tetrahydroporphyrin (Uroporphyrinogen (III)).

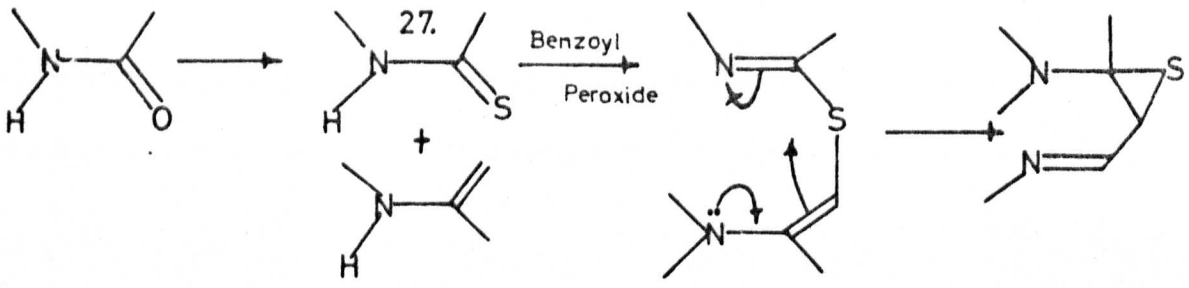
A more recent approach to corrins has also come[17] from Eschenmoser's group. Instead of an A,D to B,C type of coupling, an A,D cyclisation step is now used. Although this is similar in strategy to A. W. Johnson's route[11] it is mechanistically very different. From a study of the models of metal complexes, e.g. (25), it is apparent that one of the ring D methylene hydrogen atoms lies directly below the exocyclic methylene group of ring A. In this conformation the ligand is well disposed to undergo a sigmatropic,[18] antarafacial 1,16-hydrogen transfer to give (26). This has a 15-centre, 16-electron π-system able to undergo an exothermic antarafacial electrocyclic 1,15 ($\pi - \sigma$) cyclisation to the trans corrin. By the Woodward-Hoffmann rules[18] the initial step is disallowed in the ground state but allowed in the first excited state, i.e. cyclisation would be photochemically initiated.

Scheme III shows a second feature of this corrin synthesis which is a new coupling reaction. Coupling of the thio-lactam (27) with an enamine, using

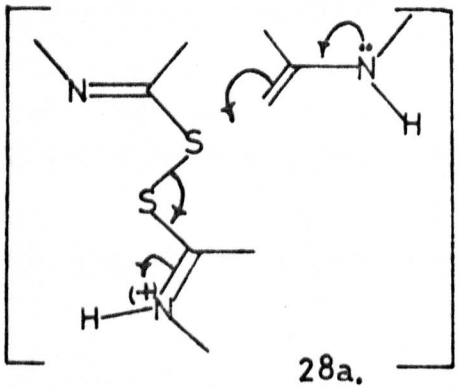


25. 26.

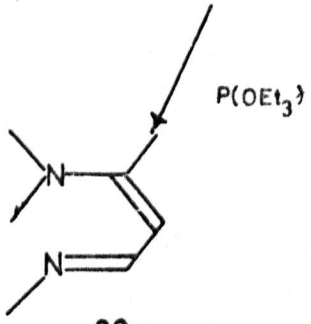
SCHEME III



28. 29.



28a.



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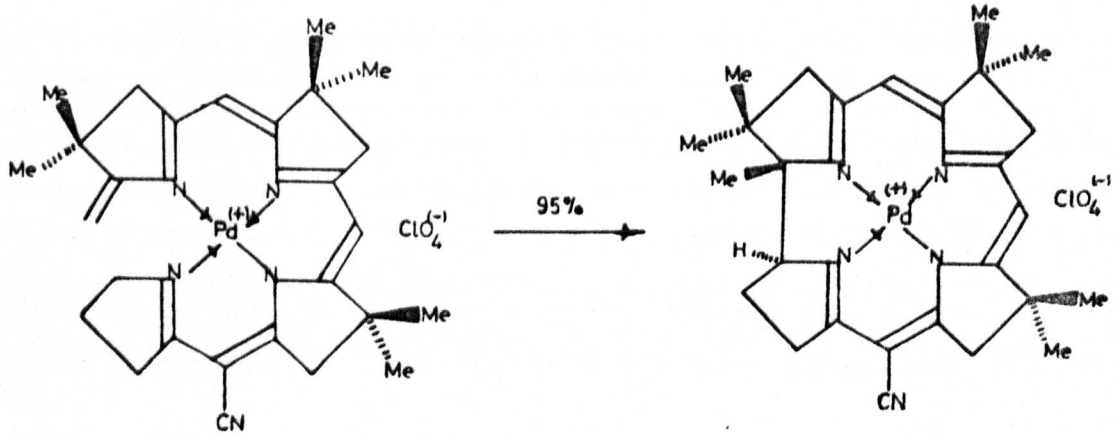


31. 32.

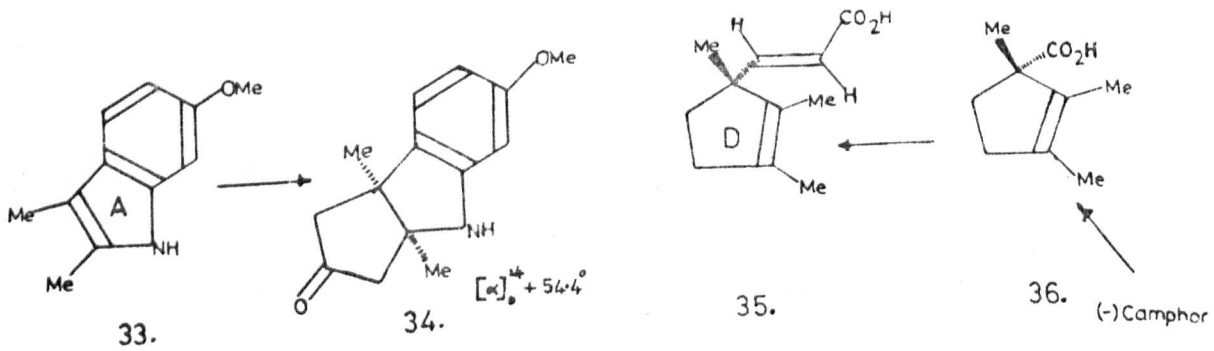
benzoyl peroxide, yields the sulphur bridged compound (28 via 28a). Treatment of (28) with triethyl phosphite leads to the vinylogous amidine (30), possibly via (29). This method had been used[19] in the synthesis of metal-free corrins and was now used in conjunction with the imino-ester route to synthesise the palladium (II) complex (31). Exposure of this complex to sunlight gave the corrin (32) identical with the compound prepared unambiguously by another route. This positive reaction is not sufficient proof that the sigmatropic shift is the actual mechanism and further research is being done.

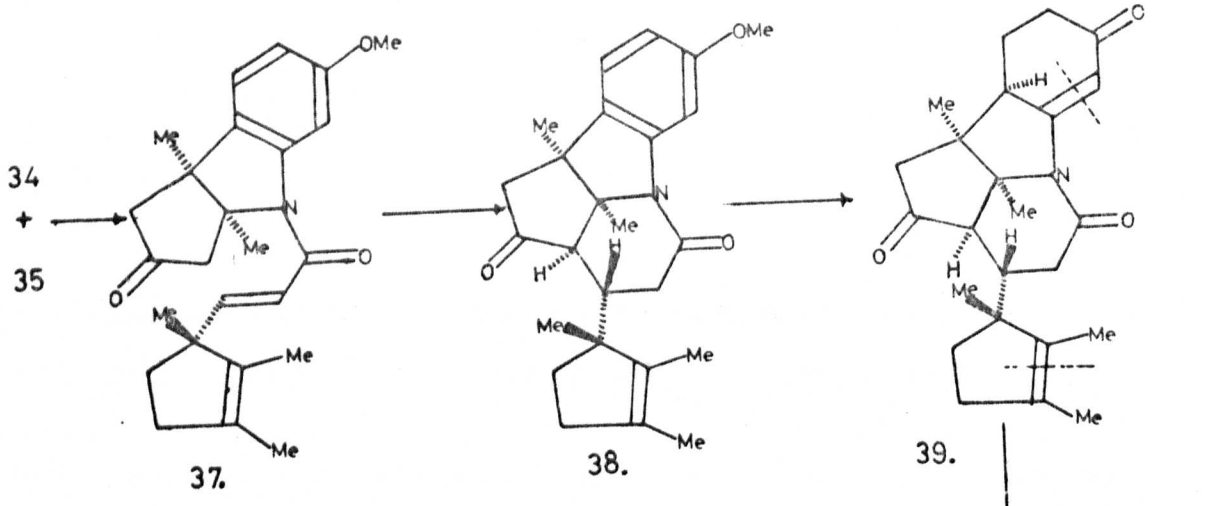
Cobyric Acid Synthesis

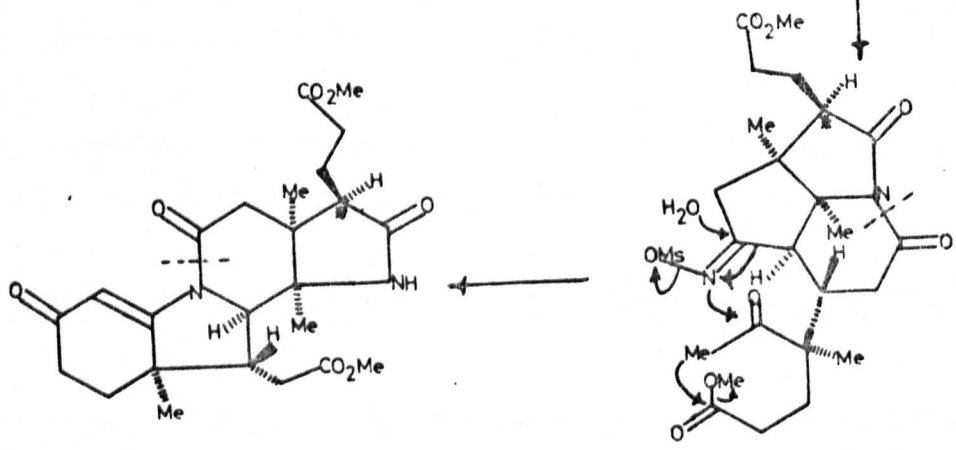
I now want to criticise some of these approaches to corrin systems in relation to their usefulness in cobyric acid synthesis. The nitrone approach has not been developed enough but although it has certain advantages, it does not seem a viable route. The approach of A. W. Johnson also does not seem to be a useful route. The problem is that the tetradehydro corrin, e.g. (21), must be stereospecifically tetra-methylated with no control of the relative stereochemistry. Thus, after each introduction of a new asymmetric centre, the correct B_{12} diastereomer would have to be separated. As a matter of principle[20] a complex synthesis is best carried out by assembling components of the correct stereochemistry, rather than elaborating intermediates in a progressive fashion.

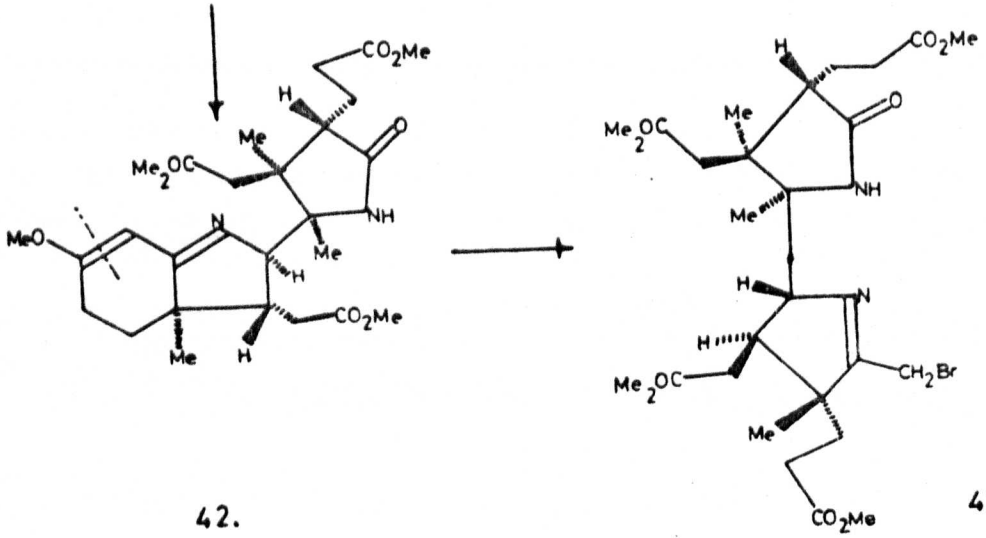
The first method from Zurich is far more suitable as it involves reduced pyrrole precursors, each of which can be developed into the correct stereochemistry before the corrin ring is assembled (see below). The second method also offers a viable approach to cobyric acid and, if possible, would represent a much simpler route than any before it. It is, however, an all or nothing process as the crucial step is the last one. So far it has worked on a model corrin precursor but the side chains in the linear B_{12} precursor may make the transition state for cyclisation unfavourable. It may be that in this case the only good model is the enantiomer of the precursor. For a complete review see ref. 21.

Two well worked-out schemes for the total asymmetric synthesis of vitamin B_{12} have appeared, that of Woodward and Eschenmoser[22] and that of Cornforth.[23] It is proposed to consider these in some detail. Woodward


OMe
Me
A
NH
Me
33.
OMe
Me
NH
Me
O
$[\alpha]_D^{14}$ + 54·4°
34.
H
CO_2H
Me
Me H
D
Me
35.
Me
CO_2H
Me
Me
36.
(-) Camphor

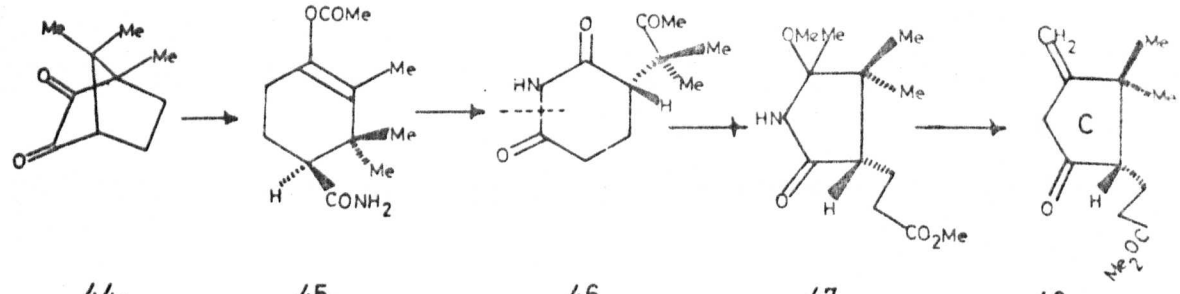

34
+
35
OMe
Me
N
Me
O
O
Me
Me
Me
37.
OMe
Me
N
Me
O
O
H
Me
Me
Me
38.
O
H
Me
N
Me
H
O
O
H
Me
Me
Me
39.


CO_2Me
H
Me
O
O
N
H_2O
Me
OMs
N
H
O
Me
Me
OMe
O
40.
CO_2Me
H
Me
O
O
N
NH
H
H
Me
CO_2Me
Me
41.

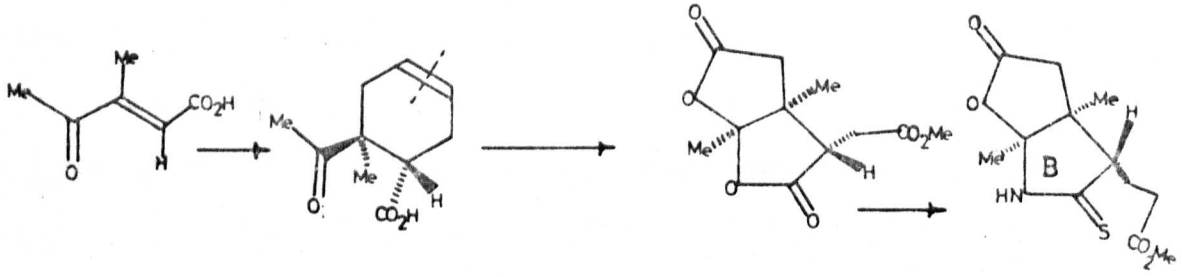

CO_2Me
H
Me
Me_2OC
O
NH
MeO
N
Me
H
CO_2Me
Me
H
42.
H
CO_2Me
Me_2OC
Me
O
NH
Me
H
N
H
Me_2OC
CH_2Br
Me
CO_2Me
43.

has published[22] the efforts of the combined Harvard/Zurich attack on cobyric acid synthesis. They decided to couple the A,D portion to the B,C portion, following Eschenmoser's early corrin synthesis, and this was used along with the principle of total asymmetric synthesis, i.e. the coupling of each precursor in its correct stereochemistry.[20]

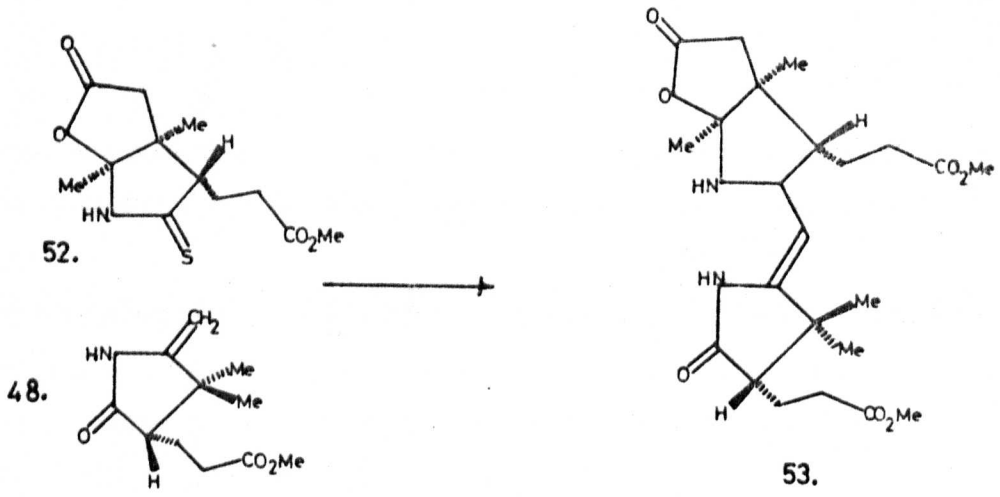
Woodward used the indole (33) as ring A precursor and developed it into the tricyclic ketone (34) which was resolved using (+) and (-) α-phenylethyl isocyanate. The enantiomers were correlated with camphor which showed which was related to vitamin B_{12} and also proved the structure of the tricyclic ketone. The ring D precursor (35) was prepared as the correct enantiomer by unambiguous degradation of D-camphor through (36). It was emphasised that all future pilot reactions were carried out on the unnatural enantiomers as these were the only true models. The acid chloride of (35) then reacted with (34) to give (37) which cyclised to (38). Two new asymmetric centres were formed which were predicted to have the correct relative configuration to A and D. The aromatic ring was now developed, after protecting the ketone and the lactam, by Birch reduction. Removal of the protecting groups gave (39). At this stage only one nitrogen atom was present and another must be introduced. This was one of the main difficulties encountered and it was solved by a Beckmann rearrangement of the mesylate of the mono-oxime (40). This was prepared from (39) by forming the di-oxime and removing the unwanted one selectively with nitrous acid. Several ozonolysis stages then gave (40) in which the centre marked (*) had the wrong relative configuration (this would be equilibrated later). Heating (40) in methanol at $170^{\circ}C$ for 2 hours in the presence of polystyrene sulphonic acid gave (41) mainly as the unnatural epimer but including a small amount of the natural one. The unnatural epimer would not be cleaved (as shown by the dotted line) but it could be equilibrated to the natural form which was easily cleaved in base to (42). The absolute configuration of the natural epimer of (41) was proved by X-ray analysis of the bromide. Ozonolysis of (42) gave a β-imino aldehyde (an unusual compound) which was converted to the alkyl bromide (43). One half of cobyric acid was now ready for coupling.



44. 45. 46. 47. 48.



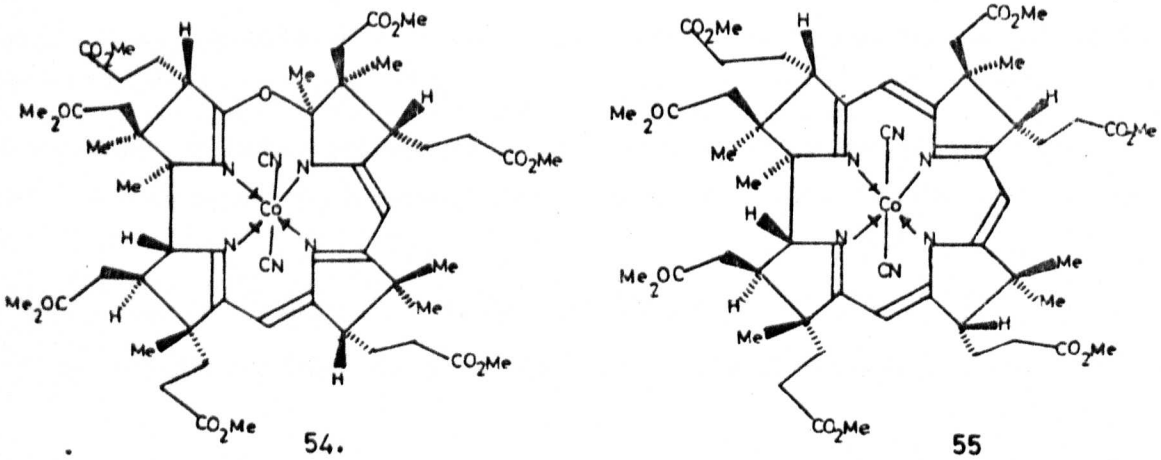
49. 50. 51. 52



52.

48.

53.



54. 55

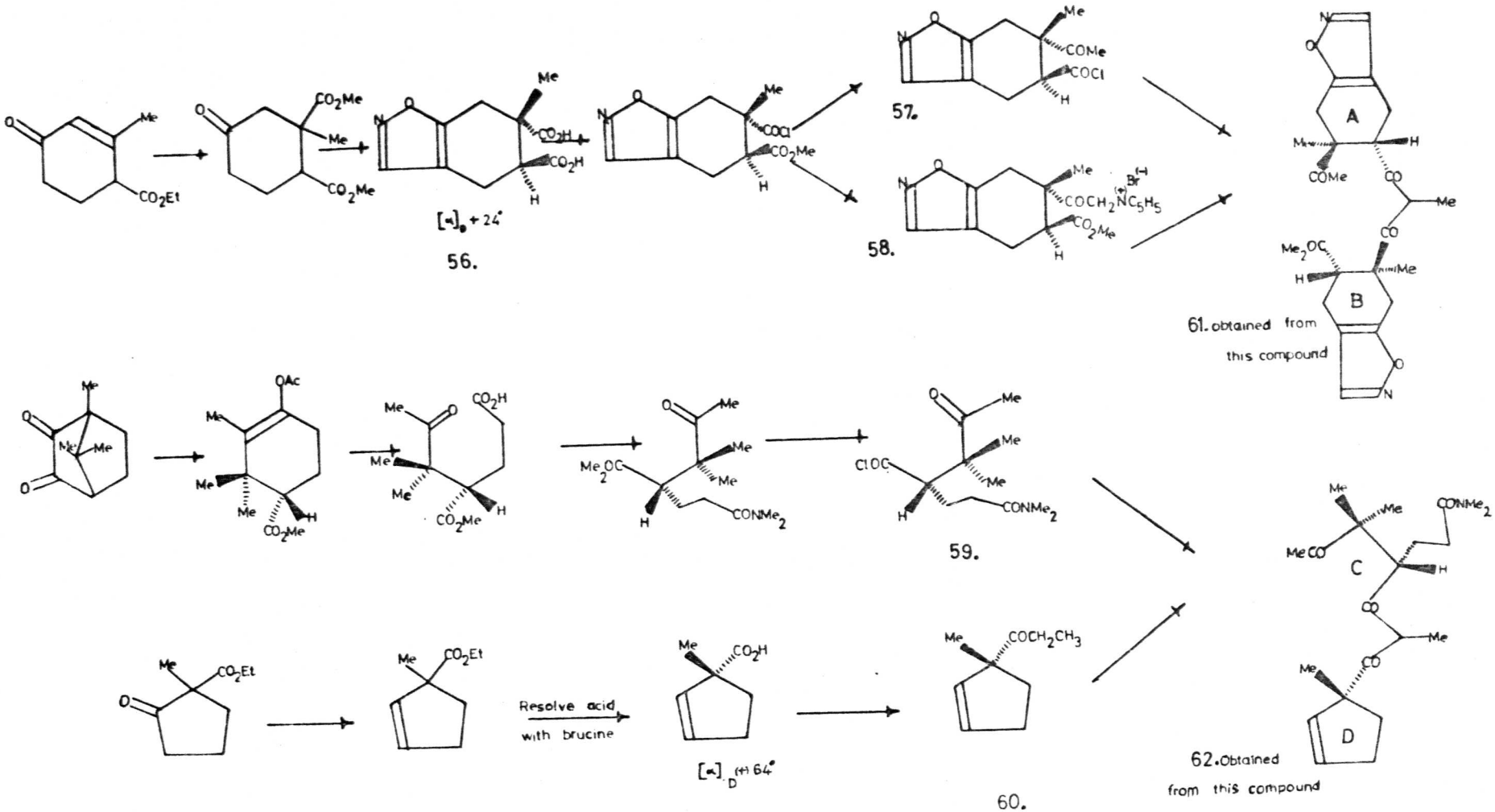
The ring (C) precursor (48) was prepared by a route first recognised by Cornforth. Mild acid treatment of (+) camphor quinone (44) did not affect the optical purity and (45) was eventually obtained. Treatment with ozone and reduction gave (46) which was transformed into the methoxy-lactam (47) by methanolic hydrogen chloride and after pyrolysis, (48) was obtained. The ring (B) precursor (52) was prepared in Zurich from trans-β-methyl-β-acetyl acrylic acid (49). Diels-alder reaction with butadiene gave racemic (50) which was resolved with (+) and (-) α-phenylethylamine and the enantiomers related to a ring B degradation product of vitamin B_{12}. Chromic acid oxidation of (50) and Arndt Eistert elongation gave (51). Treatment with methanolic ammonia and reaction with phosphorus pentasulphide gave the desired product (52). (48) and (52) were coupled by the sulphide bridge method[17] to give the B/C precursor (53).

Coupling (43) and (53) has not been straightforward and by a sulphide bridge contraction, the nearest to a corrin that Woodward reports is (54). Lately, however, the corrin (55) has been obtained[21] and has spectra (U.V., I.R., O.R.D.) which are identical to those of a corrin derived from B_{12}. This represents the nearest that anyone has come to a total synthesis of cobyric acid. The two methyl groups at 5 and 15 are missing and there is no method as yet to distinguish the propionic acid side chain at C17 from the rest of the acid side chains, the ester functions of which must be converted into amides. With other problems solved, these should not hold up a total synthesis for very long.

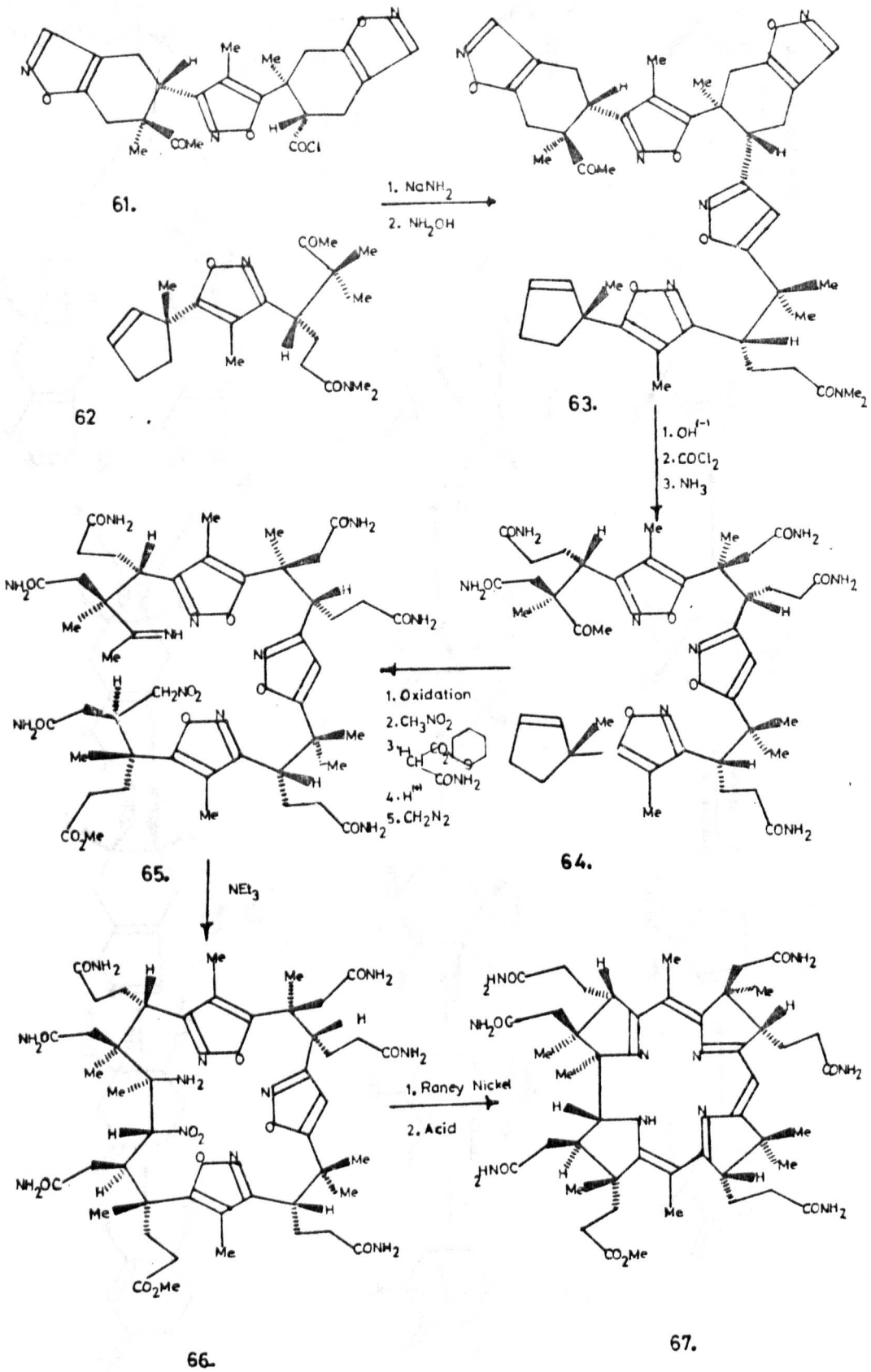
Cornforth, in 1962, put forward[23] a scheme for the total asymmetric synthesis of cobyric acid which is essentially different in strategy and tactics to that of Woodward and Eschenmoser. The main features are shown in Schemes IV and V and essentially these are :

1. Rings A and B come from the same precursor (56) which is resolved using quinine. The ring C precursor comes from (+) camphor and the ring D precursor is synthesised and resolved with brucine as shown in Scheme IV.
2. The acid chloride (57) and the N-β-keto pyridinium

SCHEME IV


Resolve acid with brucine
[α]D (+) 64°
[α]D + 24°
56.
57.
58.
59.
60.
61. obtained from this compound
62. Obtained from this compound

SCHEME V

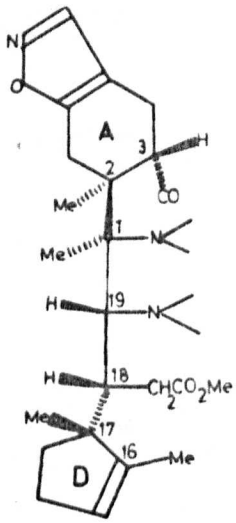

61.
1. NaNH2
2. NH2OH
62
63.
1. OH(-)
2. COCl2
3. NH3
64.
1. Oxidation
2. CH3NO2
3.
4. H(+)
5. CH2N2
65.
NEt3
66.
1. Raney Nickel
2. Acid
67.

bromide (58) are prepared, coupled and the β-diketone obtained after reduction is methylated and converted into the isoxazole (61).

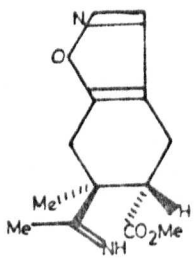
3. The acid chloride (59) is coupled with the ethyl ketone (60) in the presence of base to give the D, C component (62).
4. The B and C rings are then coupled by conversion of (61) into the acid chloride and treating with base followed by hydroxylamine to give the linear tetramer (63).
5. Strong treatment with alkali followed by conversion into the amides gives (64) which is then treated as shown to give (65).
6. Ring closure takes place on treatment with a base such as triethylamine to give (66) and hydrogenolysis of the isoxazole followed by acid catalysed condensation gives the metal-free corrin (67). (The feasibility of isoxazoles as corrin precursors has recently been shown[23a]).

Although this scheme solves all the problems of corrin synthesis and B_{12} stereochemistry on paper, there are a number of criticisms that can be made. Firstly, the cleavage of the isoxazoles in (63) to give the propionic and acetic acid side chains (64) is a very drastic reaction and may cause some epimerisation. Secondly, the introduction of the acetamide side chain at C18 is probably a non-stereospecific process. Thirdly, and probably most importantly, the cyclisation step to form the 1,19 bond (65 → 66) requires the formation of a highly hindered bond by what is essentially a reversible reaction. Along with this steric factor there is a high entropy factor against bond formation. Although the isoxazoles add some rigidity to the backbone, (65) is conformationally very mobile and the probability of the correct conformation for cyclisation is low.

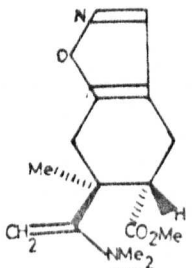
After some work to realise this scheme (mainly synthesis and resolution of precursors) the strategy was changed because of the difficulty of forming the 1,19 bond. The A,D component (68) was now to be synthesised and coupled



68.



69.



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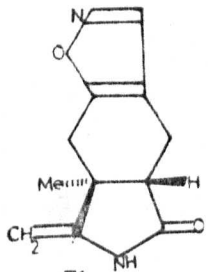

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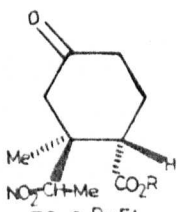
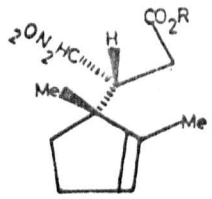
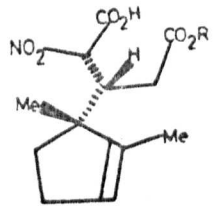


72. a. R = Et
b. R = H



73.



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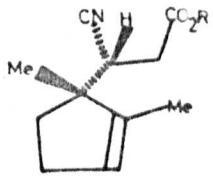
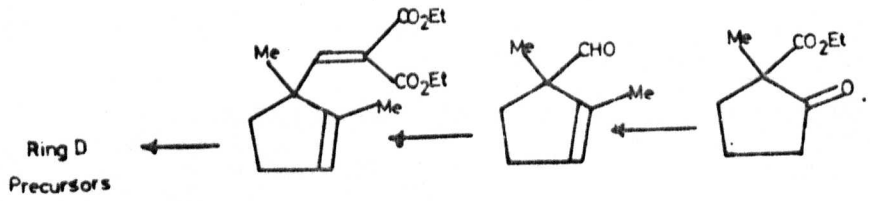
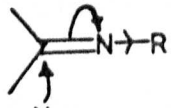


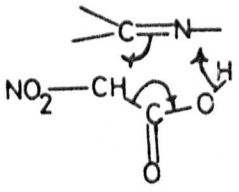
75.



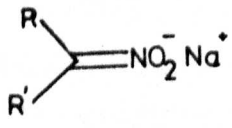
76. 77. 78.

79.  (Mayer)

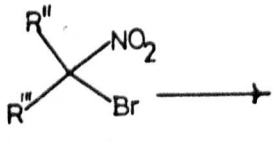
80.  (Michael)



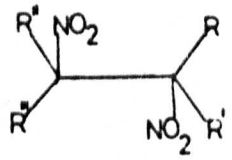
81.



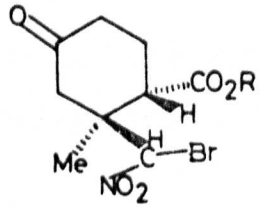
82. R = H
83. R = Alkyl



84.



85.



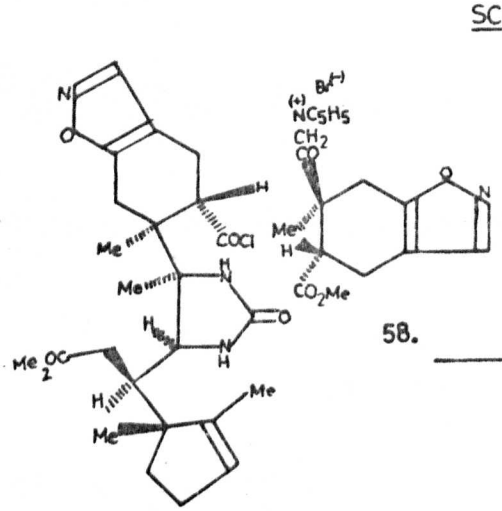
86.

with the C,D component as in the Woodward-Eschenmoser scheme. The approach to (68) was, however, rather more direct than theirs. The aim was to join stereospecifically the 1,19 carbon atoms, each bearing a nitrogen atom and each bound to highly hindered precursors.

Initial studies[24] into the feasibility of this plan used the attack of a nitro-anion on the electron-deficient carbon of a double bond (the Meyer reaction (79) or the Michael reaction (80)) with the possibility of an α-nitro acid (viz. (81)), as a more reactive variant. Ring D precursors (73), (74) and (75) were to be synthesised from (76) prepared from (78) as shown. Only (73) and (75), however, were obtainable. Ring A precursor (71) was already available from previous work and although (69) and (70) were unobtainable, (72a) was prepared by the action of nitroethane on Hagemann's ester in the presence of base. The intermolecular coupling between (71) and (73) did not take place. Intramolecular coupling between (71) and (73), which should have a more favourable equilibrium constant, failed because intermediates could not be obtained, e.g. the acylation of (71) with the acid chloride of (73) was impossible. A later idea involving acylation of the imine resulting from partial reduction of (75) with the acid chloride of (72b) followed by cyclisation was not pursued any further after models had showed that the wrong stereochemistry at C1 would be obtained with no reasonable way to invert it.

This was the stage reached when the Warwick group started working on the problem. The necessary steric hindrance at C1 and C19 seemed to preclude use of any reversible reaction for coupling. In the search for a suitable irreversible reaction, the coupling[25] of a bromo-nitro compound (84) with a secondary nitro-anion (83) leading to the dinitro compound (85) via[26] a radical or radical anion mechanism, showed promise. It was necessary to see if the coupling worked with a primary nitro-anion and research on model systems, and later with B_{12} precursors, was undertaken by Dr. W. R. Bowman. The problems dealt with in the text that follows are listed below :

SCHEME VI



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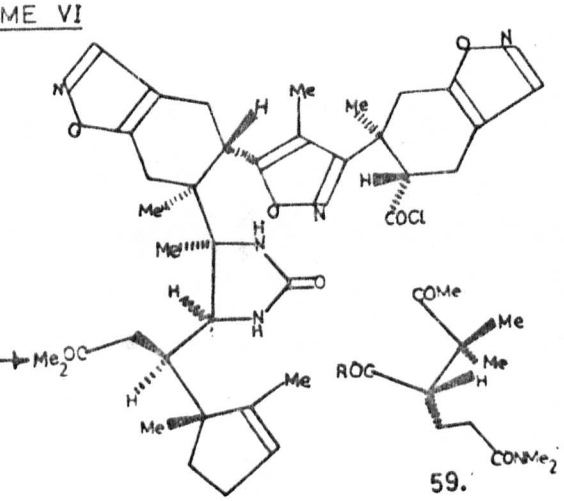

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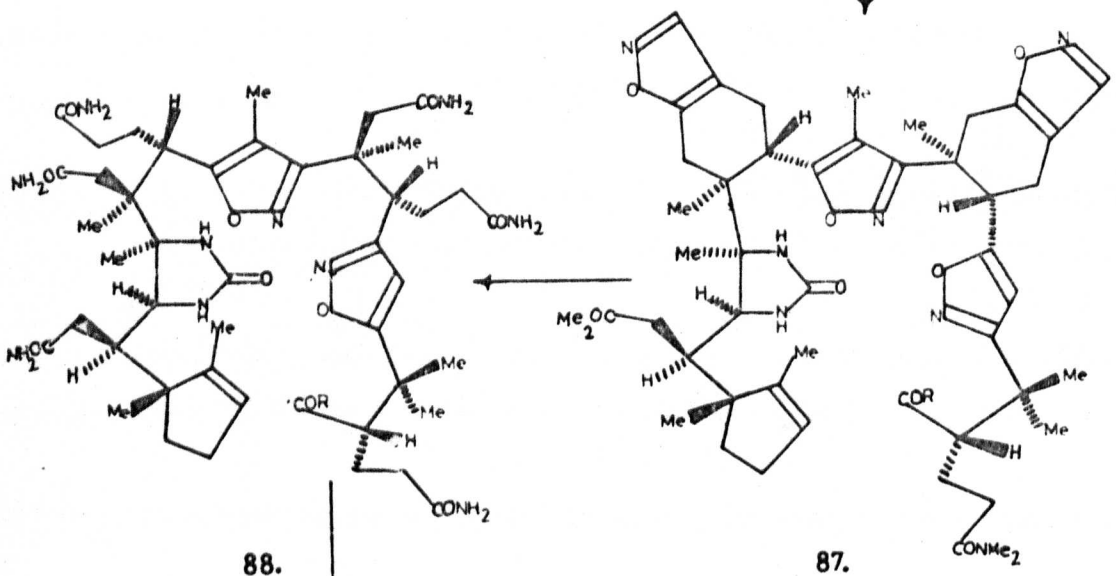
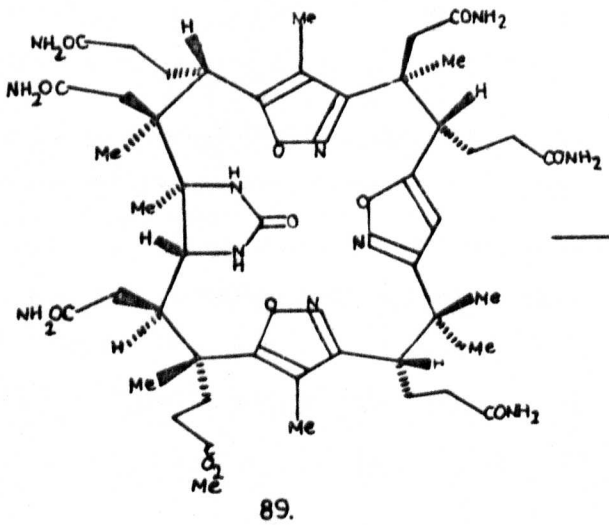


88.

87.

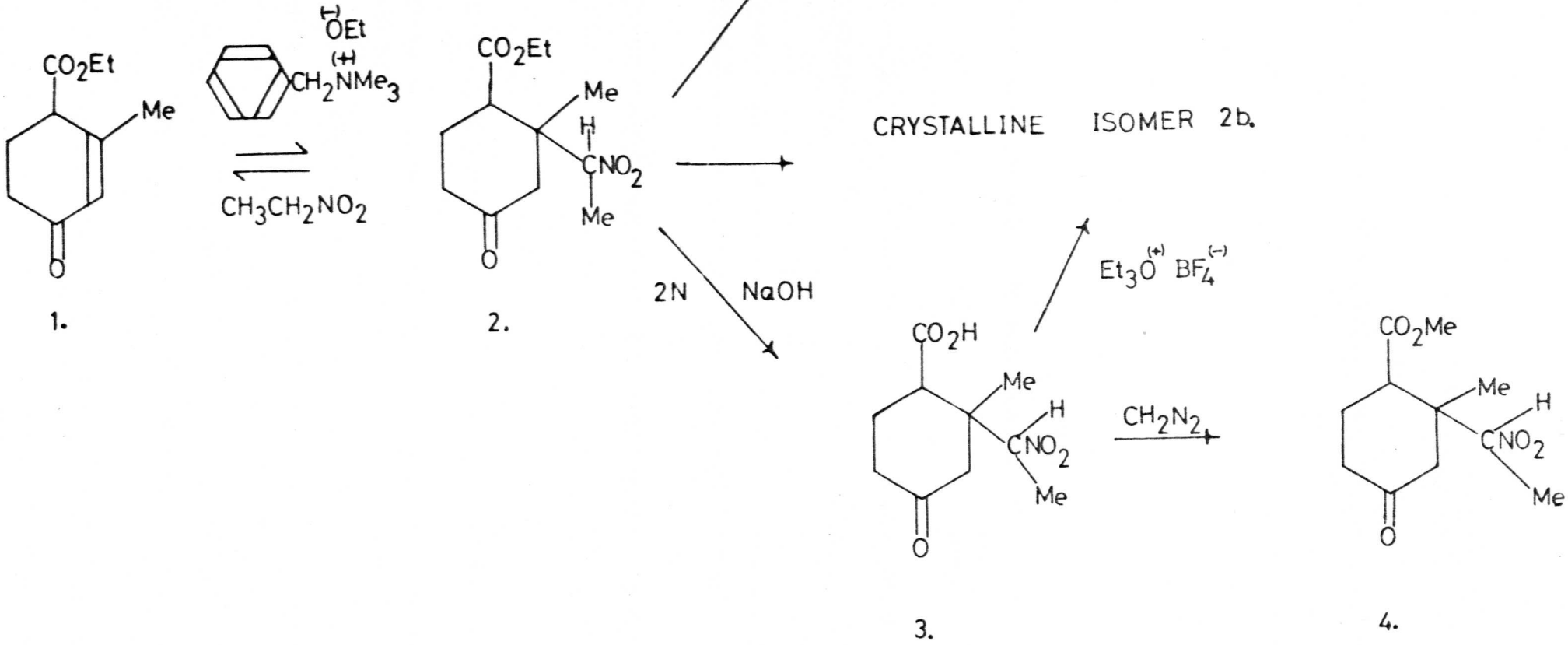


89.

CORRIN

1. The acid (72b) was important as it would have to be resolved. Previously it was synthesised in low yield and an improvement was felt to be necessary. This was to be done by introducing a t-butyl rather than an ethyl ester into (72a). (Chapter 1).
2. The trans geometry of (72a) also needed proof. A degradative route which could also be used for the enantiomers of (72b) had to be designed. (Chapter 2).
3. Assuming that the bromo-nitro coupling was successful, suitable B_{12} precursors (86) needed to be prepared. (Chapter 3).
4. The relative configuration of the ring D precursor was predicted to be correct but a procedure to prove this needed to be developed. (Chapter 4).

Scheme VI shows how the synthesis of the A,D precursor (68) could fit in with the earlier scheme V. The same B (58) and C (59) precursors could be coupled as before using the isoxazole route, to give the linear tetramer (87). Development of the side chains as before would give (88) followed by ozonolysis and cyclisation to (89). Treatment with Raney nickel and acid could then give the corrin nucleus. Certain protecting groups are shown which need not be those used when the scheme is put into practice. This route solves the problem of the 1,19 bond and introduction of the C18 acetamide group but it still has the major shortcoming of the vigorous conditions required in the step (87) → (88).


LIQUID ISOMER 2a.
CRYSTALLINE ISOMER 2b.
CO2Et
Me
OEt
CH2NMe3
CH3CH2NO2
H
CNO2
2N NaOH
Et3O(+) BF4(-)
CO2H
CH2N2
CO2Me
O

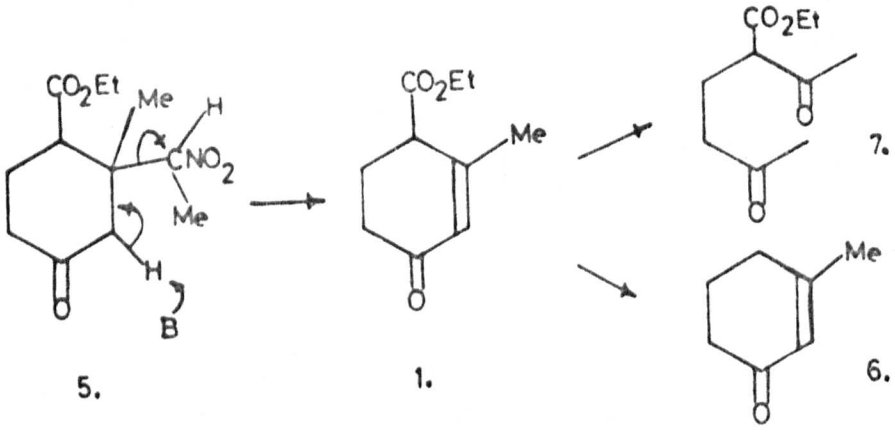
1. 2. 3. 4.

CHAPTER 1

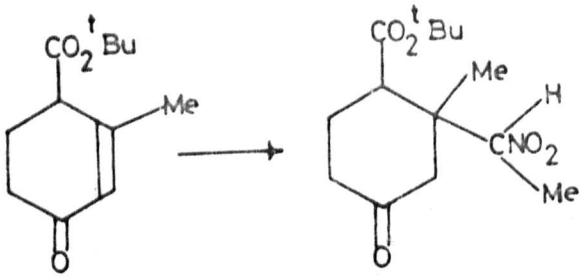
Preliminary studies[24] had shown that the acid (3) could be prepared from Hagemann's ester (1)[27] by Michael addition of nitroethane in the presence of a catalytic amount of benzyl-trimethyl ammonium ethoxide[28] followed by hydrolysis of the ester (2). This ester consisted of two isomers [N.M.R. : τ = 5.2, 5.35 (2q, 7, 1H $\underline{H}\dot{C}(NO_2)Me$), 8.52, 8.42 (2d, 7, 3H $H\dot{C}(NO_2)\underline{Me}$); I.R. : cm^{-1} = 1710 - 1730^s ($\rangle$=O), 1550^s (NO_2); G.L.C. : 2 peaks] one of which could be obtained by conversion into the semicarbazide followed by decomposition to the ketone with pyruvic acid. On shaking the mixture of esters with aqueous sodium hydroxide, the crystalline acid (3) was obtained (30%). This was a pure diastereomer as shown by its conversion to a single methyl ester [N.M.R. : τ = 5.1 (q, 7, 1H $\underline{H}\dot{C}(NO_2)Me$), 8.5 (d, 7, 3H $H\dot{C}(NO_2)\underline{Me}$); I.R. : cm^{-1} = 1550^s (NO_2)] with diazomethane.

As the yield in the hydrolysis needed to be improved, the above procedure was repeated in these laboratories. The ester (2) was obtained (65% from Hagemann's ester consumed) and one pure diastereomer (2b) crystallised out on standing [N.M.R. : τ = 5.04 (q, 7, 1H $\underline{H}\dot{C}(NO_2)Me$), 5.83 (q, 7, 2H $-O\underline{C}H_2CH_3$), 8.52 (d, 7, 3H $H\dot{C}(NO_2)\underline{Me}$), 8.69 (t, 7, 3H $-OCH_2\underline{C}H_3$), 8.85 (s, 3H $\rangle$-Me); M.S. : m/e = 257 (1%)m, 211 (35%)m $-NO_2$] leaving almost pure (2a) as the mother liquor [N.M.R. : τ = 5.33 (q, 7, 1H $\underline{H}\dot{C}(NO_2)Me$), 8.44 (d, 7, 3H $H\dot{C}(NO_2)\underline{Me}$)].

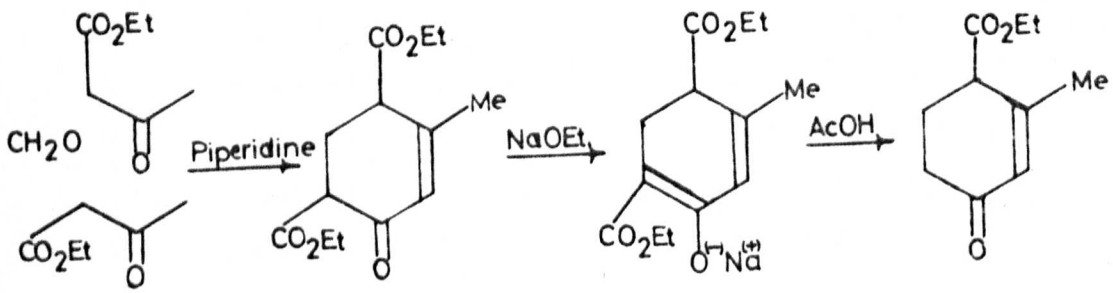
The acid (3) [N.M.R. : τ = 4.80 (q, 7, 1H $\underline{H}\dot{C}(NO_2)Me$), 8.47 (d, 7, 3H $H\dot{C}(NO_2)\underline{Me}$), 8.90 (s, 3H $\rangle$-CH_3); I.R. : cm^{-1} = 3200 - 2300^m (broad H-bonded -OH), 1707^s ($\rangle$=O), 1544^s (NO_2)] was obtained either from the mixture of isomers (2) or from the liquid isomer (2a) in 30% yield as before. Its stereochemistry was related to that of the crystalline ester (2b) by treatment of the salt with Meerwein's reagent, or of the acid with ethanol/sulphuric acid. Although the yields of (2b) in these reactions were less than 50%, the fact that one diastereomeric methyl ester was obtained from the acid in greater than 90% yield, removed any ambiguity. One



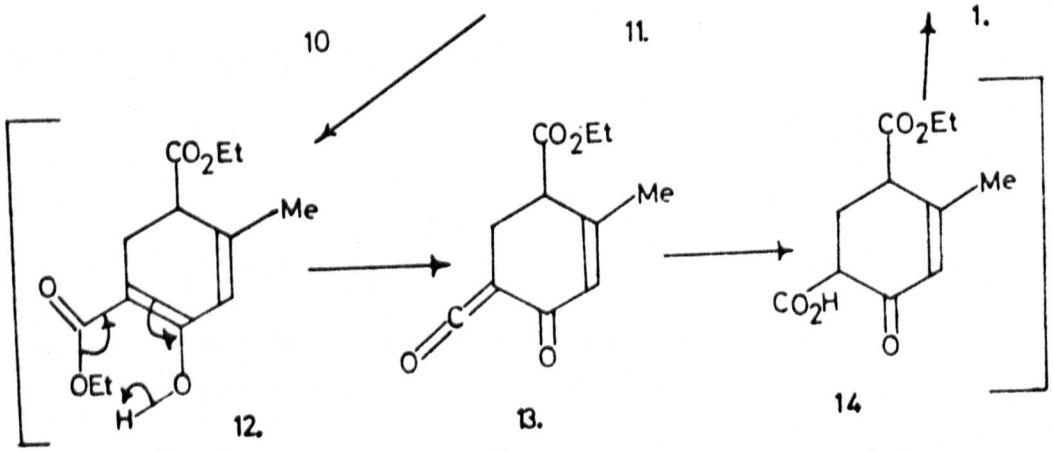
5. 1. 7. 6.



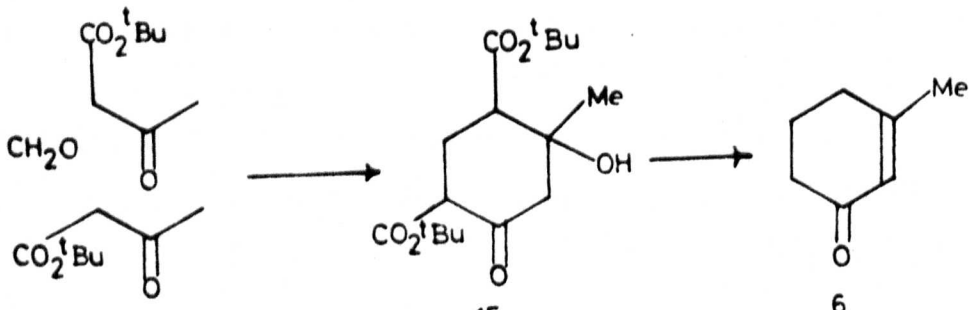
9. 8. 3.



10 11.



12. 13. 14



15 6

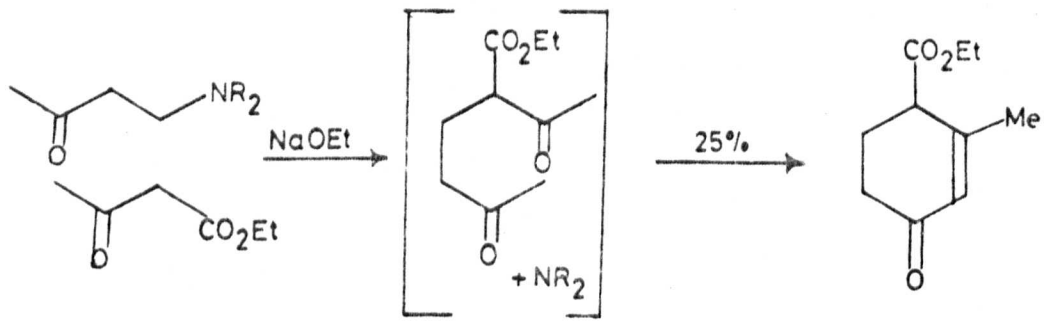
attempted improvement in the hydrolysis of (2) was the homogeneous reaction of (2b) with a dioxan, aqueous sodium hydroxide mixture. Short reaction times gave mainly the product of the Nef reaction (see chapter 2), whilst longer times gave a complex mixture of products. No more success was obtained with hydroxide, dimethyl sulphoxide[29] mixtures. It has since been shown[30] that the reverse Michael reaction (5) to give (1) with further hydrolysis to (6) and (7) is a competing side reaction in alkaline hydrolysis and this would account for the poor yields and the numerous products.

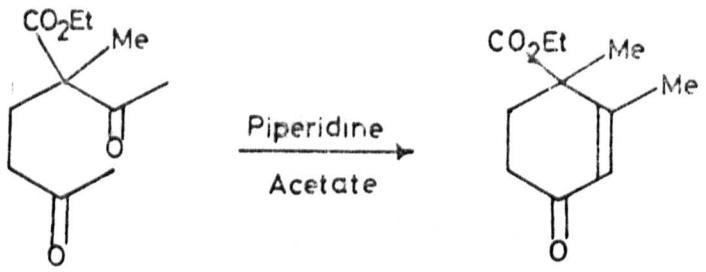
A New Route to Hagemann's Ester and its Methyl and t-Butyl Analogues .

The side reaction mentioned above could perhaps be eliminated by using acid hydrolysis, the t-butyl ester (8) being preferable because of the mild conditions[31] needed for cleavage. This could probably be prepared from t-butyl Hagemann's ester (9) by the action of nitroethane with benzyl-trimethyl-ammonium-t-butoxide and thus a method for synthesising (9) was needed. The standard preparation[32] of Hagemann's ester (1) is to condense two equivalents of ethyl acetoacetate with one of paraformaldehyde in the presence of piperidine as catalyst, followed by selective decarbethoxylation with glacial acetic acid of the sodium enolate (11a) of the ketodiester (10a) (55% yield). A possible mechanism explaining the selectivity of this reaction goes *via* the enol (12) and the ketene (13) to the β-keto acid (14) which spontaneously decarboxylates. If t-butyl acetoacetate is used in this reaction, the hydroxy-diester (15) is obtained which only gives 3-methyl-cyclohexenone (6) when selective elimination and decarboxylation is attempted.[33] It was therefore necessary to look for a new reaction leading to Hagemann type esters which should, if possible, be more straightforward than the standard procedure and give a higher yield of product.

Mannich,[34] in 1938, isolated Hagemann's ester (1) in 25% yield by treating the Mannich base (16) with ethyl acetoacetate and sodium ethoxide. This probably goes *via* dione (7) which is then cyclised by the secondary amine liberated. Similarly, Plieninger and Suehiro[35] have used piperidine acetate to selectively cyclise (17) to (18) although the structure of the latter was not certainly proved and Woodward *et al* have used[22] pyrrolidine acetate

16.





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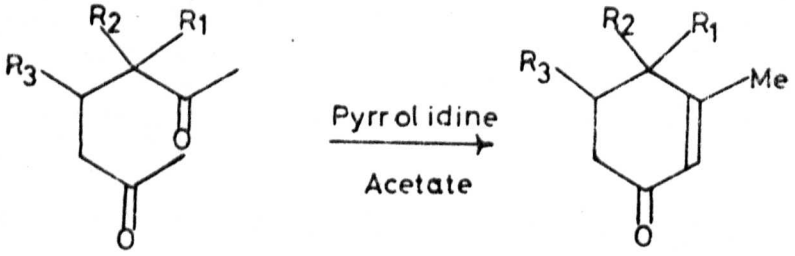

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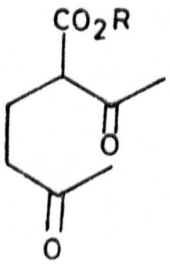
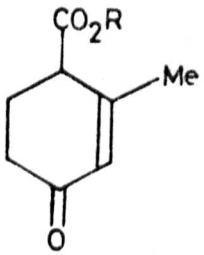
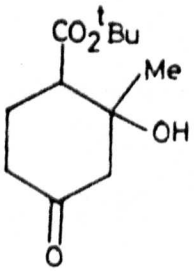


21. R = Me
7. R = Et
22. R = ^{t}Bu



23. R = Me
1. R = Et
9. R = ^{t}Bu



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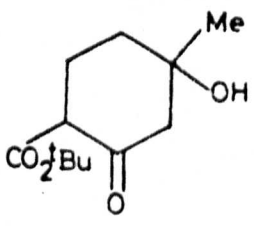


25.

to cyclise (19) to (20). Thus, the treatment of the 3-carbalkoxy-hepta-2,6-diones (21), (7), (22) with pyrrolidine acetate seemed a likely reaction to yield the required Hagemann's esters (23), (1), (9).

The diones were prepared by a literature[36,37] method for the ester (7), i.e. carefully controlled addition of methyl-vinyl-ketone to the corresponding acetoacetate at 0°C with sodium methoxide as catalyst. In this way the methyl ester (21) [N.M.R. : τ = 6.29 (s, 3H, $-CO_2Me$), 6.55 (t, 7, 1H $-CH_2\underline{C}H CO_2Me$), 7.82, 7.93 (2s, 6H, 2 $-CO\underline{C}H_3$); I.R. : cm^{-1} = 1750^s (CO_2Me), 1721^s ($\geq$0)] and the ethyl ester (7) [N.M.R. : τ = 5.86 (q, 7, 2H, $-OC\underline{H}_2CH_3$), 6.59 (t, 7, 1H $-CH_2\underline{C}H CO_2Et$), 7.85, 7.95 (2s, 6H, 2 $CO\underline{C}H_3$), 8.75 (t, 7, 3H, $-OCH_2\underline{C}H_3$); I.R. : cm^{-1} = 3420^w (enol OH), 1735^s (CO_2Et), 1715 ($\geq$0); U.V. : 249 nm / 3.25×10^2 (conjugated enol)] were prepared in 80 - 90% yield.

The reaction with t-butyl acetoacetate was slower than the two above. This could be for steric reasons but (more likely) it could be due to the sparing solubility of sodium methoxide in the mixtures of t-butyl acetoacetate and methanol used. The formation of the two epimers of (24) and/or (25) was a competing side reaction in this case and in a reaction where a temperature over 50°C was used, (24) and/or (25) were the only products, identified as a viscous oil [N.M.R. : τ = 6.4 (s, 1H -OH exchanges with D_2O), 8.5, 8.56 (2s of unequal intensity, 9H, $-CO_2{}^tBu$), 8.88, 8.91 (2s of unequal intensity 3H $Me\underline{C}OH$); I.R. : cm^{-1} = 3500^m (broad -OH), 1705^s (broad) ($\geq$0); G.L.C. : 2 components ratio 4 : 1]. However, (22) was obtainable (70 - 80%) at a lower reaction temperature (30°C) and a longer reaction time [N.M.R. : τ = 6.69 (t, 7, 1H $-CH_2\underline{C}H CO_2{}^tBu$), 7.84, 7.93 (2s, 6H, 2 $-CO\underline{C}H_3$), 8.55 (s, 9H $-CO_2{}^tBu$); I.R. : cm^{-1} = 1740^s ($CO_2{}^tBu$), 1720^s ($\geq$0)].

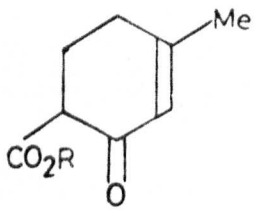
Conversion of these precursors to their respective Hagemann type esters was initially carried out by treating the diones (1 equivalent) with glacial acetic acid (0.4 equivalent), followed by pyrrolidine (0.25 equivalent). This mixture was then heated for ½ hour (80°C) and work-up gave the ester (23) [N.M.R. : τ = 4.18 (q, 1, 1H Me-C=C-H), 6.29 (s, 3H, $-CO_2CH_3$), 6.74 (t, 3, 1H $-CH_2\underline{C}H CO_2Me$), 8.0 (d, 1, 3H Me-C=C-H); I.R. : cm^{-1} = 1742^s (CO_2Me), 1681^s, 1632^m (α,β-unsaturated ketone)] from precursor (21) (75%). The

ester (1) [N.M.R. : τ = 4.2 (q, 1, 1H Me-C=C-H), 5.48 (q, 7, 2H, $-OCH_2CH_3$), 6.78 (t, 3, 1H $-CH_2\underline{C}H\underline{C}O_2Et$), 8.0 (d, 1, 3H Me-C=C-H), 8.74 (t, 7, 3H $-OCH_2\underline{C}H_3$) see plates I and II] was obtained from (7) (75%) and (9) [N.M.R. : τ = 4.21 (q, 1, 1H Me-C=C-H), 6.84 (t, 3, 1H, $-CH_2\underline{C}H\underline{C}O_2{}^tBu$), 8.0 (d, 1, 3H Me-C=C-H), 8.52 (s, 9H, $-CO_2{}^tBu$); I.R. : cm^{-1} = 1722^s ($CO_2{}^tBu$), 1671^s, 1630^m (α,β-unsaturated ketone)] was obtained from (22) (75%).

Consideration of the mechanism (see under "mechanistic studies") showed a possible way to improve the yield. Pyrrolidine is predicted to be consumed in a side reaction giving the dienamine (q.v.). This could be slowed down by the addition of water. Thus, by using 90% methanol/water as the solvent, the amount of pyrrolidine acetate used as catalyst was reduced to 10%. In this way the yield of ethyl-Hagemann's ester (1) was now 83% and this does not seem to be the limit as less pyrrolidine and longer reflux times still gave conversion, albeit much slower and probably not applicable to (22). Thus, the overall yield of (1) and (23) is now 75 - 80% as compared with 55% in the old method and the t-butyl ester (9) has been successfully prepared in 60 - 65% yield.

The spectra (N.M.R., I.R., U.V.) of ethyl-Hagemann's ester (1) prepared by the new method are identical to those of the product from the old method (see plates I and II and ref. 38). The similarity of the spectra of (23) and (9) to that of (1) (especially the N.M.R.) showed that they too were the desired isomers. For the sake of comparison, however, the iso-Hagemann's esters (26a) and (26b) were prepared by a known[36] method. As the method involves treatment with hydrogen chloride in benzene, it could not be used for the t-butyl analogue. The method also involves refluxing with N,N-dimethylaniline which is thought to convert any (27a) or (27b) to (26a) or (26b). In this way the methyl ester [N.M.R. : τ = 4.21 (s, 1H Me-C=C-H), 6.32 (s, 3H, $-CO_2Me$), 6.89 (m, 1H $-CH_2\underline{C}H\underline{C}O_2Me$), 8.03 (s, 3H Me-C=C-H)] and the ethyl ester [N.M.R. : τ = 4.21 (q, 1, 1H Me-C=C-H), 5.85 (q, 7, 2H, $-OCH_2CH_3$), 6.76 (m, 1H $-CH_2\underline{C}H\underline{C}O_2Et$), 8.03 (s, 3H Me-C=C-H), 8.74 (t, 7, 3H $-OCH_2\underline{C}H_3$)] were obtained.

The spectra of the isomeric Hagemann's esters are very similar, the main differences being in the fingerprint region of the I.R., in the N.M.R.

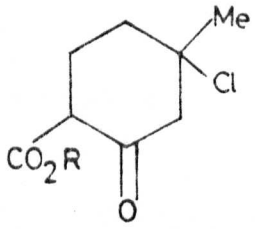


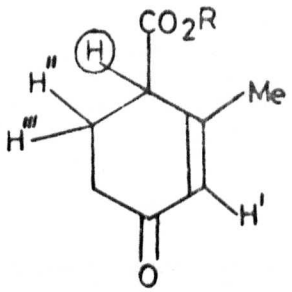
26 a. R = Me

b. R = Et

27a. R = Me

b. R = Et





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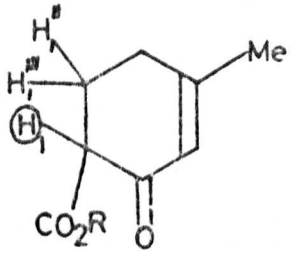

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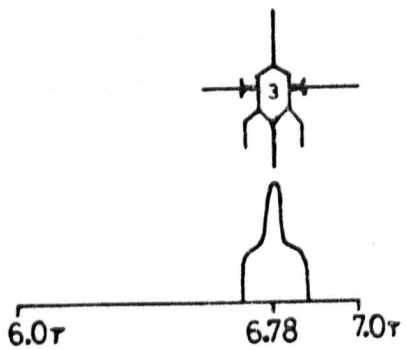

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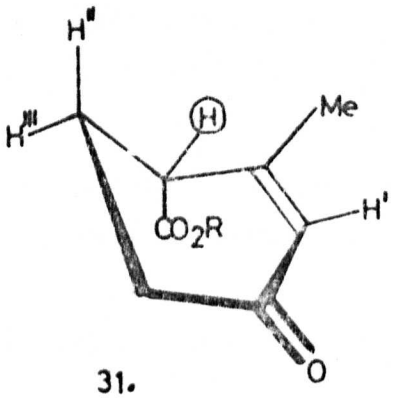

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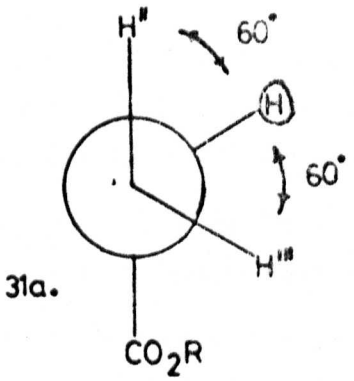
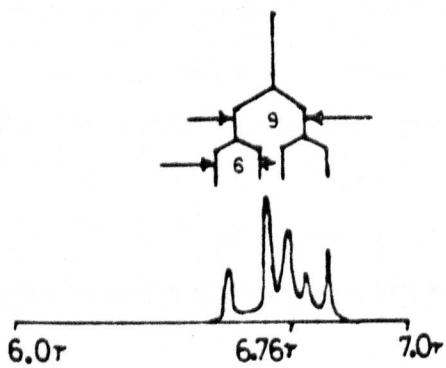


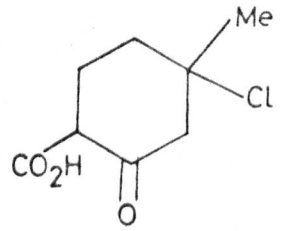
31a.



32.

chemical shifts and in the structure of the spin-spin splitting pattern, in the N.M.R., of the methine proton next to the ester grouping (the ringed protons in (28) and (29)). In (28) Ⓗ is coupled to H', H'' and H'''. It is a broadened triplet (30) with a coupling constant of 3 c.p.s., consistent with Ⓗ being coupled equally to H'' and H''', i.e., there is a dihedral angle of 60° between them (see 31a). Conformationally this is equivalent to an axial ester in the envelope conformation[39] of the cyclohexeneone (31). This is probably favoured because of a high energy interaction with the 3-methyl group in the equatorial position. The broadening of the triplet may be due to a small allylic coupling with H'. All three Hagemann's esters prepared have this spin-spin pattern. In (29) $\textcircled{H}_1$ is coupled to H''_1 and H'''_1. It is a multiplet whose structure is shown in (32). It is slightly more complex than the simple quartet expected for unequal coupling but the reason for this is not clear. The same pattern is, however, shown by both iso-Hagemann's esters. The chemical shift differences are slight but allow the detection of a small amount of Hagemann's ester (5%) (1) in iso-Hagemann's ester (26b). The quartet and the triplet of the ethyl group of (26b) showed those of (1) superimposed. Hagemann's ester (1) prepared by either route also showed about 5% of the isomer.

In the preparation of the iso-Hagemann's esters (26), a white crystalline substance was consistently obtained as a by-product in about 4% yield. It could be recrystallised as fine needles which were unstable at room temperature (fumed and darkened). Its N.M.R. : τ = 1 (broad s, 2.5H exchanges D_2O), 7.3 (s, 2H $-CO\underline{CH_2}-$), 8.3 (s, 3H $\underline{Me}\overset{|}{\underset{|}{C}}Cl$) changed rapidly at room temperature with evolution of gas to give a new spectrum τ = 4.18 (s, 1H Me—C=C—H), 7.5-7.9 (m, 6H $-CH_2CH_2CH_2-$), 8.03 (s, 3H Me—C=C—H). This, taken with the I.R. : cm^{-1} = 3400 - 2300^m broad (H-bonded O-H), 1655^s, 1595^s; the U.V. : 250nm / 4.65 x 10^3 (added NaOH gave 234nm / 7.8 x 10^3, α,β-unsaturated ketone) and the M.S. : m/e = 192/190m ratio 1 :4, 174/172m $-H_2O$, 140 - 146m $-CO_2$) led to the formulation of (33) and (34) as possible structures. Proof that (33) was



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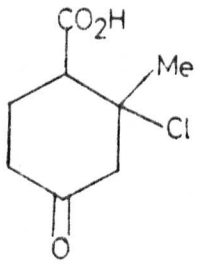

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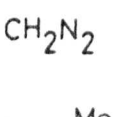

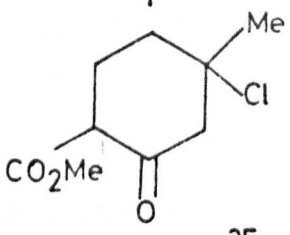

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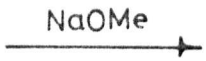
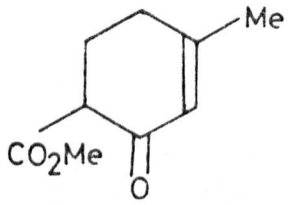
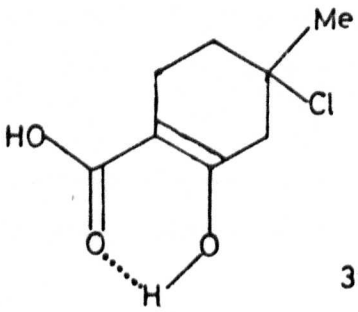




25a.



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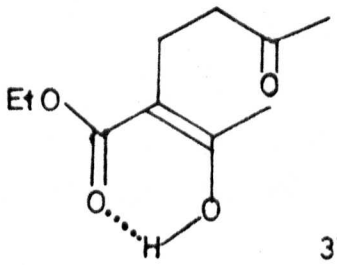

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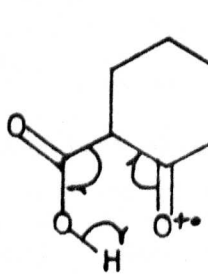
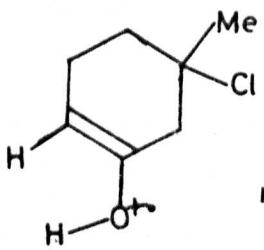


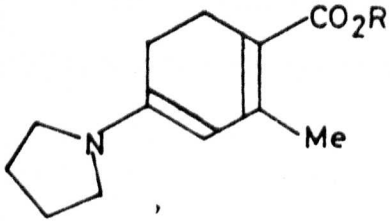
m\e 190\192

38.



m\e 146\148

39.

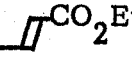


40. a R=Me

b R=Et

c R=^{t}Bu

the correct structure was obtained by treatment with diazomethane to give (35) [N.M.R. : τ = 6.23 (s, 3H $-CO_2Me$), 7.48 (s, 2H $-CO\underline{CH_2}-$), 8.34 (s, 3H $\underline{Me}-\overset{|}{\underset{|}{C}}Cl$)] which gave, on treatment with sodium methoxide in methanol, a product (100%) with identical N.M.R. and I.R. to methyl iso-Hagemann's ester (26a). The I.R. supports the enol structure (36). Normally acid and ketone bands are around 1700 cm^{-1} whereas this compound has two bands lower down at 1655 and 1595 cm^{-1}. The U.V. spectrum also supports this formulation. The maximum at 250nm is the same as the enol form (37) of the dione (7) but the absorption coefficient is ten times that of the dione. If one assumes that the latter is 10% enolised (cf. ethyl acetoacetate) then the former is ca. 100% enolised, i.e. (36). This should have two rapidly exchangeable protons which is supported by the N.M.R. spectrum. The change of the N.M.R. with time and the U.V. on addition of base supports the change (33) → (6). Finally, the loss of carbon dioxide (44 mass units) in the mass spectrum adds further evidence for this structure (see (38) → (39)). Several β-keto acids related to this compound are known[40, 41] and one method of preparation is by the action of ice-cold concentrated hydrochloric acid on β-keto esters. Nowhere, however, is the ca. 100% enol formulation discussed.

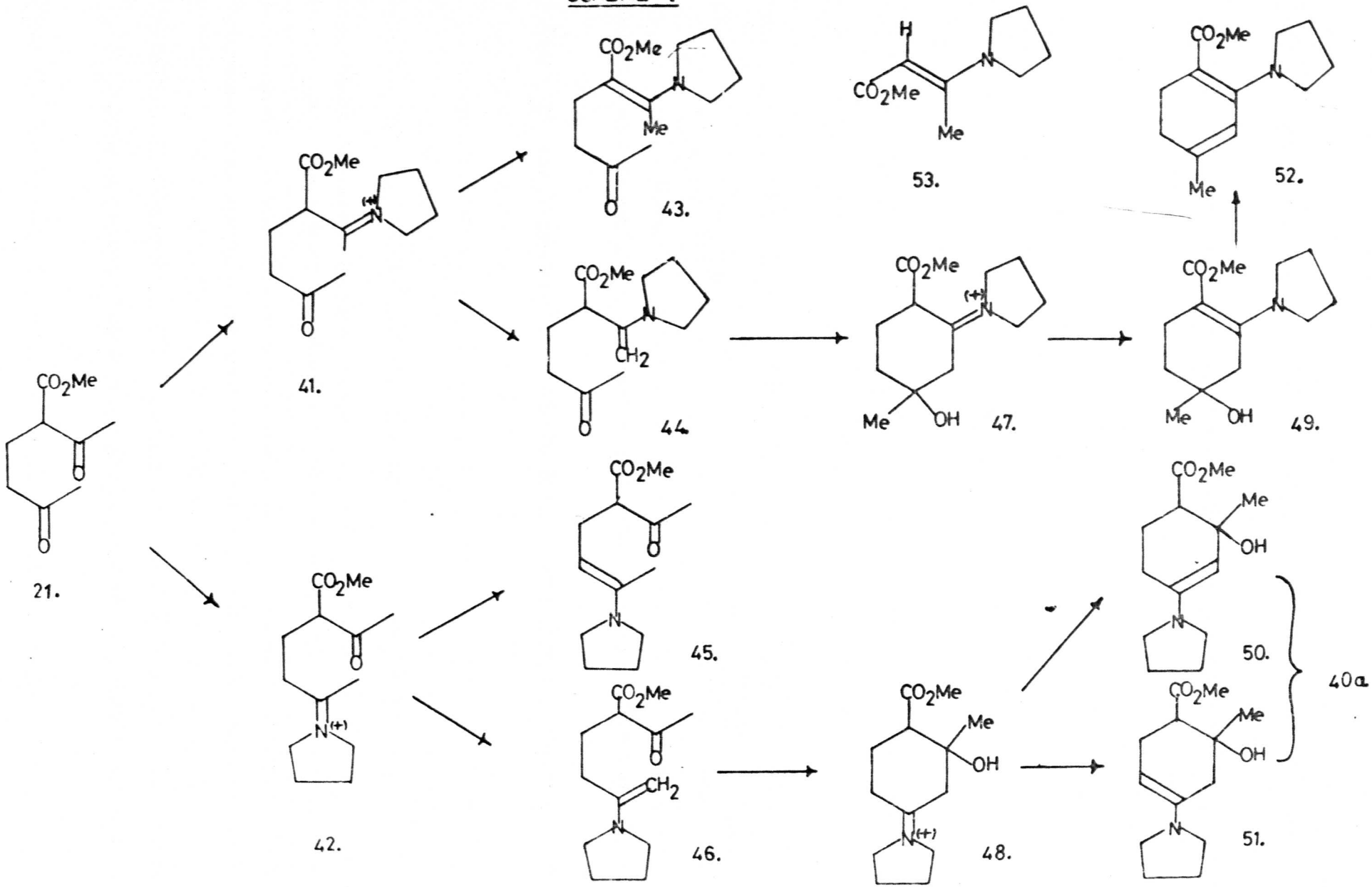
On treatment of the diones (21), (7), (22) or the Hagemann's esters (23), (1), (9) with 0.1 mole excess of pyrrolidine, an exothermic reaction took place followed by solidification of product. The products were identified as the dienamines (40a), (40b), (40c) respectively, e.g. (40b) [N.M.R. : τ = 5.53 (s, 1H H–C=C–Me), 5.92 (q, 7, 2H $-O\underline{CH_2}CH_3$), 6.72 (m, 4H $-N(CH_2)_2$), 7.86 (s, 3H H–C=C–Me), 8.73 (t, 7, 3H $-OCH_2\underline{CH_3}$); I.R. : cm^{-1} = 1683^{s} (conjugated ester), 1615^{m} (conjugated double bonds); U.V. : 386nm / 3.16 x 10^4 (); M.S. : m/e = 235 (98)m, 206 (15)m $-C_2H_5$, 190 (44)m $-OC_2H_5$, 162 (100)m $-CO_2Et$]. These compounds were identical when obtained from either the diones or the Hagemann's esters and were formed in over 90% yield. They are unstable in air, probably due to oxidation to aromatic systems, but with such characteristic properties, act as derivatives for identifying the corresponding Hagemann's esters (or diones). The dienamines from the iso-Hagemann's esters have not, as yet, been

prepared but attempts show that their formation is far more difficult than for the isomeric compounds. Attempted hydrolysis of the dienamine (40b) with dilute hydrochloric acid at reflux, 98% acetic acid under reflux or 70% acetic acid at room temperature for two days, gave only partial reaction showing that the enamines are probably too stable in these conditions to be intermediates in the new route to Hagemann's esters.

Mechanistic Studies

In order to probe the mechanism of the cyclisation reactions mentioned, the reaction of 3-carbomethoxy-hepta-2,6-dione (21) with pyrrolidine, in tetradeuteromethanol was studied by N.M.R. spectroscopy. The initial spectra of the dione [N.M.R. : τ = 6.25 (s, $-CO_2Me$), 6.35 (s, 7, $-CH_2\underline{C}\underline{H}CO_2Me$), 7.51 (t, 7, $-CO\underline{C}H_2CH_2$), 7.78, 7.88 (2 s, 2 $-COCH_3$), 8.05 (q, 7, $-CH_2\underline{C}H_2CH$)] and pyrrolidine [N.M.R. : τ = 6.98 - 7.25 (m $-N(CH_2)_2$), 8.1 - 8.4 (m $(CH_2)_2$)] were taken separately. The two reactants dissolved in tetradeuteromethanol were then mixed together (equimolar amounts, in an N.M.R. tube), shaken vigorously and the N.M.R. spectrum run immediately on fast speed. The initial spectrum [N.M.R. : τ = 5.34 (s, CD_3OH), 6.28 (s, $-CO_2Me$), 6.98 - 7.3 (m), 7.51 (t), 7.78 - 7.89 (2 s of unequal intensity), 8 - 8.4 (m), 8.68, 8.74 (2 s of unequal intensity)] showed several interesting features. Firstly, the triplet at 6.35 τ ($CH_2\underline{C}\underline{H}CO_2Me$) had disappeared and this was not necessarily accounted for by deuterium exchange as a control experiment in chloroform also showed immediate disappearance of this triplet. The result is probably explained by a rapid exchange of a proton with pyrrolidine which broadens the signal.

SCHEME I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O
O
21.
CO2Me
(+)
N
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N
Me
O
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CO2Me
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O
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CO2Me
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(+)
Me
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47.
H
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Me
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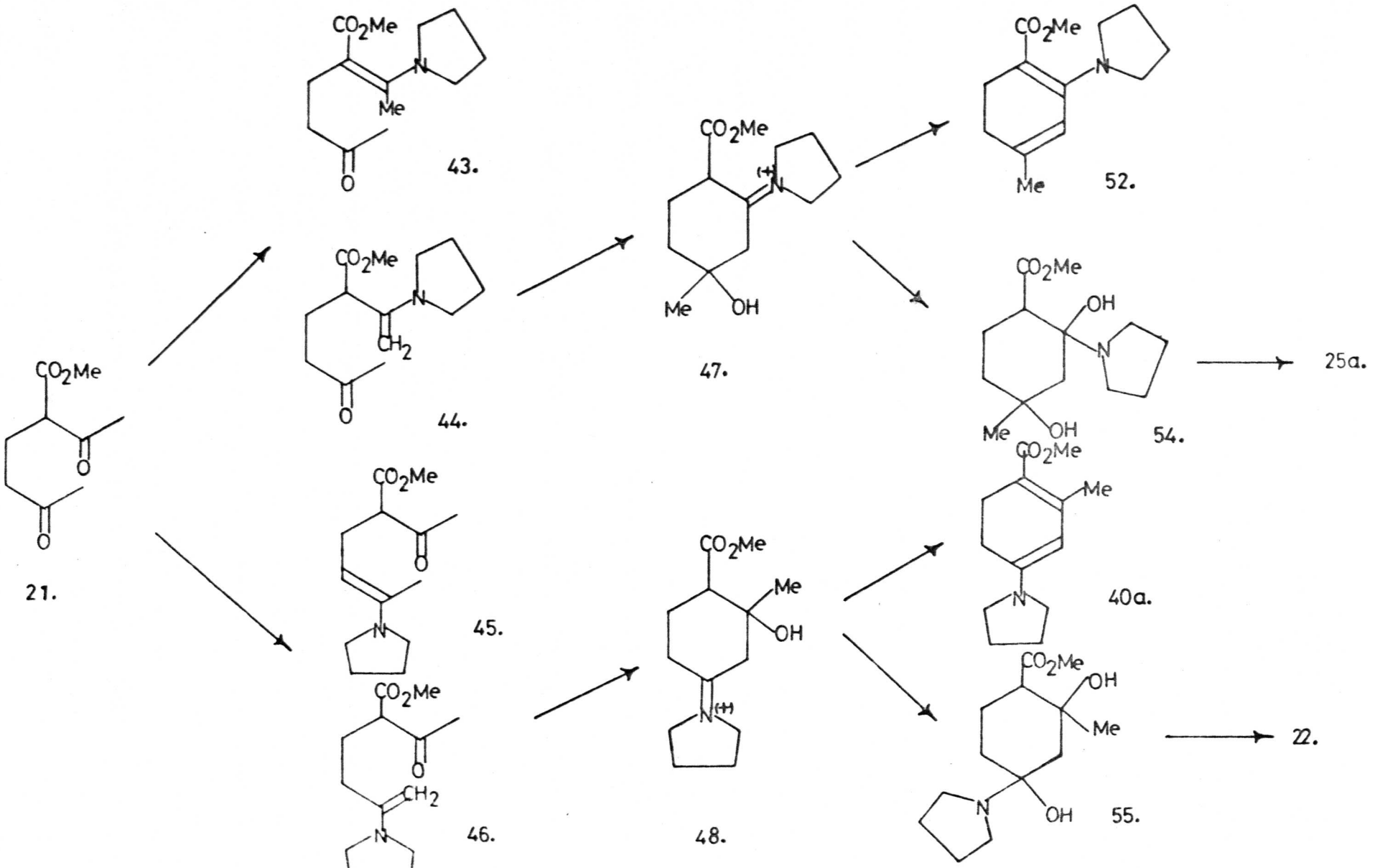
CO2Me
N
Me
52.
CO2Me
N
Me
OH
49.
CO2Me
N
(+)
42.
CO2Me
O
N
45.
CO2Me
CH2
O
N
46.
CO2Me
Me
OH
N
(+)
48.
CO2Me
Me
OH
N
50.
CO2Me
Me
OH
N
51.
40a

Secondly, the two singlets due to the acetyl methyl groups which initially had equal intensity, now had unequal intensity. This may be explained by one carbonyl group reacting more quickly with pyrrolidine. Thirdly, there was the appearance of a characteristic pair of singlets of unequal intensity at 8.68 and 8.74 τ. Also there was no appearance of olefinic protons downfield which could arise from possible intermediate enamines, and there was no sign of the product dienamine (40a). Spectra run consecutively after this showed the following trends. The appearance of the dienamine peaks came in the second run through (i.e., after about 1 minute) and continued to increase at the expense of the dione and pyrrolidine peaks. The characteristic pair of singlets around 8.71 τ remained, although with decreased intensity, and were still present when all the pyrrolidine was used up. At this stage there was still a small singlet at 6.25 τ which could be the carbomethoxy group of the starting material or an intermediate. Addition of more pyrrolidine (2 drops) gave a spectrum [N.M.R. : τ = 5.32 (s H  Me), 6.30 (s $-CO_2Me$), 6.68 (m $-N(CH_2)_2$), 7.55 (broad s, allylic-CH_2), 7.8 (s H  Me), 7.92 - 8.19 (m pyrrolidine $(CH_2)_2$)] corresponding exactly to the dienamine (4a).

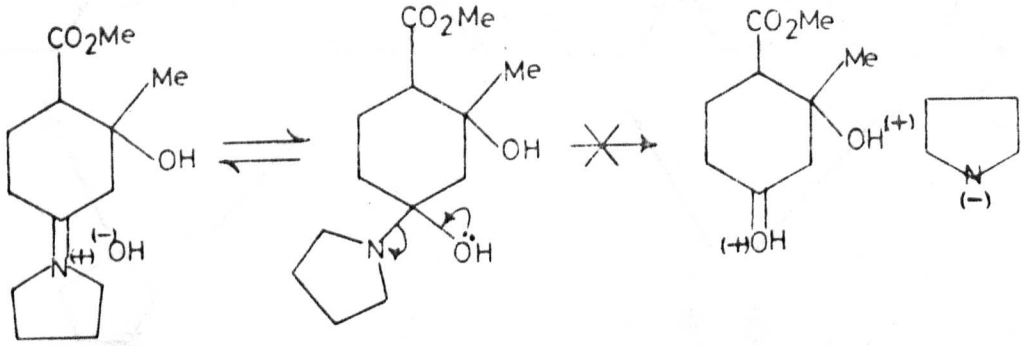
A proposal for the mechanism is outlined in scheme I. The initial attack of pyrrolidine on the dione (21) to give the Schiff's baselike intermediates (41) and (42), followed by a prototropic shift to give the corresponding enamines (43), (44), (45) and (46), would give a predominance of the least hindered enamines (45) and (46). This argument has been used by Woodward,[22] but in his compound (19), the steric hindrance is far more pronounced as also in Plieninger's compound (17). Of the possible intermediate enamines, only (44) and (46) can reasonably cyclise to 6-membered rings. One cannot say a priori if (43) predominates over (44); although (43) has a large delocalisation energy, it is more sterically compressed. (45) and (46) are much closer in energy and the cyclisation (46) to (48) would represent the major reaction pathway. In order to explain the approximately 100% conversion to dienamine (40a), one must assume that all the intermediate enamines are in equilibrium and also, to explain the absence of enaminic protons in the initial stages, one must assume that the cyclisation and pre-equilibrium stages are extremely

SCHEME II

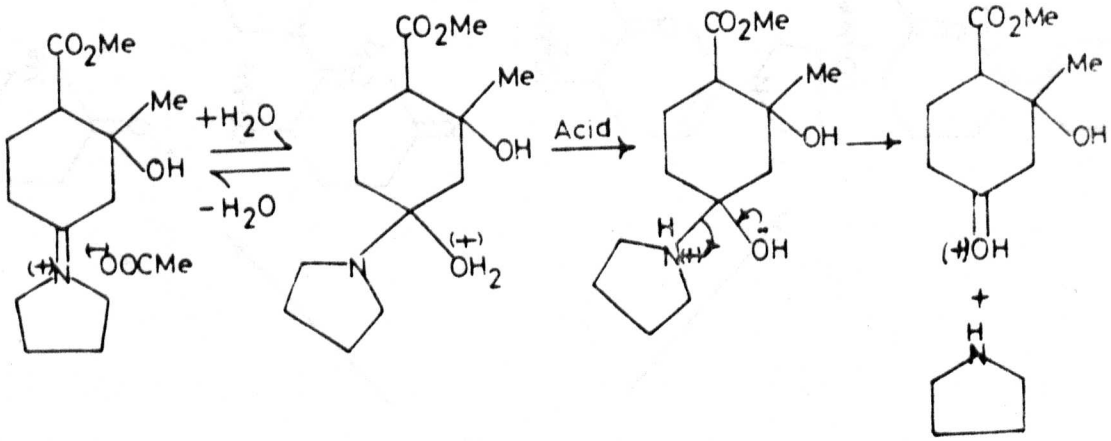


SCHEME III

NO ACID



ACID

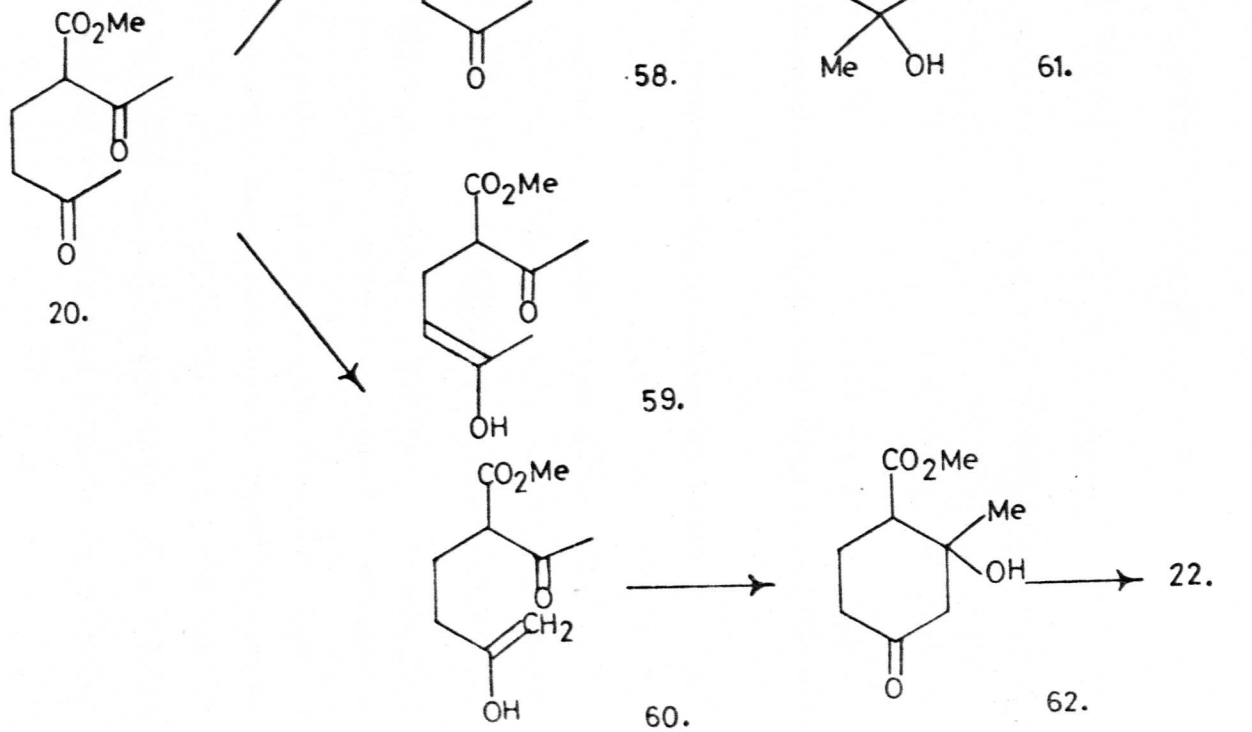


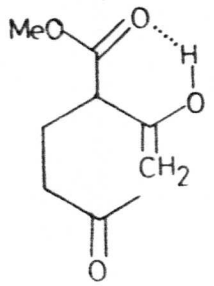
rapid so that intermediates cannot build up. The first likely stable intermediates are (50) and (51) whose structures would account for the pair of singlets at 8.68 and 8.74 τ (Me - $\overset{|}{\underset{|}{C}}$OH) and the fact that they remain after all the pyrrolidine is used up. Presumably, excess of base is necessary to eliminate water to give (40a) which, indeed, happens on addition of excess pyrrolidine. This mechanism implies that deuterium be incorporated at certain stages but the only detectable effect is the reduction in intensity of the peak at 7.8 τ (s, H $\underset{|}{\overset{|}{C}}$=$\underset{|}{\overset{|}{C}}$ Me). Dienamines (52) and (40a) may be expected to have similar spectra and, owing to the unavailability of (52) from iso-Hagemann's ester, the only proof that none of this is formed is that the N.M.R. spectrum of the final product is exactly similar to that of the dienamine obtained from methyl-Hagemann's ester.

The enamine (43) has a characteristic chromophore which is very similar to that derived from methyl acetoacetate and pyrrolidine[42] (53) [N.M.R. : τ = 5.55 (s, 1H H$\underset{|}{\overset{|}{C}}$=$\underset{|}{\overset{|}{C}}$-$CO_2$Me), 6.42 (s, 3H -$CO_2$Me), 6.75 (m, 4H -N($CH_2$)$_2$), 7.58 (s, 3H Me $\underset{|}{\overset{|}{C}}$=$\underset{|}{\overset{|}{C}}$ N), 7.90 - 8.18 (m, 4H pyrrolidine (CH_2)$_2$)]. The methyl protons at 7.58 τ were not detected, by comparison, in the reaction of the dione with pyrrolidine and this is tentative evidence that neither (43) nor (49) are formed in appreciable quantities.

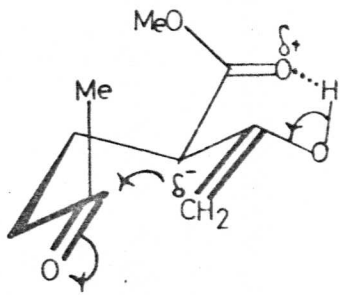
It seems reasonable to propose that the cyclisation of the diones to the respective Hagemann's esters with pyrrolidine acetate would take place by a very similar mechanism to scheme I, with the acid intervening at a particular stage. It is important to note that it is a catalytic reaction and that a substantial amount of acid soluble material (dienamine) is obtained. Scheme II gives a proposed mechanistic sequence in outline. The four possible enamines are formed as in scheme I and the same arguments as to which is the main mode of cyclisation apply. The intermediates (47) and (48) now have two choices. Firstly, they can tautomerise and eventually give the dienamines and secondly, the Schiff's base can add water, followed by an acid-catalysed elimination of pyrrolidine to give the Hagemann's ester (23) or (26a). The hydrolysis of the Schiff's base is not a competing process in the absence of acid because the pyrrolidine anion (56) is a worse leaving group than hydroxide

SCHEME IV





63.



64.

(see scheme III). In acid, pyrrolidine can now be eliminated with ease, thus giving a catalytic reaction. Some dienamine would be expected as a by-product as is found to be the case, and this reaction acts as a catalyst scavenger which lowers the yield of Hagemann's ester. This side reaction could be suppressed by having excess water in the reaction mixture to enhance the hydrolysis of the Schiff's base and this is exactly what happens (see earlier). Approximately 5% of the iso-Hagemann's ester is formed in this process, which gives a measure of the selectivity of the formation of the respective enamines and of their rate of cyclisation.

The opposite mode of cyclisation, using hydrogen chloride, probably goes through enol intermediates (57), (58), (59) and (60) as shown in scheme IV. Of the four possible enols only (58) and (60) can reasonably cyclise to give 6-membered rings and of these (58) would be expected to predominate as it is stabilised by hydrogen bonding (63). This enol would also be expected to cyclise more rapidly than (60) for the following reasons :

1. The carbonyl group attacked is the least hindered of the two.
2. The hydrogen bond makes the preferred conformation for cyclisation statistically more favourable as it adds rigidity to the backbone (see (64)).
3. Also, the carbonyl group of the ester participating in the hydrogen bond acts as a general base catalyst, i.e. it makes the enol a more powerful nucleophile (see (64)).

With the ready availability of t-butyl Hagemann's ester (9), it was now possible to try out the Michael addition of nitroethane. Firstly, however, the progress of the reaction in the aprotic solvent dimethylsulphoxide with potassium t-butoxide as base was investigated using ethyl Hagemann's ester (1). This was carried out under nitrogen at 40°C with a ratio of nitroethane to t-butoxide of 6:1. Samples removed at intervals and analysed by G.L.C. showed that the reaction had come to equilibrium after 68 hours and that there was a 50/50 ratio of product (2) to starting material. This is no significant improvement on previous conditions. The absence of a solvating shell around the nitroethane anion makes it a better nucleophile, but this only enables the equilibrium to be reached faster and does not alter the position, compared with the Triton bases. The reaction also has the disadvantage that dimethylsulphoxide is only removed with difficulty. Attempts to alter the position of equilibrium in favour of product by using more nitroethane have failed, probably because of a competing self-destructive side reaction.[43] It seems that approximately 2.5 moles excess is the optimum concentration.

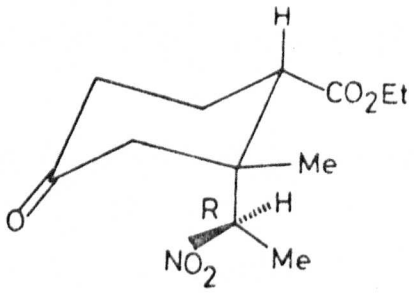
The Michael addition using Triton bases was followed simultaneously for all three Hagemann's esters (23), (1), (9). The respective Triton bases (benzyl-trimethyl ammonium methoxide, ethoxide, t-butoxide) were available by modification of an organic synthesis procedure.[28] The mixtures of nitroethane, base and Hagemann's ester were heated under nitrogen at 40°C and the reactions were followed by removing samples at intervals and analysing them (G.L.C.). They all had approximately the same rate, coming to equilibrium after about 94 hours. The methyl ester gave a 55/45 mixture of product to starting product as shown by the N.M.R. integration (excess nitromethane removed in vacuo) and the Michael adduct was a mixture of two isomers, 40% [N.M.R. : τ = 5.05 (q, 7, $\underline{H}C(NO_2)Me$)] and 60% [N.M.R. : τ = 5.35 (q, 7, $\underline{H}C(NO_2)Me$)]. There were other peaks in this spectrum not corresponding to any expected product. The ethyl esters gave a cleaner reaction mixture containing a 55/45 mixture of product and starting material, the product being a mixture of two isomers obtained in previous reactions in a ratio of 40 [N.M.R. : τ = 5.05 (q, 7)] to 60 [N.M.R. : τ = 5.35 (q, 7)].

In contrast, the t-butyl adduct was only obtained in a ratio of 40 to 60 of the Hagemann's ester. Fractionation gave a viscous liquid which was a mixture of two diastereomers, 40% [N.M.R. : τ = 4.97 (q, 7, $\underline{H}\dot{C}(NO_2)Me$), 8.47 (d, $H\dot{C}(NO_2)\underline{Me}$), 8.86 (s $\rightarrow$ $\underline{Me}$)] and 60% [N.M.R. : τ = 5.26 (q, 7, $\underline{H}\dot{C}(NO_2)Me$), 8.42 (d, 7, $H\dot{C}(NO_2)\underline{Me}$), 8.90 (s $\rightarrow$ Me)]. The recovered yield of neutral material was approximately 85% in all cases.

Application of this reaction on a large scale gave a mixture of isomers (30% overall, 75% from (9) consumed) from which one crystallised [N.M.R. : τ = 5.21 (q, 7, 1H $\underline{H}\dot{C}(NO_2)Me$), 8.38 (d, 7, 3H $H\dot{C}(NO_2)\underline{Me}$), 8.48 (s, 9H $-CO_2{}^tBu$), 8.86 (s, 3H $\rightarrow$ Me); I.R. : cm^{-1} = 1723^{sh} ($CO_2{}^tBu$), 1719^{s} ($\rightarrow$ 0) 1553^{s} (NO_2); M.S. : m/e = 285 (0.1)m, 57 (100) $\rightarrow^{(+)}$] leaving a mother liquor containing approximately 15% of this crystalline isomer. Presumably, the overall yield in the Michael addition is lowered by a steric factor affecting the equilibrium constant.

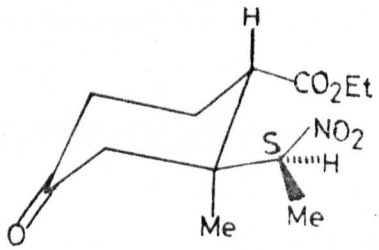
Attempts to remove the t-butyl group with trifluoroacetic acid in an N.M.R. tube failed, probably because any isobutylene formed could not escape. However, the N.M.R. spectrum showed the proton next to the ester group as a well-resolved quartet (J = 6 and 8 c.p.s.) at 6.86 τ (1H). These coupling constants point to a twisted chair conformation as will be discussed in chapter 3. The t-butyl ester was successfully cleaved by refluxing with p-toluene sulphonic acid in benzene to give the acid [N.M.R. : τ = 5.03 (q, 7, 1H $\underline{H}\dot{C}(NO_2)Me$), 8.33 (d, 7, 3H $H\dot{C}(NO_2)\underline{Me}$), 8.90 (s, 3H $\rightarrow$ Me)] in 93% yield. This acid is the epimer of that obtained by the alkaline hydrolysis of the ethyl esters [N.M.R. : τ = 4.88 (q, 7, 1H $\underline{H}\dot{C}(NO_2)Me$), 8.47 (d, 7, 3H $H\dot{C}(NO_2)\underline{Me}$), 8.84 (s, 3H $\rightarrow$ $\underline{Me}$)] and this proves that the crystalline t-butyl compound is of the opposite configuration to the crystalline ethyl ester (see chapter 3 for a full discussion of these relative stereochemistries).

The aim of improving upon the yield of the acid had thus been achieved, it now being (68 - 70%) based on Hagemann's ester consumed rather than 24% as before.



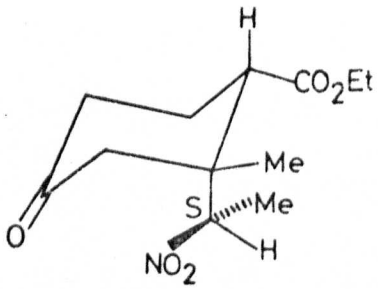
1a.

CIS

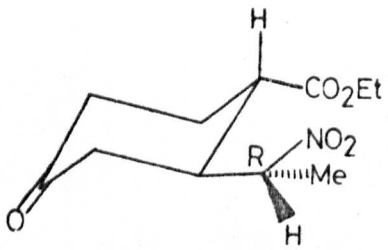


2a.

TRANS

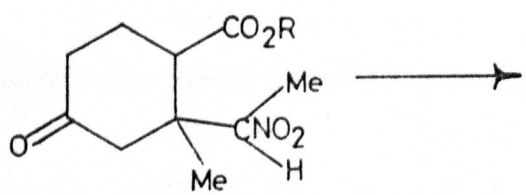


1b.



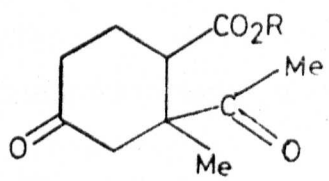
2b.

SCHEME I



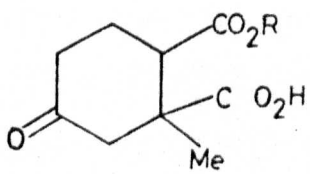
3 a. R = Et

b. R = H



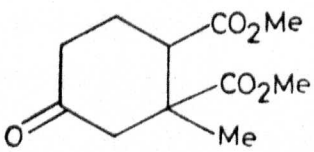
4 a. R = Et

b R = H



5 a. R = Et

b. R = H



6.

CHAPTER 2

It has been shown (chapter 1) that the Michael addition of nitroethane to Hagemann's esters gives an equilibrium mixture of two isomeric nitro-adducts and starting material. There are four diastereomers, two cis epimers (1a) and (1b) and two trans epimers (2a) and (2b) that may be formed in this reaction. Because of the nature of the reaction, the structure of the products will be governed by thermodynamic considerations, but if the A-value[44] of the 2-nitroethyl group is assumed to be between that of methyl (1.7) and that of isopropyl (2.1) (i.e. about 2), a mixture of cis and trans isomers is predicted. As the reaction conditions are basic this points to all four diastereomers being formed. Assuming that the two isomeric nitro-adducts obtained are pure, this argument must be false and other considerations affecting the stability of the isomers (e.g. dipole moment interactions) should be considered. It needed to be shown that :

1. The two isomers were epimeric at the 2-nitroethyl group.
2. The geometry at the ring was cis (1) or trans (2).

Scheme I shows a possible route by which these stereochemical problems would be solved. Conversion of the nitroethyl group of the ester (3a) or the acid (3b) into the ketone destroys one asymmetric centre, and if both isomers of (3a) give the same ketone (4a) and acid (4b) then the source of their difference lies in this centre (assuming that no epimerisation takes place on the ring). The Nef reaction,[45] which requires conversion of the nitro-compound to its salt followed by slow addition to acid at low temperatures, is the most direct way to achieve this transformation. The optimum conditions for certain aliphatic nitro-compounds have been shown[46] to be 8N—28N sulphuric acid at -5 to 0^{o}C. If the temperature is raised, or the order of addition reversed, the yield is reduced, but the counter anion has little effect. The Nef reaction is thought[46] to be relatively sensitive to steric hindrance, e.g. i-propyl nitromethane gives only 36% of the corresponding aldehyde whereas n-propyl

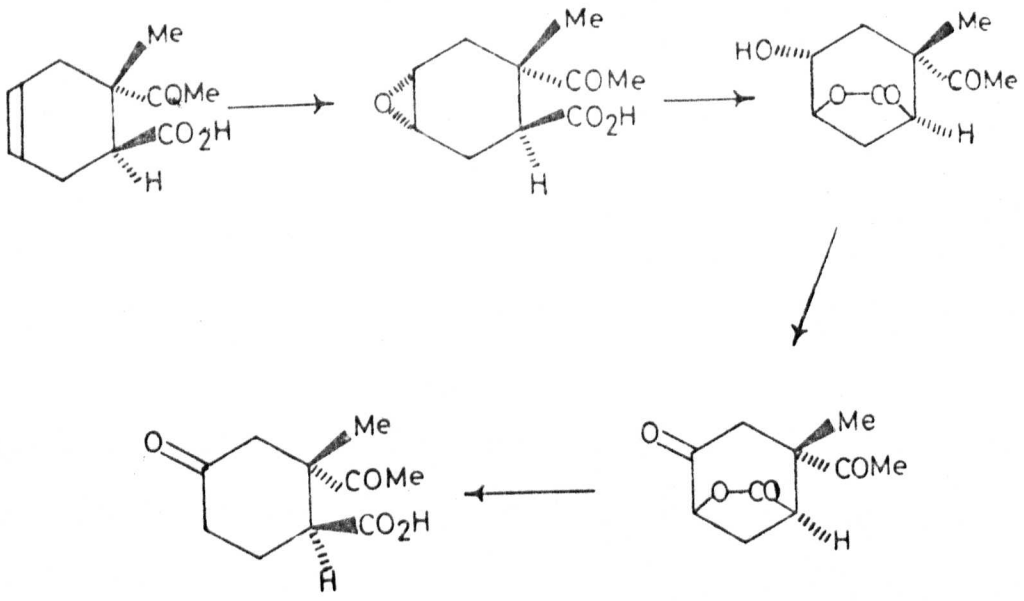
nitromethane gives 78%. This result would seem to imply that (3a), which has a hindered secondary nitro group, would give a poor yield of (4a) but this is not the case (see chapter 3).

An ethanolic solution of the sodium salt of (3a) (liquid isomer) was added slowly to 17N sulphuric acid at $0^{o}C$. A product was obtained which showed one major component (70%) and no starting material. This was identified as ketone (4a) [N.M.R. : τ = 5.81 (q, 7, 2H $-OC\underline{H}_2CH_3$), 6.67 (q, 5 and 10, 1H $-CH_2\underline{C}H\underline{C}O_2Et$), 7.78 (s, 3H $-COCH_3$), 8.72 (t, 7, 3H $-OCH_2C\underline{H}_3$), 8.75 (s, 3H $>\underline{C}Me$); I.R. : cm^{-1} = 1715^{s} ($>C=O$); M.S. : m/e = 226 (20)m, 110 (100) $C_7H_{10}O^{+}$, 43 (100) $CH_3\overset{+}{C}O$]. Acidic hydrolysis gave the keto-acid (4b) [M.P. $158^{o}C$ (plates); N.M.R. : τ = 6.51 (q $-CH_2\underline{C}H\underline{C}O_2H$), 7.76 (s, 3H $-COCH_3$), 8.77 (s, 3H $>\underline{C}Me$); I.R. : cm^{-1} = $3250 - 2200^{m}$ (broad OH), 1717^{s} ($>C=O$), 1693^{s} (CO_2H); M.S. : m/e = 195 (5)m, 110 (100) $C_7H_{10}O^{+}$, 43 (250) $\overset{+}{C}OCH_3$].

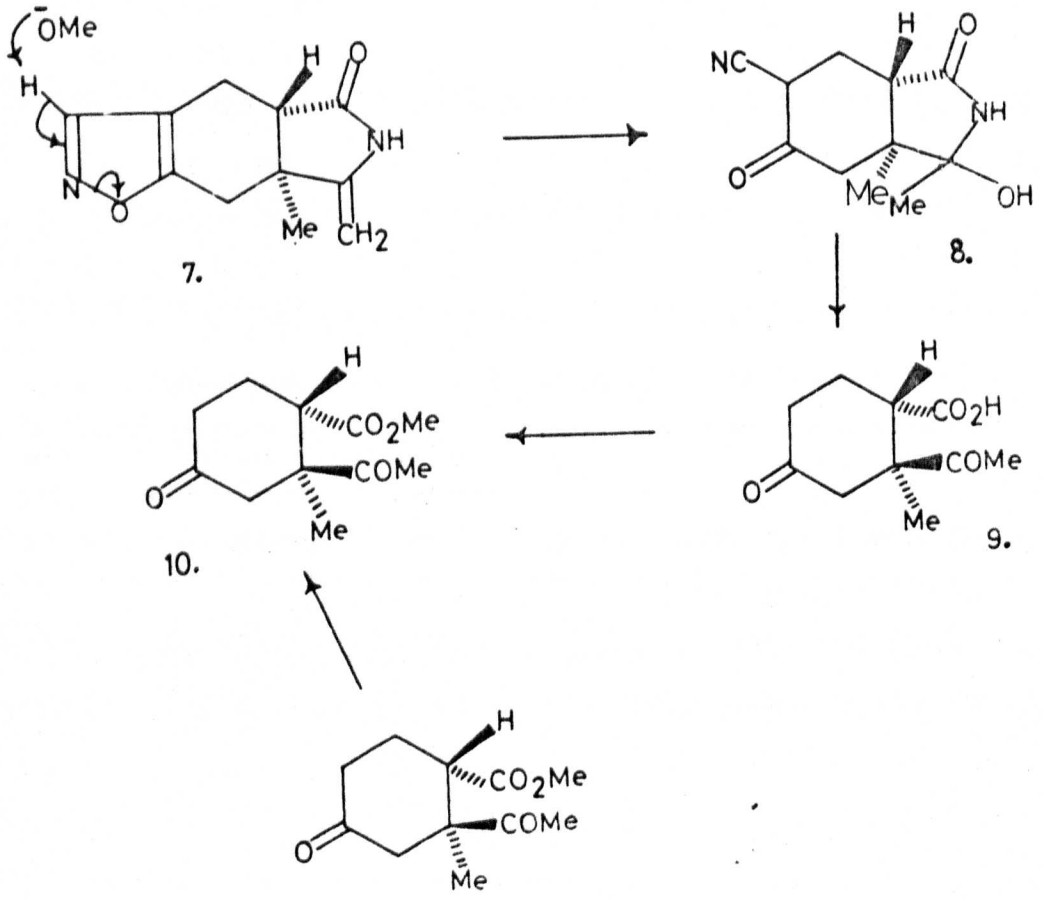
The sodium salt of (3a) (crystalline isomer) was treated similarly to give a product similar to (4a) [N.M.R. : τ = 5.80 (q, 7, 2H), 6.68 (q, 5 and 10, 1H), 7.79 (s, 3H), 8.72 (t, 7, 3H), 8.76 (s, 3H)] which was hydrolysed to give a crystalline acid [N.M.R. : τ = 6.5 (q), 7.75 (s, 3H), 8.76 (s, 3H); I.R. of N.M.R. sample : cm^{-1} = 2220^{m} (O-D), 2080^{m} (O-D), $1715 - 1690^{s}$ broad ($>C=O$)]. The I.R. of keto-acid (4b) after dissolution in tetra-deutero methanol was identical in every respect to this latter compound. This, along with the other evidence, leads to the conclusion that the two acids were the same compound (4b). Thus, either isomer of (3a) leads to the same keto-ester (4a) and acid (4b), proving that they are related as epimers at the nitro-ethyl group. Any ambiguity arising from epimerisation on the ring was removed by using only a slight excess of ethoxide to prepare the sodium salts of (3a).

Further confirmation of this stereochemistry was obtained by equilibrating the liquid diastereomer [N.M.R. : τ = 5.32 (q, 7, 1H $\underline{H}C(NO_2)Me$), 8.44 (d, 7, 3H $HC(NO_2)\underline{M}e$), 8.91 (s, 3H $>C\underline{H}_3$)] with trimethylamine in a sealed N.M.R. tube. After two weeks the N.M.R. [τ = 5.00 (q, 7, 0.5H), 5.28 (q, 7, 0.5H), 8.42, 8.49 (2d, 7, 3H), 8.83, 8.91

SCHEME II



SCHEME III



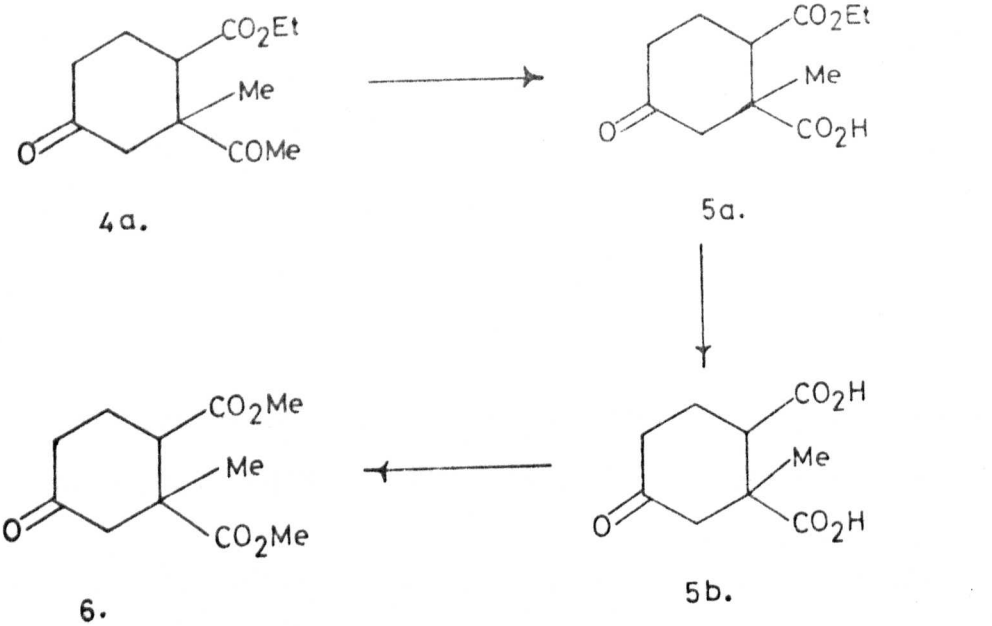
(2s, 3H)] showed a 50/50 mixture of the two epimers. These results do not explain why an unequal mixture of isomers was obtained in the preparation of (3a). This is to do with kinetic protonation of the nitro-anion to be discussed in chapter 3.

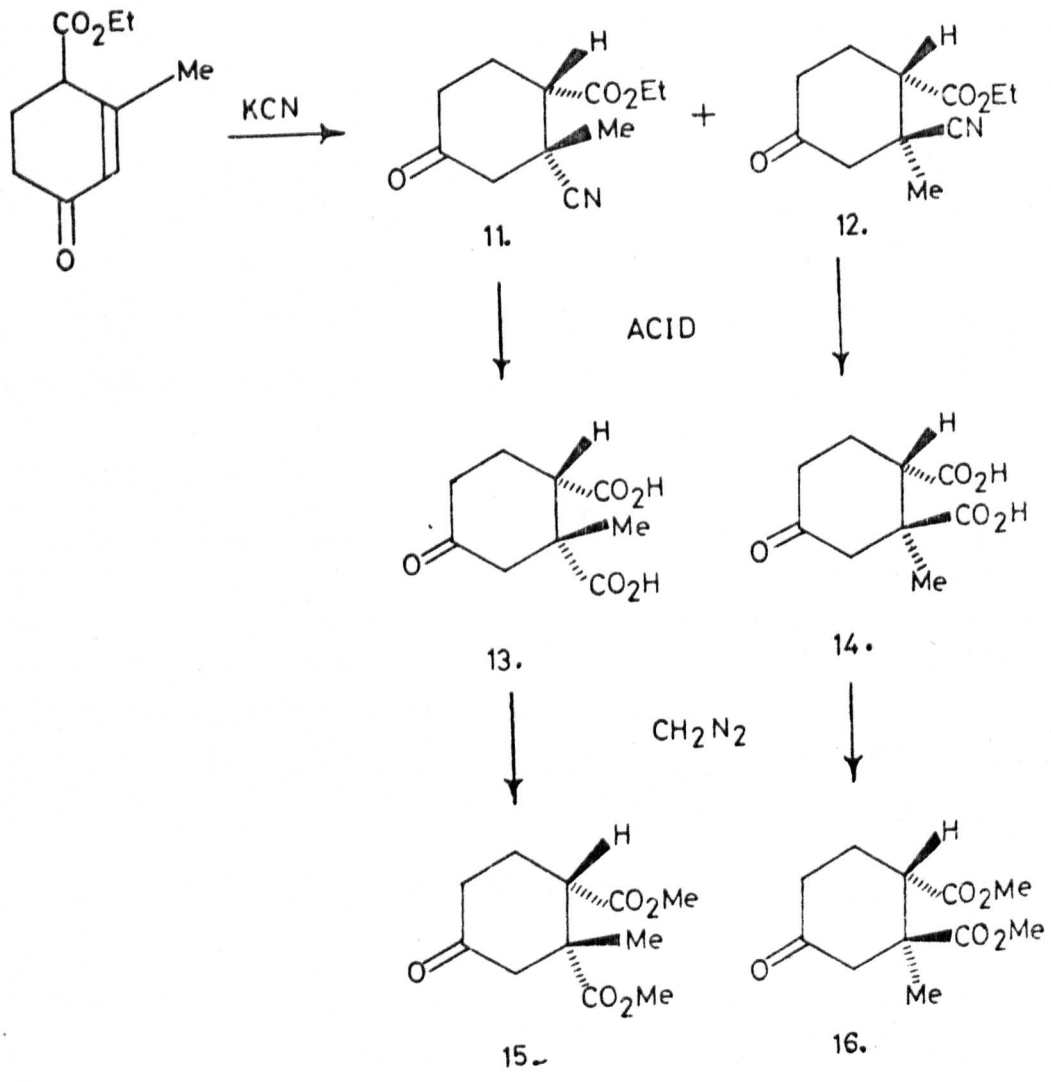
The Nef reaction on the acid (3b) (isomer obtained from alkaline hydrolysis) was tried by making the disodium salt using sodium hydride in dimethyl-formamide. Addition to 17N sulphuric acid at 0°C however, only gave recovery (92%) of the starting acid [N.M.R. (d^6 acetone) : τ = 4.78 (q, 7, 1H $\underline{H}C(NO_2)Me$), 8.45 (d, 7, 3H $HC(NO_2)\underline{Me}$), 8.82 (s, 3H $>\underline{Me}$)]. This failure of the Nef reaction is important to certain mechanistic arguments discussed in chapter 3. It also means that the acid must be esterified before it can be degraded to the ketone, a fact important in the determination of the absolute configuration of the resolved acids.

Strong evidence for the trans configuration of (4a) and (4b) comes from the fact that trans (4b) has been prepared in Eschenmoser's group[47] by a totally different route (see Scheme II). By this route its M.P. is 158°C, the I.R. (nujol) coincides exactly in intensity and position with that of (4b) and the N.M.R. (d^6 acetone) [τ = 6.42 - 6.77 (m, 1H), 7.77 (s, 3H), 8.76 (s, 3H)] is very similar to the N.M.R. (CD_3OD) of (4b).

Another way of relating (4b) to a compound of known configuration is shown in Scheme III. The enamide isoxazole (7) had been prepared[48] in earlier studies and a small sample was available. It is a well-known property[49] of 3-unsubstituted isoxazoles that they are cleaved to α-cyano-ketones by base (see 7). When (7) was treated with sodium methoxide in methanol, a compound [I.R. (nujol) : cm^{-1} = 2200^w (CN)] was obtained which was probably (8). The reaction was followed by the decrease in U.V. absorption at 224nm and the increase at 264nm. The former was probably due to hydration of the enamide chromophore, and therefore not indicative of ring cleavage, but the latter was probably due to the enolate anion of the product and so was a reaction monitor. (8) was not characterised any further but immediately subjected to prolonged acid hydrolysis. The acidic components were separated from the crude product, and methylated to give a crude residue

SCHEME IV


CO2Et
Me
COMe
O
4a.
CO2Et
Me
CO2H
O
5a.
CO2H
Me
CO2H
O
5b.
CO2Me
Me
CO2Me
O
6.


CO2Et
Me
O
KCN
H
CO2Et
Me
CN
O
11.
+
H
CO2Et
CN
Me
O
12.
ACID
H
CO2H
Me
CO2H
O
13.
H
CO2H
CO2H
Me
O
14.
CH2N2
H
CO2Me
Me
CO2Me
O
15.
H
CO2Me
CO2Me
Me
O
16.

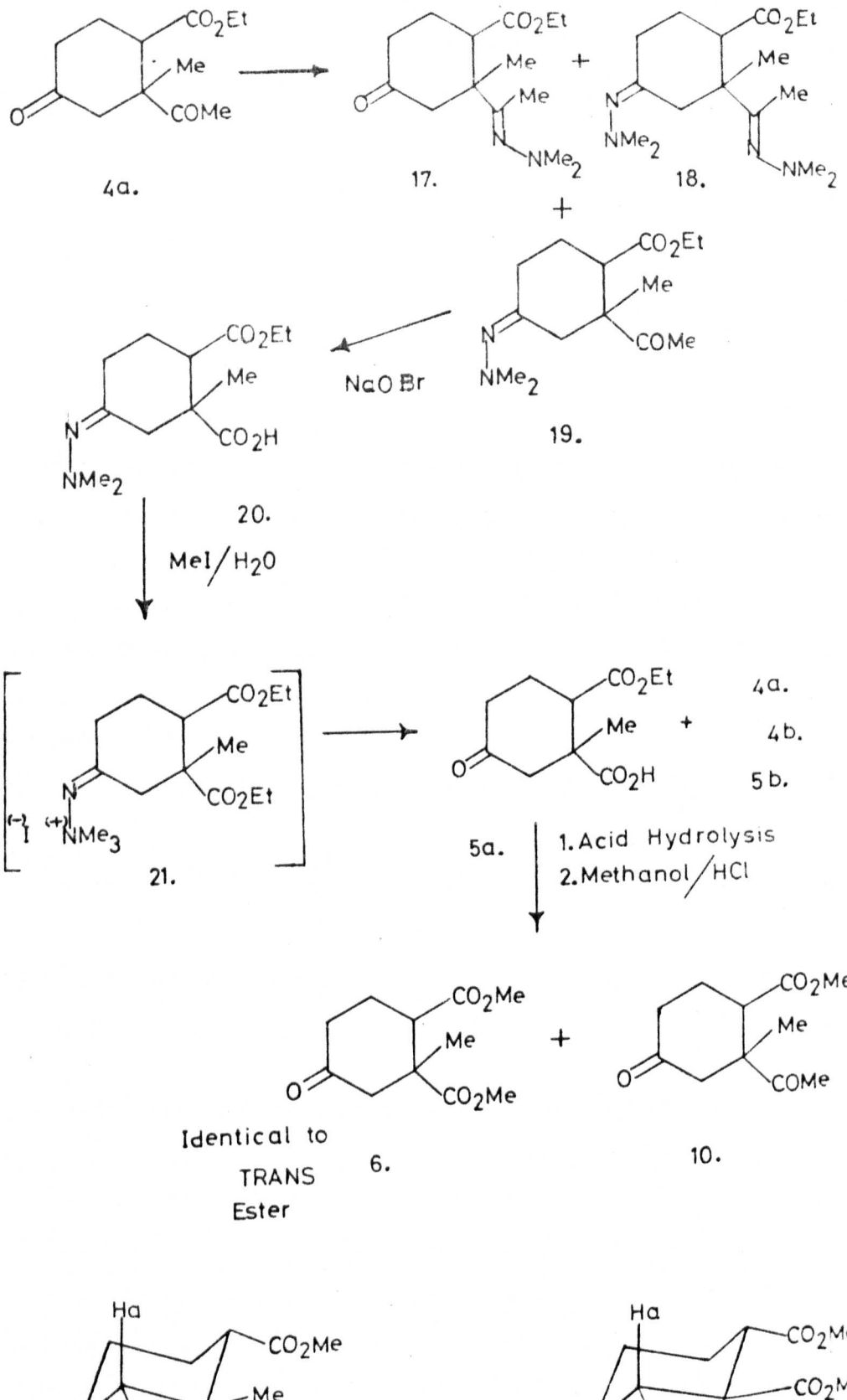
which had six components. A component (7 mg, 14%) with the same R_f as authentic (10) could be separated. The I.R., however, was not identical and at this stage the route was abandoned, firstly because of poor yields from a not readily available starting material, and secondly, in favour of a degradative method which could be used for the enantiomeric acids (3b).

The latter stages of the degradation, shown in Scheme IV, could be carried out by a combination of the alkaline hypohalite oxidation[50] to give (5a), followed by hydrolysis to (5b) and esterification to the dimethyl ester (6). Both the cis (15) and the trans (16) dimethyl esters are available[51] from Hagemann's ester by treatment with potassium cyanide followed by separation of the mixture of cyano-ketones (11) and (12). Hydrolysis of the latter compounds followed by esterification of the diacids (13) and (14) gives the required diesters. The trans-diacid (14) has been related[52] to a degradation product of ergosterol and therefore its configuration is certain. Comparison of the unknown (6) with (15) or (16) would thus show the relative cis or trans geometry of the starting nitro-ester (3a) (assuming an unambiguous degradation).

When the keto-ester (4a) or the keto-acid (4b) were treated with alkaline sodium hypobromite at $0^{o}C$ and the acidic products extracted, the mixture obtained was complex and this situation could not be improved upon. Presumably, bromination α- to the ring keto-group and ring opening are competing processes with bromination and cleavage of the hindered methyl ketone. This problem could be circumvented by protecting the ring keto-group in preference to the acetyl group.

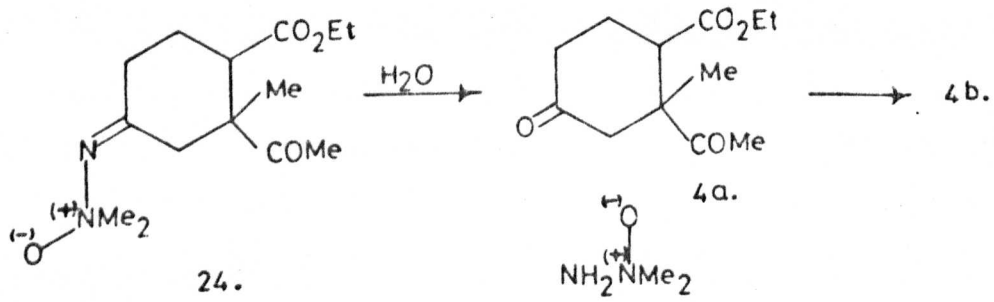
A protecting group that has recently been used[53] under alkaline conditions is the N,N-dimethyl hydrazone, prepared by the condensation of unsym-dimethyl hydrazine with a ketone. It was decided to try this in the hypobromite oxidation to compare its usefulness to the standard 1,3-dioxolane protecting group. On mixing the pure diketo-ester (4a) with a slight excess of unsym-

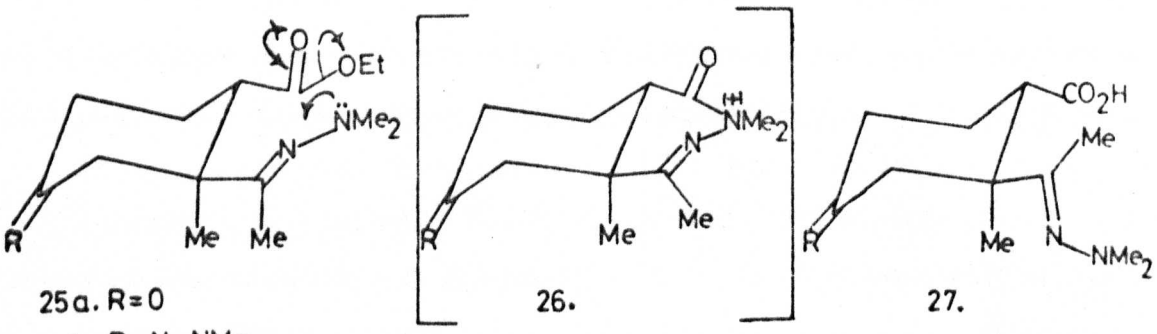
SCHEME V


CO2Et
Me
COMe
4a.
17.
18.
19.
20.
NaOBr
MeI/H2O
NMe2
CO2H
NMe3
21.
4a.
4b.
5b.
5a.
1. Acid Hydrolysis
2. Methanol/HCl
CO2Me
6.
10.
Identical to TRANS Ester
Ha
Hb
22.
23.

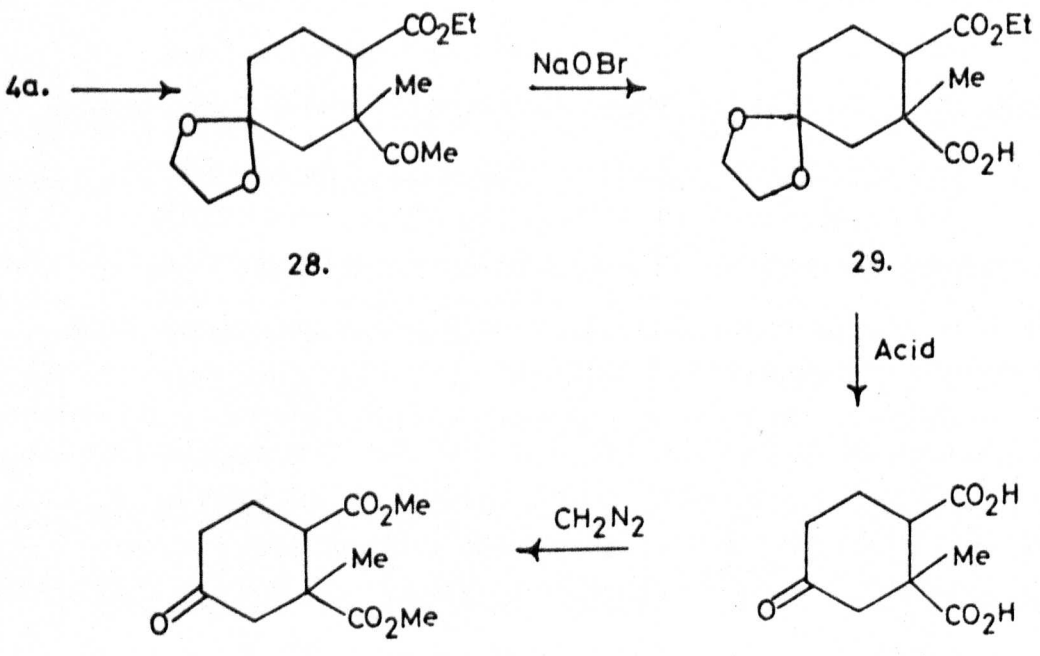
dimethyl hydrazine, an exothermic reaction took place and water was precipitated. The excess hydrazine and water were removed to give an oil (103%). This contained two components, neither of which was starting material. One component was very polar and the other had a slightly smaller R_f than the starting ester. The N.M.R. spectrum showed an ethyl group 5.83 τ (q) and 8.76 τ (t) with another ethyl group 5.81 τ (q) and 8.75 τ (t) superimposed, the latter representing about 20% of the mixture. Also present were a singlet at 7.61 τ ($N(CH_3)_2$) and a pair of singlets at 7.63 τ, approximately 1 c.p.s. apart, which could have been due to the two methyl groups of $-N(CH_3)_2$ in a restricting environment. The singlets at 7.78 τ and 8.82 τ could have been the acetyl and tertiary methyl groups respectively. The multiplet at 6.7 - 7.0 τ ($CH_2\underline{C}HCO_2Et$) was more complex than the corresponding signal in (4a) indicating more than one component. In the I.R. the absorptions at 2784^s and 2830^s cm^{-1} indicated $N-CH_3$ groups, those at 1730^s and 1710^s cm^{-1} (equal intensity) the ester and ketone groups, and at 1645^m cm^{-1} the $-C=N-$ grouping. The above evidence pointed to some non-selective hydrazone formation, possibly with 80% of the mono-form (19) and 20% of the di-(18) and the alternate mono-form (17). Some attempt was made to separate the components by chromatography but hydrolysis was a competing side reaction.

The mixture of hydrazones was treated with 3 moles of alkaline hypobromite. After neutralising, the mixture was refluxed with excess of methyl iodide to decompose any hydrazone, e.g., via (21). The neutral product (25%) was mainly diketo-ester (4a). The acidic product (53%) contained three components, the total material recovered being 78%. Acidic hydrolysis of the acid fraction followed by methylation gave a residue (20%) which consisted of two components in approximately equal proportion. Preparative T.L.C. gave one component (43%) with the same R_f and I.R. as the methyl ester (10). The other component (57%) had the same R_f as the authentic cis (15) and trans (16) dimethyl esters (which have the same R_f). Its N.M.R. [τ = 6.33, 6.35 (2s, 6H $-2CO_2Me$), 6.80 (q, 5 and 9, 1H $-CH_2\underline{C}HCO_2Me$), 7.2 - 8.0 (m, 6H alicyclic H), 8.81 (s, 3H)]


CO2Et
Me
COMe
N
(+)NMe2
(-)O
H2O
O
NH2(+)NMe2
4b.
4a.
24.


OEt
NMe2
R
Me
Me
25a. R=O
b. R= N—NMe2
26.
CO2H
27.

SCHEME VI


4a.
CO2Et
Me
COMe
NaOBr
28.
29.
Acid
CO2Me
CH2N2
CO2H
6.
5b.

was identical to that of the trans diester (16) [τ = 6.33, 6.35 (2s, 6H, $2CO_2\underline{Me}$), 6.8 (q, 5 and 9, 1H, $-CH_2\underline{C}HCO_2Me$), 7.2 - 8.0 (m, 6H alicyclic H), 8.81 (s, 3H $\rightarrow\underline{Me}$)] and substantially different from that of the cis diester (15) [τ = 6.34, 6.38 (2s, 6H, $2CO_2\underline{Me}$), 6.94 - 7.17 (m, 2H, $-CH_2\underline{C}HCO_2Me$ + geminal H), 7.63 - 7.8 (m, 5H alicyclic H), 8.79 (s, 3H $\rightarrow\underline{Me}$)]. Interestingly, the multiplet between 6.94 and 7.17 τ of the cis-compound represents two protons whereas in the trans-compound there is only one proton signal in this region. In this multiplet there is one large coupling constant (12 c.p.s.), probably due to a geminal proton (Ha or Hb) (see 22) shifted downfield with respect to the same proton of (23) by the axial carbomethoxy group. Added proof of the identity of (6) and the authentic trans-compound (16) came from the I.R. spectra. Those of (6) and (16) were almost identical and were substantially different from that of cis-compound (15). (See plates III, IV and V for photographic evidence).

Several features of the degradation need to be amplified.

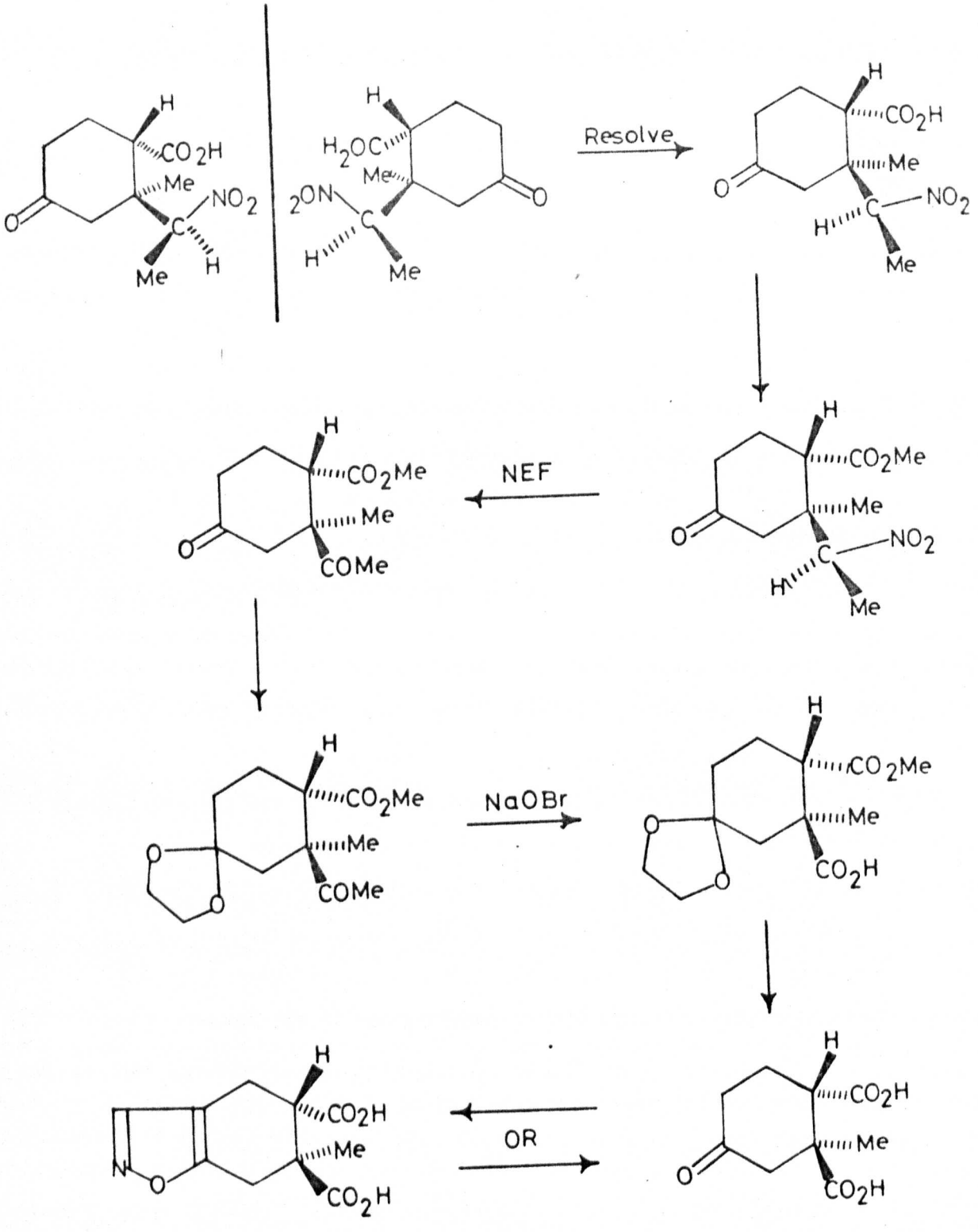
(a) The recovery of 25% of the keto-ester (4a).

(b) The three acidic components from the hypobromite reaction.

(c) The approximately equal amounts of (10) and (6).

Firstly, although the N,N-dimethyl hydrazone destabilises an α-carbanion with respect to the enolate anion, thus preventing bromination, it is open to oxidation at the nitrogen bearing the two methyl groups (see 24). The N-oxide can now easily hydrolyse (cf. the quaternary iodide) to give the keto-ester (4a) which, in turn, could be partially hydrolysed by the excess alkali to (4b). In this way not only is oxidant consumed, thus upsetting the stoicheiometry of the hypobromite reaction, but unprotected ketone is produced. Secondly, the two hydrazones (25a) and (25b) could easily hydrolyse via (26) to (27) which would give the keto-acid (4b) after decomposition of the hydrazones. This, along with direct alkaline hydrolysis, would account for one of the three acidic products, and the appearance of (10) in the final product. The other two acidic components would be the half ester (5a) and the diacid (5b) formed from the hypobromite oxidation and hydrolysis of (5a).

SCHEME VII



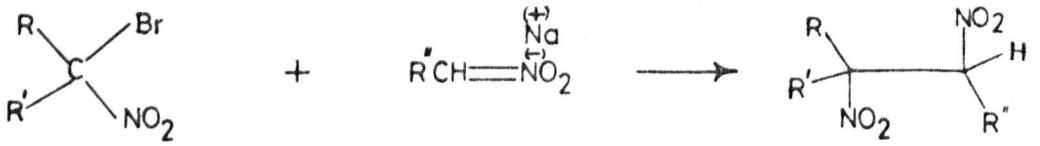
Although the required degradation had been achieved, the yield of trans-dimethyl ester was only 12% and in an attempt to improve upon this situation, the ethylene ketal (28) was prepared. Refluxing the keto-ester (4a) with excess ethylene glycol and a trace of para-toluene sulphonic acid, gave a semi-crystalline solid on purification (90 - 95%). This was identified as (28) [N.M.R. : τ = 5.93 (q, 7, 2H $-OCH_2CH_3$), 6.12 (s, 4H $-OCH_2CH_2O-$), 6.98 (q, 4 and 7, 1H $-CH_2\underline{C}H\underline{C}O_2Et$), 7.91 (s, 3H $-COCH_3$), 8.79 (t, 7, 3H $-OCH_2\underline{C}H_3$), 8.83 (s, 3H >—Me); I.R. : cm^{-1} = 1730^s (CO_2Et), 1710^s ($-COCH_3$); M.S. : m/e = 270 (5)m, 99 (100) $C_5H_7O_2^+$, 86 (85) $C_4H_6O_2^+$, 43 (20) CH_3CO^+]. All the data showed it to be a single compound. This selectivity is markedly different from hydrazone formation, probably because the tetrahedral ketal is a more bulky protecting group than the trigonal hydrazone.

The purified ketal (28) was treated with alkaline hypobromite at room temperature to give a crystalline solid (61%) [N.M.R. : τ = 5.84 (q, 7, 2H $-OCH_2\underline{C}H_3$), 6.03 (s, 4H $-OCH_2CH_2O-$), 8.70 (s, 3H >—Me), 8.76 (t, 7, 3H $-OCH_2CH_3$); I.R. : cm^{-1} = $3300 - 2300^m$ (CO_2H), 1730^s (CO_2Et), 1705^s (CO_2H)] identified as (29). Acidic hydrolysis gave diacid (5b) [N.M.R. : τ = 0.7 (2H, CO_2H), 6.67 (q, 5 and 9 $-CH_2\underline{C}H\underline{C}O_2H$), 8.72 (s, 3H >—Me)] identical to authentic material. Treatment with excess ethereal diazomethane gave a residue which was essentially one component. The R_f and N.M.R. [τ = 6.31, 6.33 (2s, 6H $-CO_2Me$), 6.78 (q, 6 and 9, 1H $-CH_2\underline{C}H\underline{C}O_2Me$), 8.78 (s, 3H >—Me)] showed it to be the trans-ester (16). The overall yield from the ketal was 40% and from the starting nitro-ester (3a), 25%.

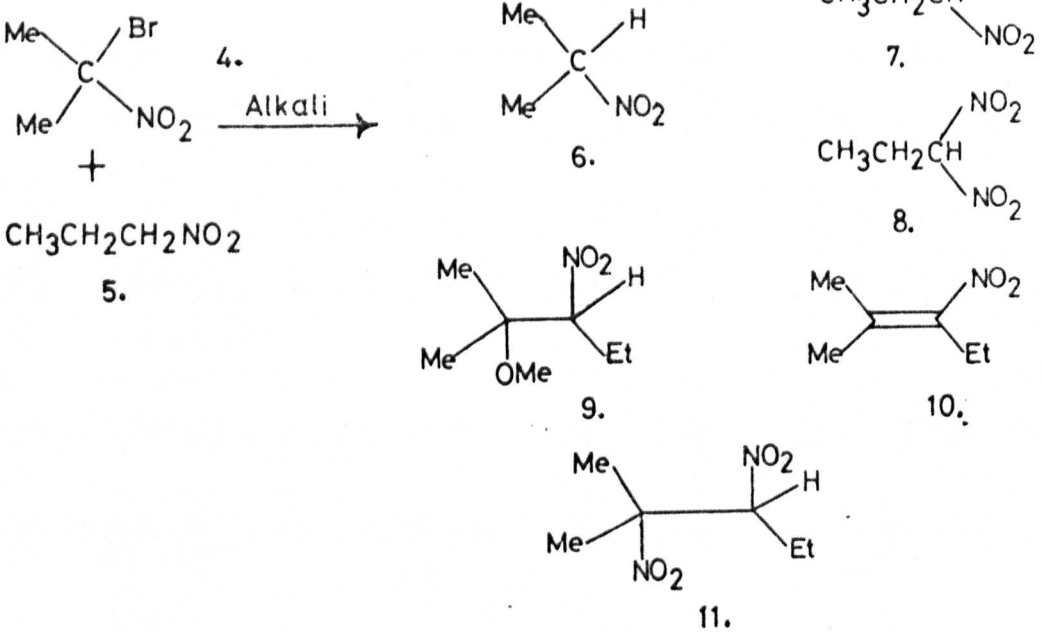
This yield is now good enough to ensure the success of Scheme VII in the determination of the absolute stereochemistry of the enantiomers of the acid (3b). The acids can be converted in high yield to the methyl esters and so the scheme is shown for the methyl ester with the configuration of vitamin B_{12}. The correlation of the enantiomer (5b) with the enantiomer (30) of known[54] absolute configuration, finally proves the configuration of the acids. This correlation could be carried out by treating the isoxazole with base, followed by hydrolysis of the α-cyano ketone or by converting (5b)

into the isoxazole by a known[55] method. It has been assumed that the degradation is unambiguous. There are only two possible reactions where the geometry at the ring could be altered; in the Nef reaction and the alkaline hypobromite reaction. This is eliminated in the Nef reaction by using an equivalent of base to make the salt. In the hypobromite reaction, a mole of base is required for the reaction which is so fast as to preclude any racemisation. The isolation of pure trans-ester (16) from this degradation using T.L.C. by which the cis and trans-esters are inseparable, shows that epimerisation at the ring does not occur. It is thus fairly certain that no racemisation of the enantiomers could occur in Scheme VII.

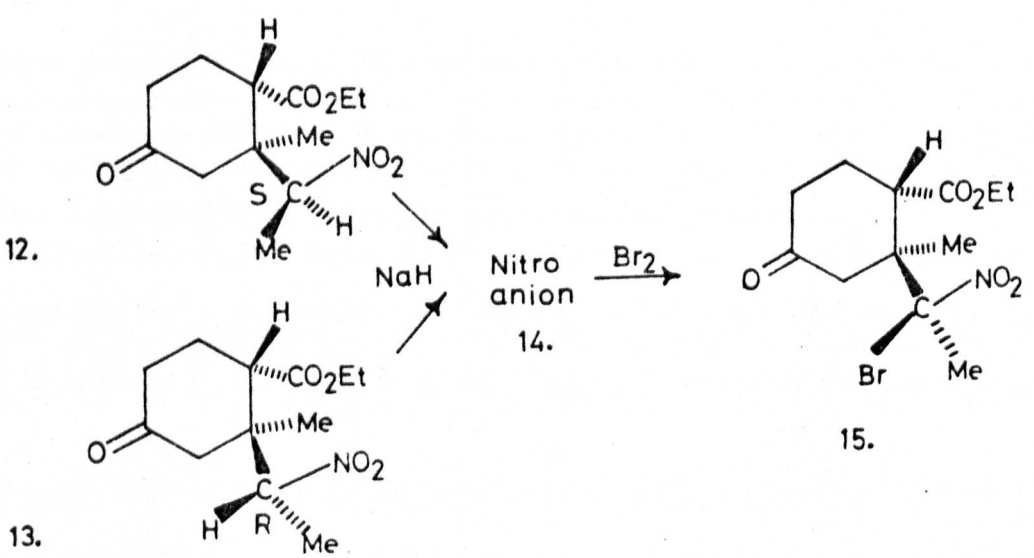
SCHEME I



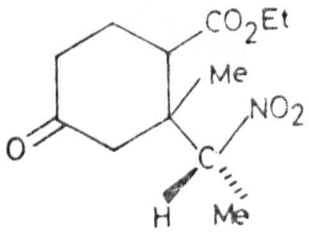
1. 2. 3.



4. 5. 6. 7. 8. 9. 10. 11.

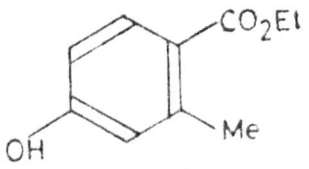


12. 13. 14. 15.



13.

1. Alkali
2. Br_2



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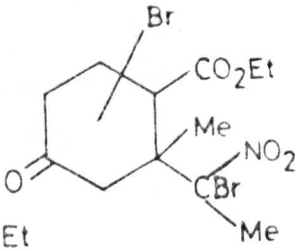

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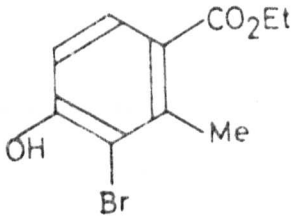

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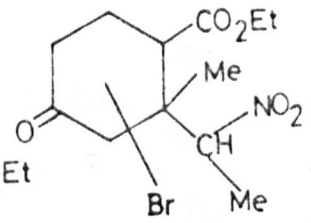

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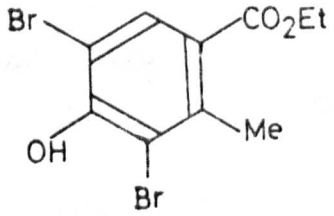

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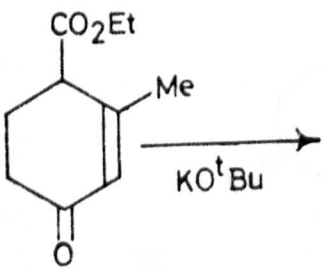

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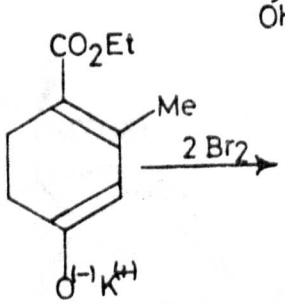

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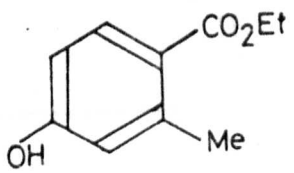

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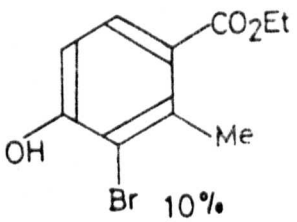

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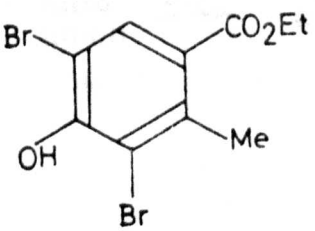

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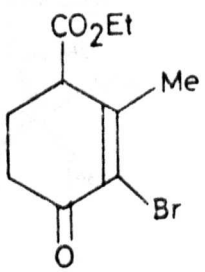
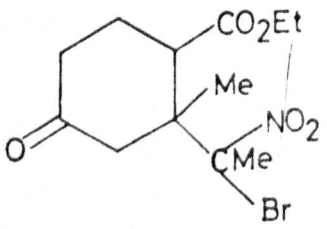


23. 9%

CHAPTER 3

In the key step, joining ring A and ring D of vitamin B_{12}, the coupling of a secondary bromo-nitro compound (1) with a primary nitro-anion (2) to give a dinitro-compound (3) could possibly be used. Preliminary experiments[56] using a variety of conditions and model compounds, showed that this was, in practice, a complex reaction. In one of the more promising cases, for example, treatment of a mixture of 2-bromo-2-nitropropane (4) and 1-nitropropane in 85% methanol/water with two equivalents of sodium hydroxide gave the following mixture. Compounds (6), (7) and (8), which are the products of bromine and nitro group exchange, were formed in about 30%. The products of the desired unsymmetrical coupling (9) and (10) were formed in about 40% along with the symmetrical coupled product (11) in about 10%. It was decided to use these conditions in a trial reaction with ring A precursor (15) which would function as (1) in Scheme I.

Treatment of the nitro-anion (14), derived from either of the epimers (12) or (13) (relative configuration shown is assumed) by reaction with a mole of sodium hydride in dimethyl formamide, with a slight excess of bromine, gave the bromo-nitro compound (15) [N.M.R. : τ = 5.86 (q, 7, 2H $-OCH_2CH_3$), 7.0 (m, 1H $-CH_2CHCO_2Et$), 7.72 (s, 3H $BrC(NO_2)Me$), 8.57 (s, 3H $>CMe$), 8.70 (t, 7, 3H $-OCH_2CH_3$); I.R. : cm^{-1} = 1723^s ($>C=O + CO_2Et$), 1555^s ($Br-C(NO_2)$); M.S. : m/e = 337, 335 (0.1)m, 291, 289 (10)m $-NO_2$]. This was identified as a single diastereomer by its sharp melting point and its simple N.M.R. spectrum. There was, however, a complication with this reaction. Attempts to prepare large quantities of (15) from the liquid isomer (13) by the above method led to a complex product mixture of which only a small proportion was the desired compound. Isolation[57] of some of the components of this mixture showed them to be the phenols (16), (17) and (18). These could be derived from Hagemann's ester (formed by the reverse Michael reaction already described in chapter 1) by oxidation and bromination. That this was indeed possible was shown by treatment[57] of the enolate (22)

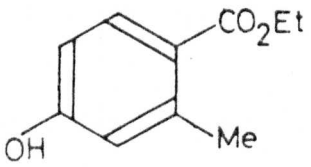


15. +

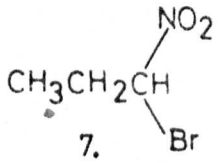
$CH_3CH_2CH_2NO_2$

5.

NaOH / MeOH



16.



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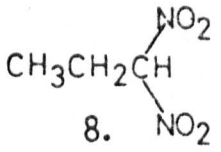
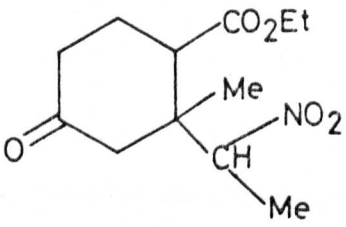


8.



12. + 13.

Mechanism

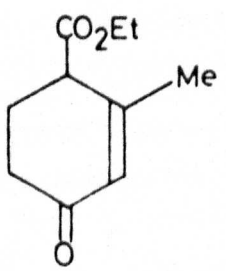
Reverse Michael

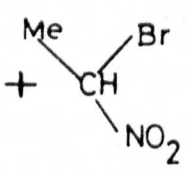
$Br^{(+)}$ Extraction by nitro-anion or NaOH

12. + 13. and 7.

NO_2^+ Extraction

8.





24.

Oxidation

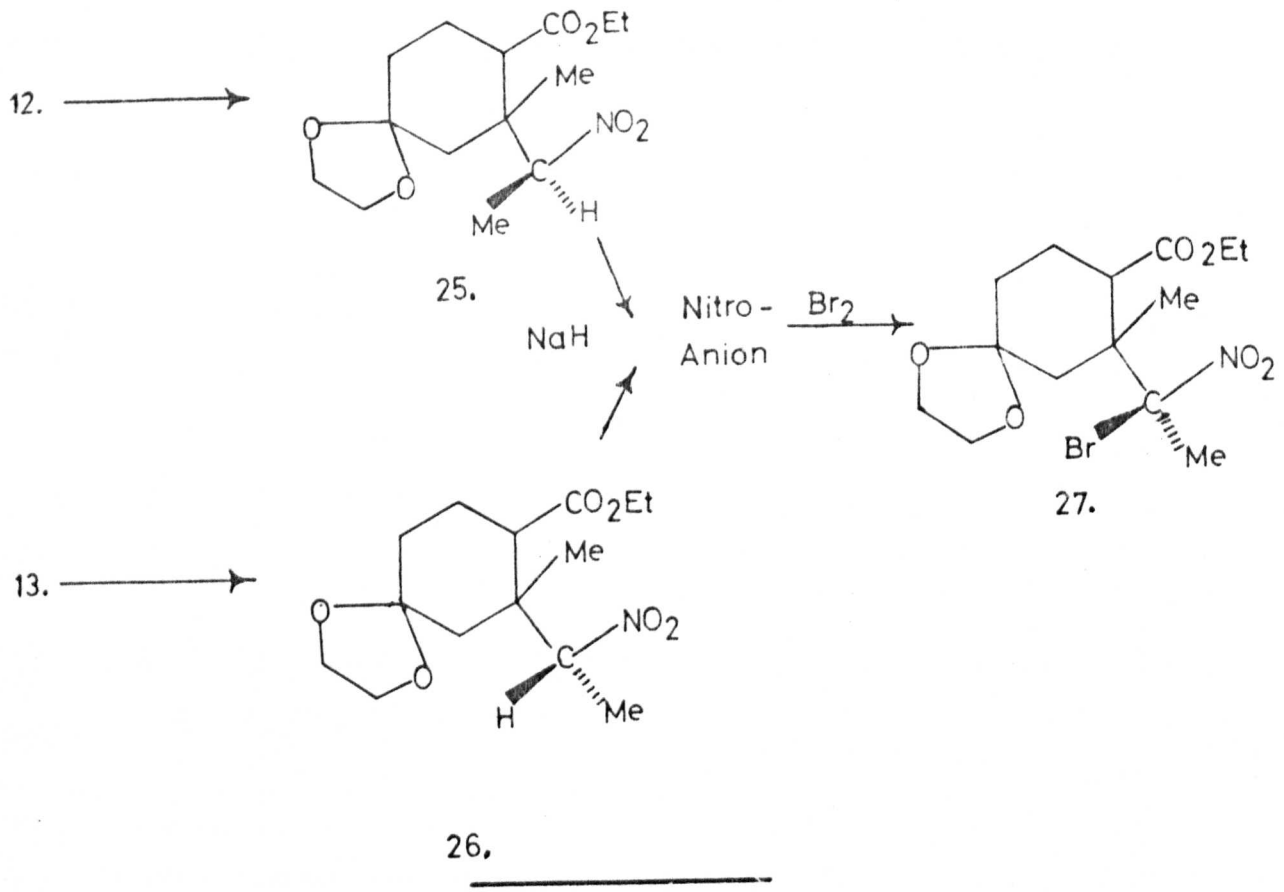
16.

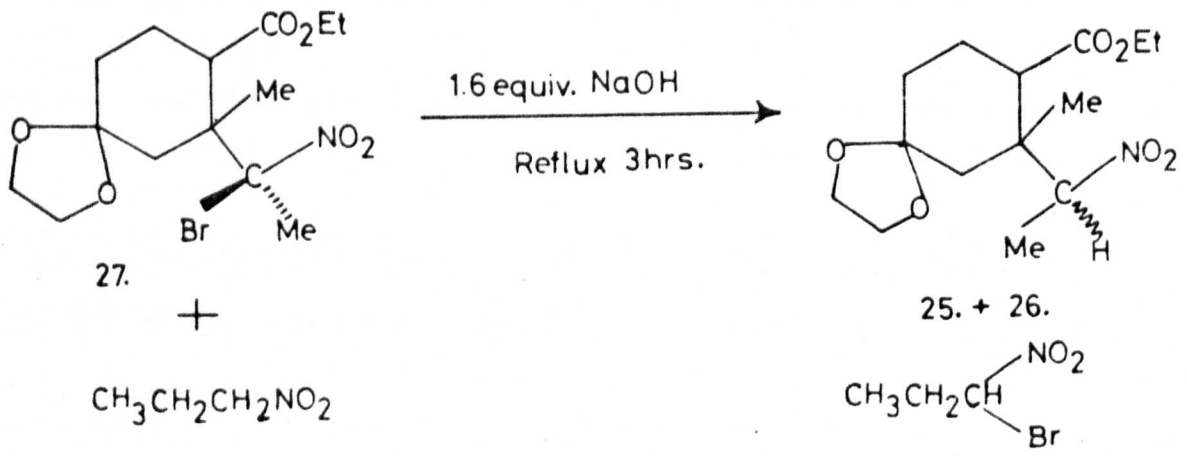
HOBr + $CH_3CH_2NO_2$

of Hagemann's ester (21) with 2 equivalents of bromine. The phenols (16), (17) and (18) were isolated in the yields shown, along with the non-aromatic bromo-compound (23). In the bromination of the anion from (15), two non-aromatic components formulated as (19) and (20) were also obtained. (19) is definitely a dibromo-compound as shown by its mass spectrum but the position of the second bromine atom is not certain. (20) is definitely a secondary nitro-compound as shown by the methine proton in the N.M.R. and the presence of bromine is shown by the mass spectrum but its position is not certain.

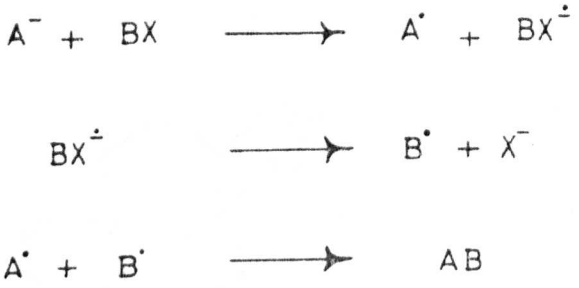
The above results are important to the analysis of the products obtained from the first coupling reaction. Ring A precursor (15) was stirred[57] with 1-nitropropane and 2 equivalents of sodium hydroxide in 85% methanol/water for 8 hours at room temperature with the exclusion of oxygen. The product mixture consisted mainly of the phenol (16), the nitro-compound as a mixture of isomers (12) and (13), and the products of bromine and nitro-group exchanges (7) and (8). Nothing identifiable as coupled products was obtained. The phenol (16) is probably derived by oxidation of Hagemann's ester with hypobromous acid. This could be formed by bromine extraction from 1-bromo-1-nitroethane (24) eliminated in the reverse Michael reaction. 1-Bromo-1-nitropropane can be formed by direct bromine extraction from (15) or by oxidation of the 1-nitropropyl anion with hypobromite. The mixture of isomeric nitro-compounds (12) and (13) is obtained in the bromine extraction process.

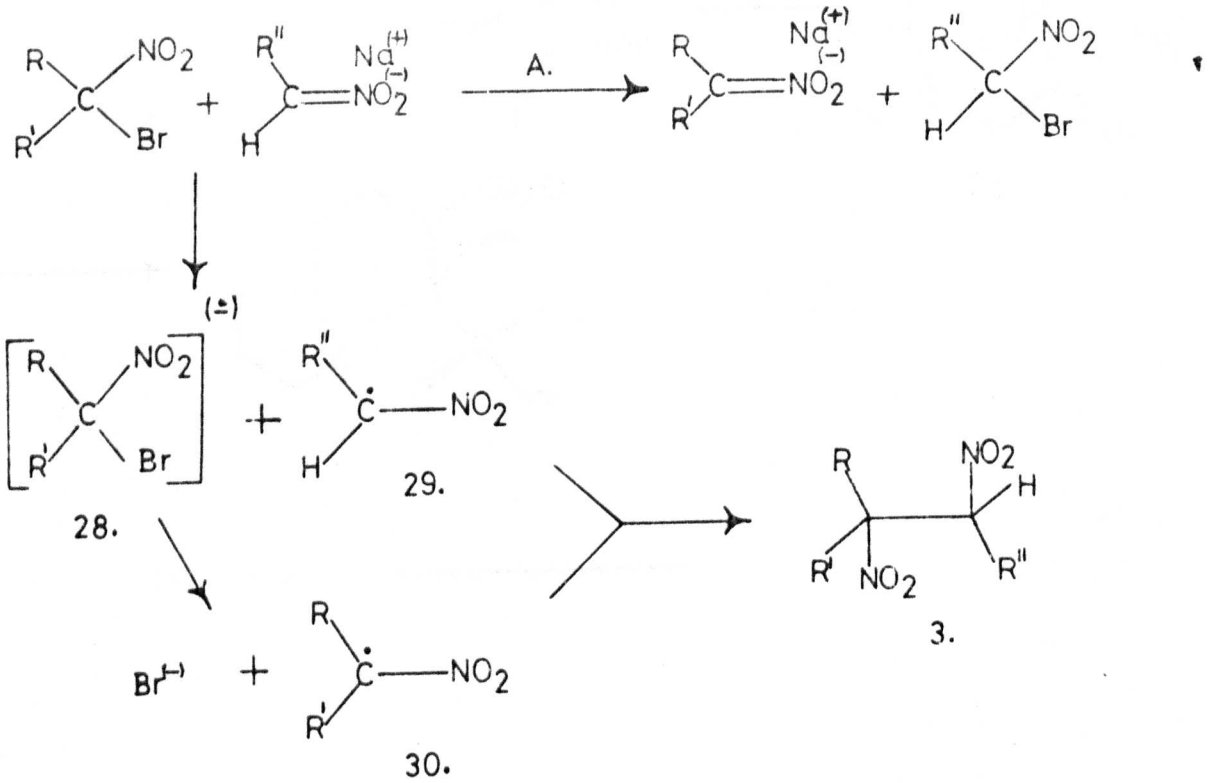
The reverse Michael reaction could be suppressed by using the bromo-ketal (27) in place of the bromo-ketone (15). This ketal was prepared by first converting the isomeric nitro-compounds (12) and (13) into their ethylene ketal derivatives. The ketals (25) [N.M.R. : τ = 5.10 (q, 7, 1H $\underline{H}$-$\overset{|}{C}(NO_2)Me$), 5.91 (q, 7, 2H $-OC\underline{H}_2CH_3$), 6.13 (s, 4H $-OCH_2CH_2O-$), 7.73 (m, 1H $(CH_2\overset{|}{C}\underline{H}CO_2Et)$, 8.55 (d, 7, 3H $H-\overset{|}{C}(NO_2)\underline{Me}$), 8.70 (t, 7, 3H $-OCH_2C\underline{H}_3$), 8.80 (s, 3H $\rangle\!\!-\underline{Me}$)] and (26) [N.M.R. : τ = 5.07 (q, 7, 1H $\underline{H}$-$\overset{|}{C}(NO_2)Me$), 5.87 (q, 7, 2H $-OC\underline{H}_2CH_3$), 6.13 (s, 4H $-OCH_2CH_2O-$), 7.65 (m, 1H $-CH_2\overset{|}{C}\underline{H}CO_2Et$), 8.48 (d, 7, 3H $H-\overset{|}{C}(NO_2)\underline{Me}$), 8.75 (t, 7, 3H $-OCH_2C\underline{H}_3$),


12.
CO2Et
Me
NO2
C
H
Me
25.
NaH
Nitro-
Anion
Br2
CO2Et
Me
NO2
Br
C
Me
27.
13.
CO2Et
Me
NO2
C
H
Me
26.

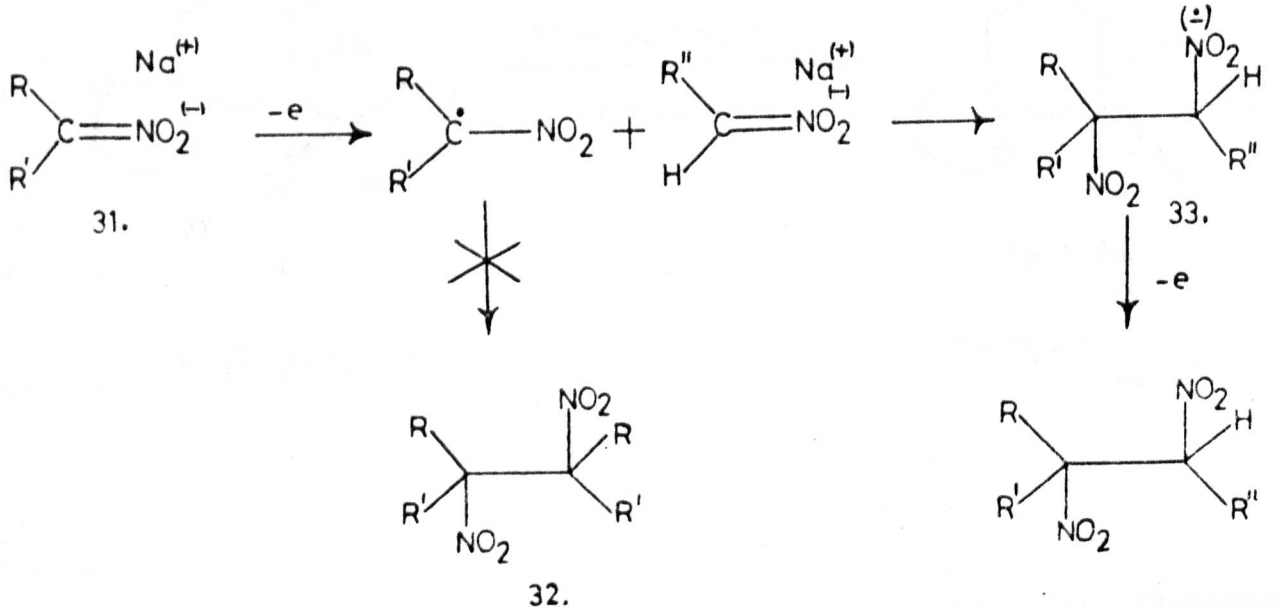

CO2Et
Me
NO2
Br
C
Me
27.
+
CH3CH2CH2NO2
1.6 equiv. NaOH
Reflux 3hrs.
CO2Et
Me
NO2
C
Me
H
25. + 26.
NO2
CH3CH2CH
Br

SCHEME II





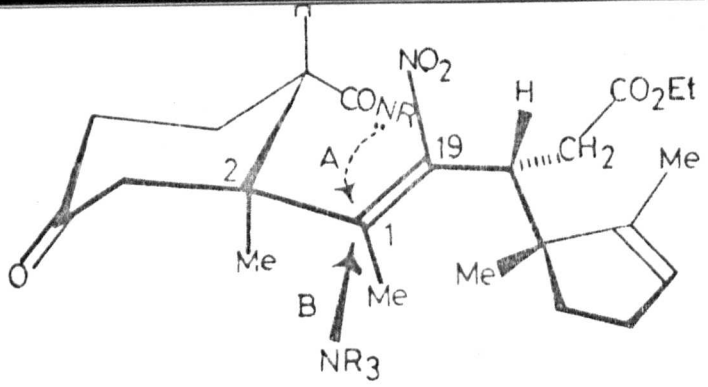
SCHEME III



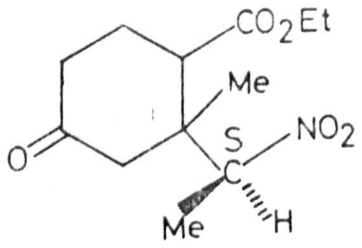
8.91 (s, 3H $\rangle$—Me)] were converted without further characterisation into their anions with potassium t-butoxide. Treatment with a slight excess of bromine gave (27) [N.M.R. : τ = 5.91 (q, 7, 2H $-OCH_2CH_3$), 6.13 (s, 4H $-OCH_2CH_2O-$), 7.42 (m, 1H $-CH_2CHCO_2Et$), 7.66 (s, 3H $BrC(NO_2)Me$), 8.43 (s, 3H $\rangle$—Me), 8.73 (t, 7, 3H $-OCH_2CH_3$); I.R. : cm^{-1} = 1740-20^s (broad $\rangle$=O + CO_2Et), 1550^s ($BrCNO_2$); M.S. : m/e = 335, 333 (2)m $-NO_2$, 99 (100) $C_5H_7O_2^{+\cdot}$, 86 (90) $C_4H_6O_2^{+\cdot}$] which was identical when formed from either source.

When the bromo-nitro-compound (27) was stirred with 1-nitropropane (1 equivalent) and sodium hydroxide (1.6 equivalents) in 80% methanol/water for 8 hours at room temperature, only a small amount of bromine exchange took place and pure starting material was isolated. If this experiment was repeated at reflux for 3 hours, only the two isomeric ketals (25) and (26) were obtained along with 1-bromo-nitropropane. No coupled products could be isolated. It thus seems that this reaction is not useful for coupling, having the inherent drawback that bromine exchange is much faster than radical formation. Scheme II shows one proposal[26] for the mechanistic sequence. Reaction A represents the bromine transfer reaction which, in the case just considered, must be appreciably faster than transfer of an electron from the primary nitro-anion (2) to an anti-bonding orbital of the bromo-nitro-compound (1) to give a radical anion (28) and a radical (29). (28) can extrude a bromine anion to give the neutral radical (30) which then couples with (29) to give the dinitro-compound (3). Modifications of (3) then give the observed products.

Recently, however, Norman has obtained E.S.R. evidence[58] for the preferential reaction of the radical (30), formed from the nitro-anion (31) with a 1-electron oxidant, and the nitro-anion (2) to give the anion radical (33), rather than coupling of two radicals (30) to give (32). This may also be the mechanism of persulphate oxidation of nitro-anions[59] and the bromo-nitro coupling. The E.S.R. evidence must not, however, be taken too seriously as a preparative pointer as the signal may come from a minute amount of anion-radical formed in a side reaction. Another method for generating radicals from anions is by electrolysis and this has been applied successfully to couple[60] two secondary nitro-anions. Future work on the A,D coupling

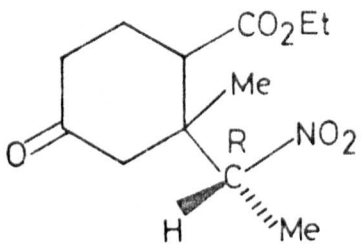


34.

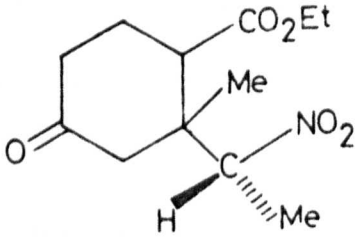


100% S

90%

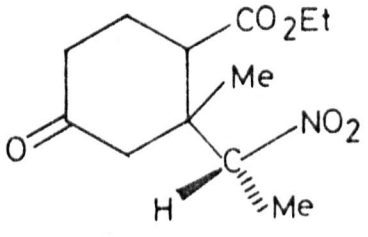


95% R

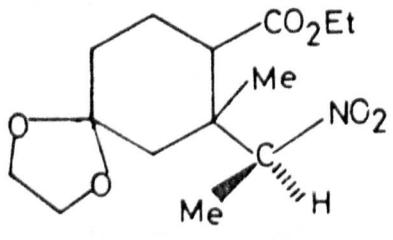


90% R

90%

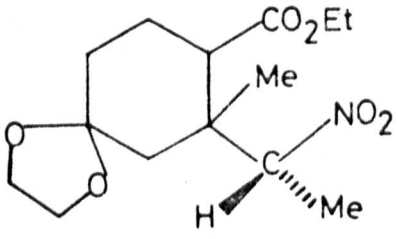


95% R

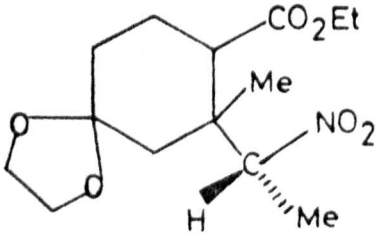


100% S

70%

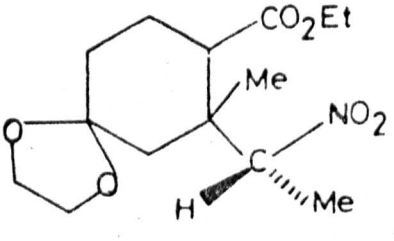


60% R



90% R

90%



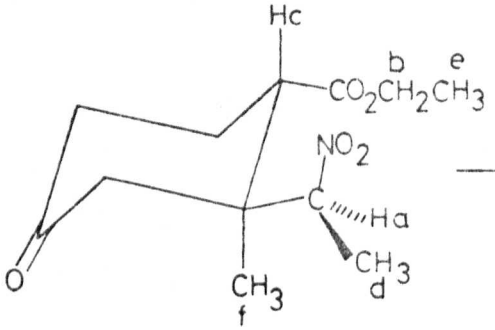
95% R

reaction will pursue these two above possibilities with the intention of obtaining a good yield by generating, first the secondary nitro-radical and then exposing this to a high concentration of primary nitro-anions.

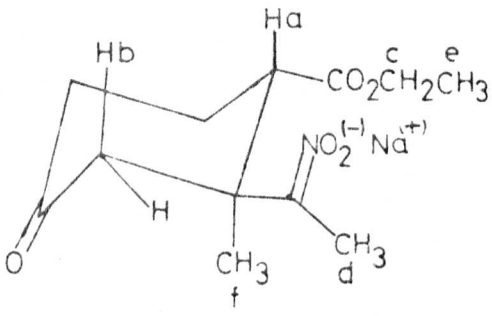
Epimerisation Reactions

The fact that the two isomeric nitro-compounds (12) and (13) give a single bromo-isomer (15), as do the isomeric ketals (25) and (26) give only (27), leads to the conclusion that bromination is kinetically controlled. This implies that the same nitro-anion is obtained from both isomers, and that the anion is fixed in a rigid conformation, allowing attack by bromine from one side only. Earlier studies had shown that the nitro-olefin (34) might be a major product (cf. 10) in the final coupling reaction, presenting the problems of developing the correct position 1 stereochemistry and at the same time introducing nitrogen functionality. The nitro-olefin could react with nucleophiles at position 1 as shown in (34). This process is somewhat similar, as regards conformational preference and steric regulation to the direction of approach of reagent, to the reaction of the nitro-anion (14) with electrophiles (e.g. bromine). The fact that bromination was stereo-specific thus suggested that selective development of (34) would be possible. Intuitively, the conformation shown would be the most stable, and in this case the nitrogen atom must attack from the most hindered side to give the correct stereochemistry. A suitable group in the 3 position (e.g. an amide) is ideally placed to achieve this by intramolecular attack, making the situation very flexible. Even though the bromo-nitro coupling had failed, the nitro-olefin is a likely product from a number of other coupling processes. It was thus decided to study in some detail the specificity of acid quenching of a number of nitro-anions.

There is the danger of a Nef reaction inherent in this quenching process but according to Kornblum,[61] if the acid is dilute and mixing is rapid, good yields of nitro-compounds can be obtained. In the following description, a relative stereochemistry of isomers is assumed to show clearly when inversion or retention takes place. The nitro-anions were prepared by treatment with sodium hydride in dimethyl formamide and quenched by rapidly

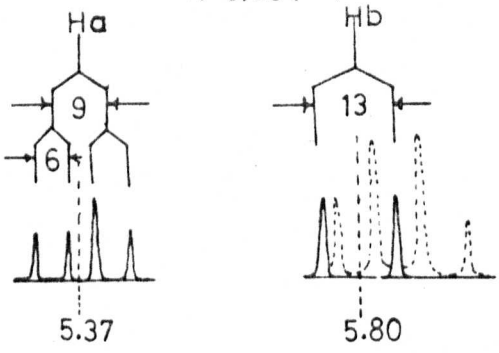


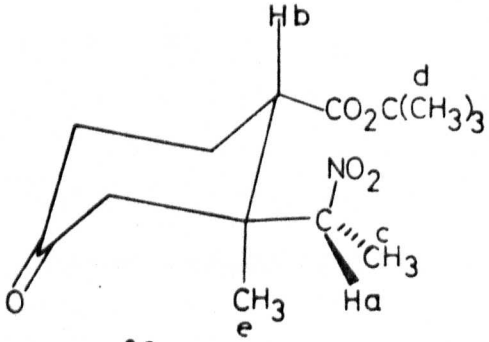
35.



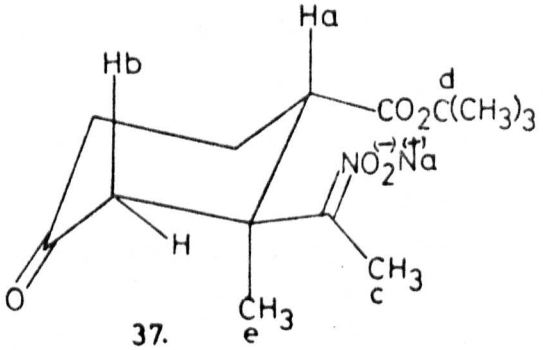
τ = a. 5.02(q,7)
b. 5.81(q,7)
c. 7.13(q)
d. 8.52(d,7)
e. 8.76(t,7)
f. 8.92(s)

τ = c. 5.81(q,7)
d. 8.11 (s)
e. 8.80(t,7)
f. 8.93(s)





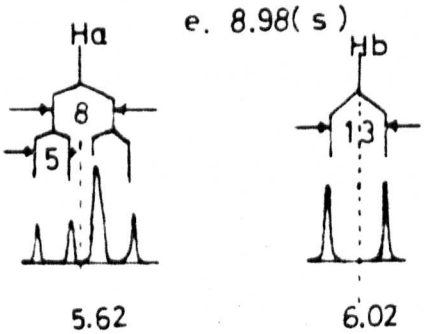
36.



37.

τ = a. 5.25(q,7)
b. 7.09(q)
c. 8.43(d,7)
d. 8.54(s)
e. 9.00(s)

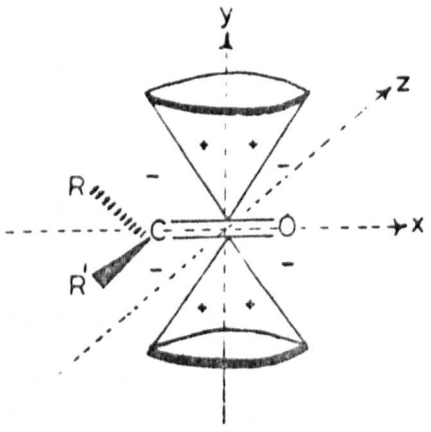
τ = c. 8.18 (s)
d. 8.62(s)
e. 8.98(s)



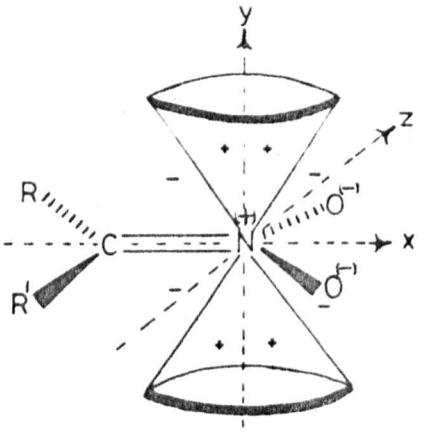
mixing with 5% acetic acid. Estimation of isomer purity was based on the N.M.R. spectra of the products. The nitro-ketone (12) designated as (S) gave its (R) isomer (13) with 95% inversion of configuration and in 90% recovered yield. The nitro-ketone (13) (90% (R)) gave 95% (R) in 90% recovered yield. An example of these results is shown in Plate VI. The ketal (25) (100% (S)), did not give such a high inversion, the product containing (26) (60% (R)). As the yield (70%) was also low, the anomalous result may be due to poor quenching. Ketal (26) (90% (R)) gave 95% (R) in 90% yield, adding further evidence that the result with (25) is spurious.

It was necessary to prove that the anions from the nitro-esters (12) and (13) were indeed identical and also to study the nature of this anion. This was achieved by dissolving either (12) or (13) in hexadeutero-dimethyl sulphoxide, recording the N.M.R. spectrum and then adding a slight excess of sodium hydride in anhydrous conditions. When effervescence had subsided, the solution was almost clear and gave an N.M.R. spectrum (35) (see Plate VI) which was identical from either source. The anion slowly decomposed to Hagemann's ester, about 20% of the latter being present after 2 days (the rate of decomposition was faster if the N.M.R. cap fitted loosely). Both N.M.R. samples gave the (R) isomer (13) on quenching, proving that the epimerisation reactions had gone via the anion.

Interestingly, the N.M.R. of the anion (35) showed the methine proton next to the carbethoxy group (Ha) as a quartet 5.37 τ (J = 6 and 9 c.p.s.). Also superimposed on the quartet of the ethyl group was a doublet 5.81 τ (J = 13 c.p.s.), the whole multiplet representing 3 protons. This doublet is assigned to one of the geminal protons, e.g. (Hb) because of the large coupling constant. Both of these signals have shifted downfield by nearly 2 τ. In order to see these signals clear of any others in the region, the sodium salt (37) of t-butyl ester (36) was prepared as above. The two signals were now apparent as a quartet at 5.62 τ (J = 5 and 8 c.p.s.) representing 1 proton and as a doublet at 6.0 τ (J= 13 c.p.s.) representing 1 proton. Two other features of these spectra are worth noting. Firstly, the methyl group (Hd or Hc) in the salt is moved downfield by 0.28 τ compared to the



38.



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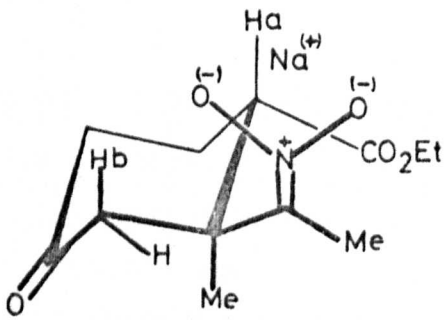
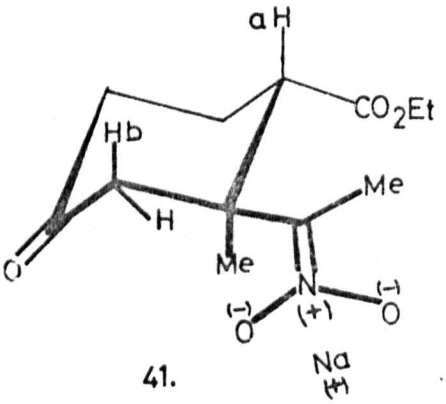


40.



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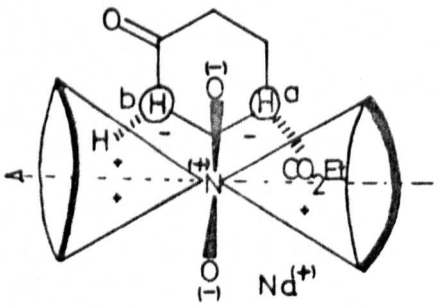
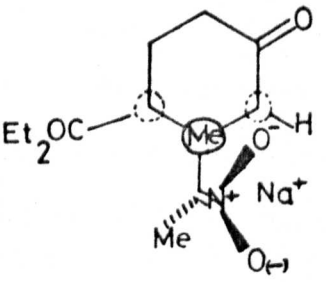


42.

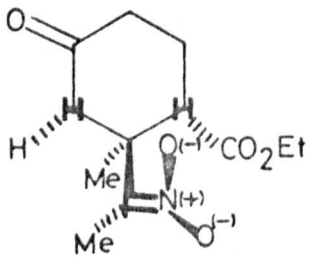


43.

nitro-compound as one would expect for the trigonal formulation of the salt. This is in agreement with the results for nitromethane.[62] Secondly, the tertiary methyl group (Hf or He) is hardly changed vis-à-vis the nitro-compound.

It is thought that the movement of the two protons downfield is due to the cone of anisotropy of the nitro-anion. If one looks at the cone of anisotropy of the carbonyl group (38)[63] it is symmetrical about the plane of the π-electrons (xy plane). Any groups in the xz plane will be outside the cone and therefore deshielded. Any groups on the y axis will be shielded. Other groups will be shielded or deshielded according to their co-ordinates, the strength of the effect also depending on their positions. If one extends this argument to the nitro-anion, one gets a cone of anisotropy as shown (39). Because of the electron delocalisation, the origin of the cone is somewhere near the nitrogen atom. This implies that the trigonal groups R and R' are farther from the cone in (39) than in (38), i.e. they are possibly less deshielded.

Of the two extreme conformational possibilities (40) and (41), (40) is predicted to be the most stable as it does not have the eclipsing interaction between the nitro-anion and the tertiary ring methyl group. In an intermediate rotational position there is a large interaction with the carbethoxy group. If the picture described above for the anisotropy of the nitro-anion is now applied to conformers (40) and (41), one gets the situations (42) and (43) viewing from above and below the molecule respectively. In (42), the two axial protons Ha and Hb are situated in a strongly deshielding region and therefore, shifted downfield in the N.M.R. as is found. The equatorial geminal proton and the carbethoxy group are in a weakly deshielding region and would be expected to shift upfield as is found for the triplet of the ethyl group. The axial tertiary methyl group would not be affected and this is the case. In (43), the eclipsing interaction between tertiary methyl group and anion would rotate the axis of the cone but the methyl group should still be strongly deshielded. This does not agree with the facts. A rational interpretation of these results, therefore, points to (40) as the stable conformer but does not exclude the possibility of an equilibrating mixture of (44) and (45).



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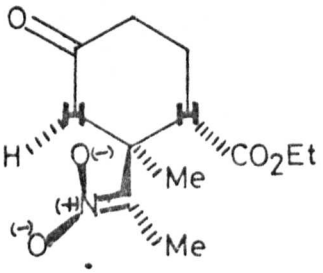

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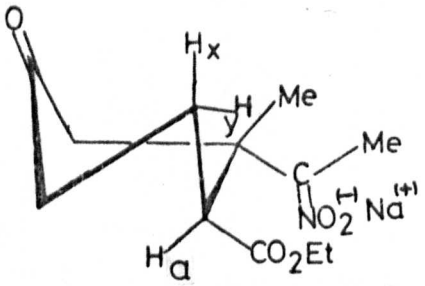
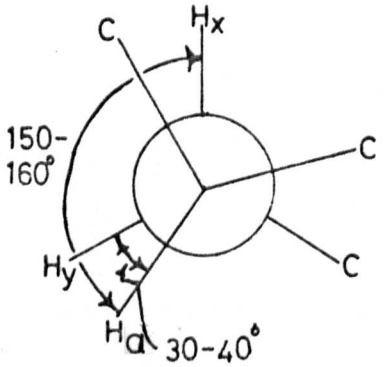


Twist-Chair 46.



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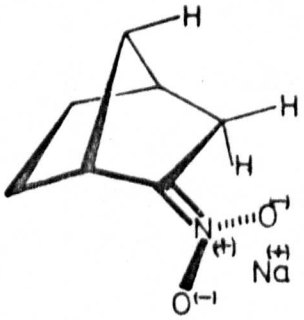
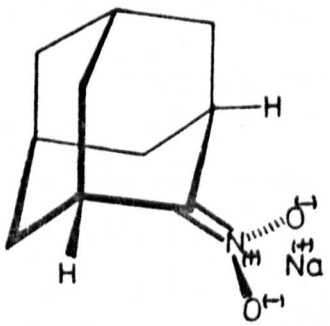


48.



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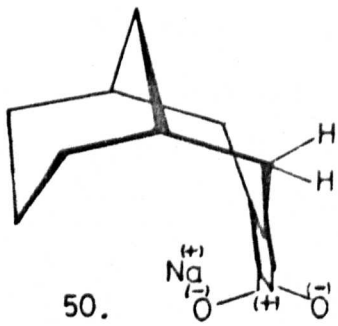
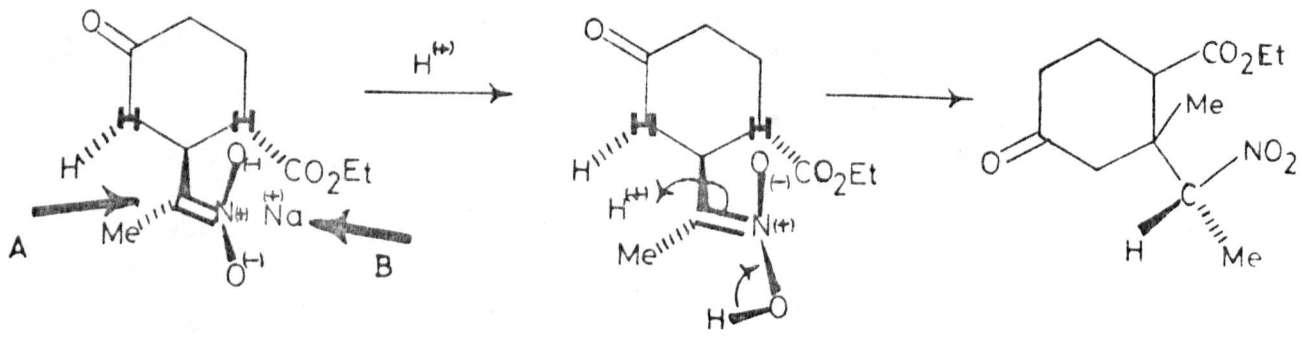
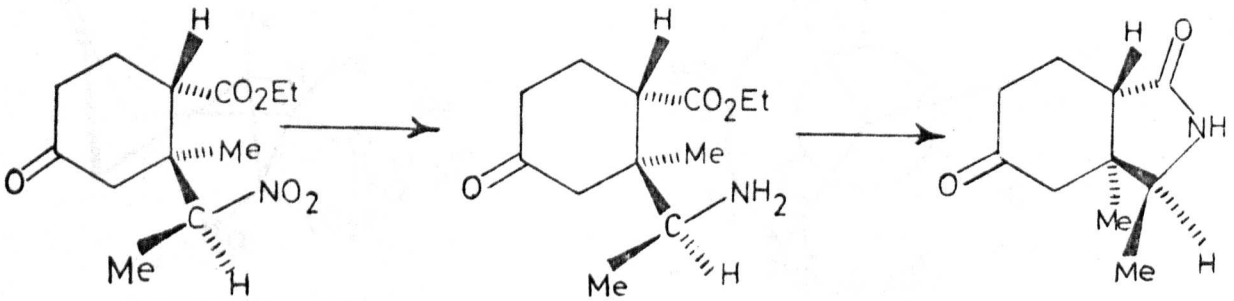


50.

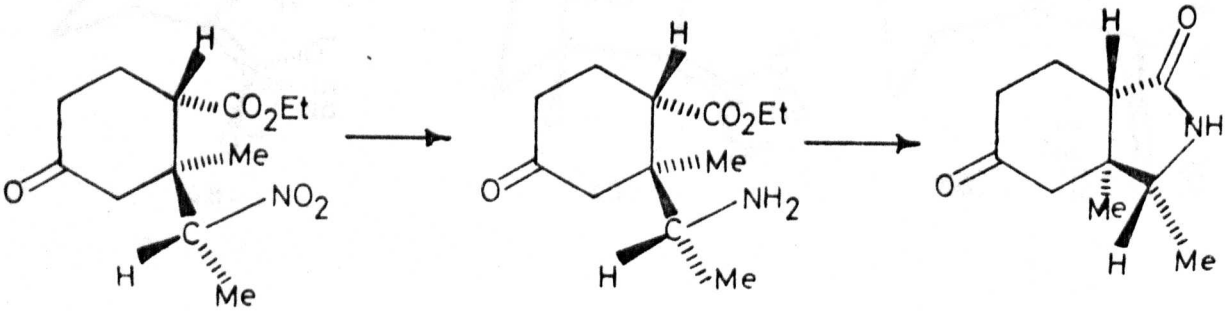


51. 52. 13R.

SCHEME IV



12. 53. 55.



13. 54. 56.

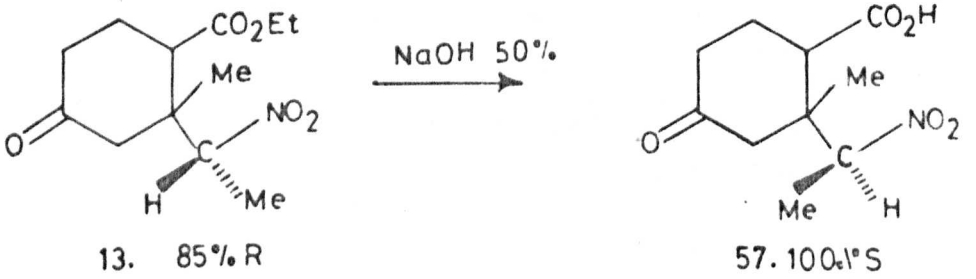
(44) is the most stable of these as the interaction between the methyl group and the carbethoxy group is reduced.

More conformational information is available from the N.M.R. (35). Proton Ha is a quartet caused by vicinal coupling with Hx and Hy (see 46) with J = 6 or 9 c.p.s. Using the Karplus equation[64] this implies that the dihedral angle between Ha and Hy is 30 - 40°, and that between Ha and Hx is 150 - 160° (see 47). For a normal chair these angles are 60° and 120° respectively and thus the anion is probably in the twist-chair conformation (46).

In order to look at the anisotropy effects of the nitro-anion (which have been little studied in the past) in more detail, a series (48), (49) and (50) is being studied in which particular protons are fixed in a rigid spacial position with respect to the anion. No conclusions can be drawn as yet, as only a few poor spectra have been obtained.

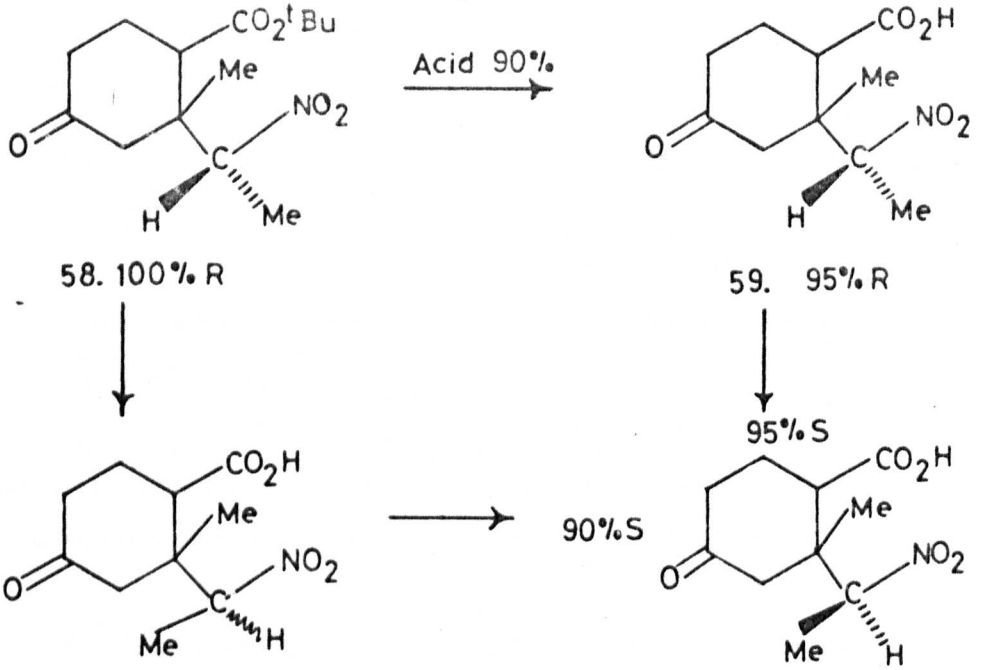
A picture of the nitro-anion (51) as a fairly rigid conformer with one face sterically unhindered (A) and the other highly hindered (B) has been built up. It should be mentioned that the mechanism of protonation requires that it is the nitronic acid (52) that is protonated on carbon (initial protonation on oxygen is much faster). However, as this is also trigonal it will remain in the same conformation as the nitro-anion and be protonated preferentially from side A. This leads to the isomer (13) with the R configuration. That this is the case could be proved by the following scheme. Selective reduction of the nitro-group of the pure isomer (12S) will give (53) which will cyclise to (55). A similar series of steps on isomer (13R) via (54) gives the lactam (56). In this lactam the two methyl groups are eclipsed and there should be a large interaction detectable as a nuclear Overhauser effect.[65] This would be absent in the isomeric lactam (55).

EPIMERISATION OF NITRO-ACIDS



13. 85% R

57. 100% S



58. 100% R

59. 95% R

26.R

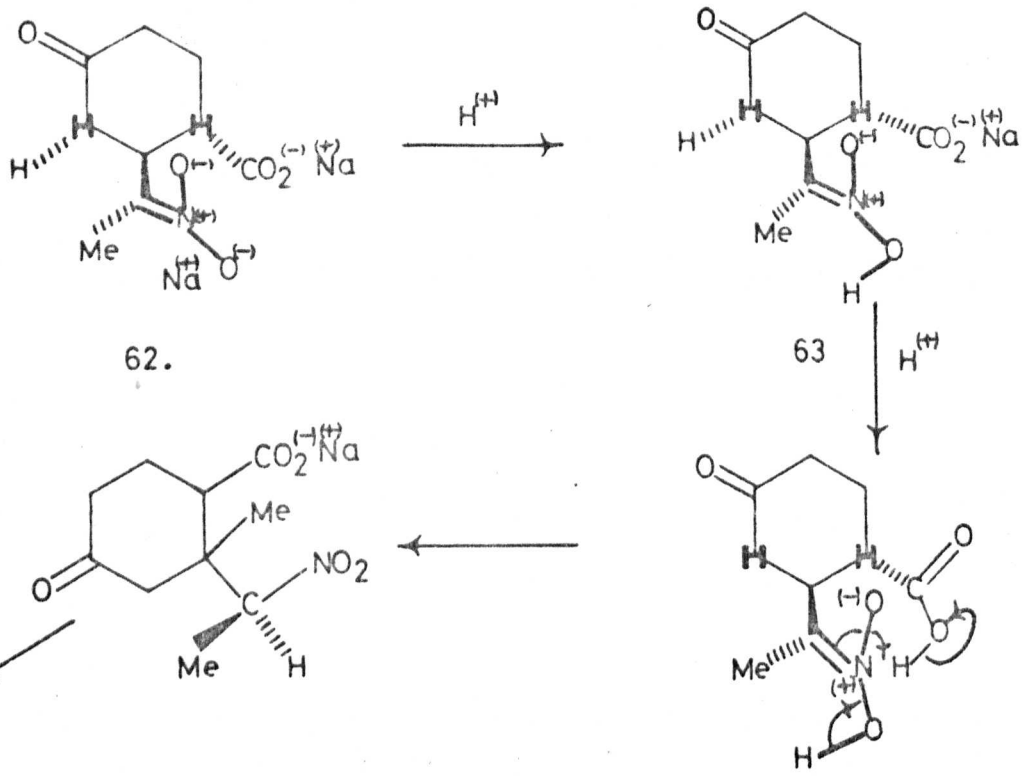
60. 60% R

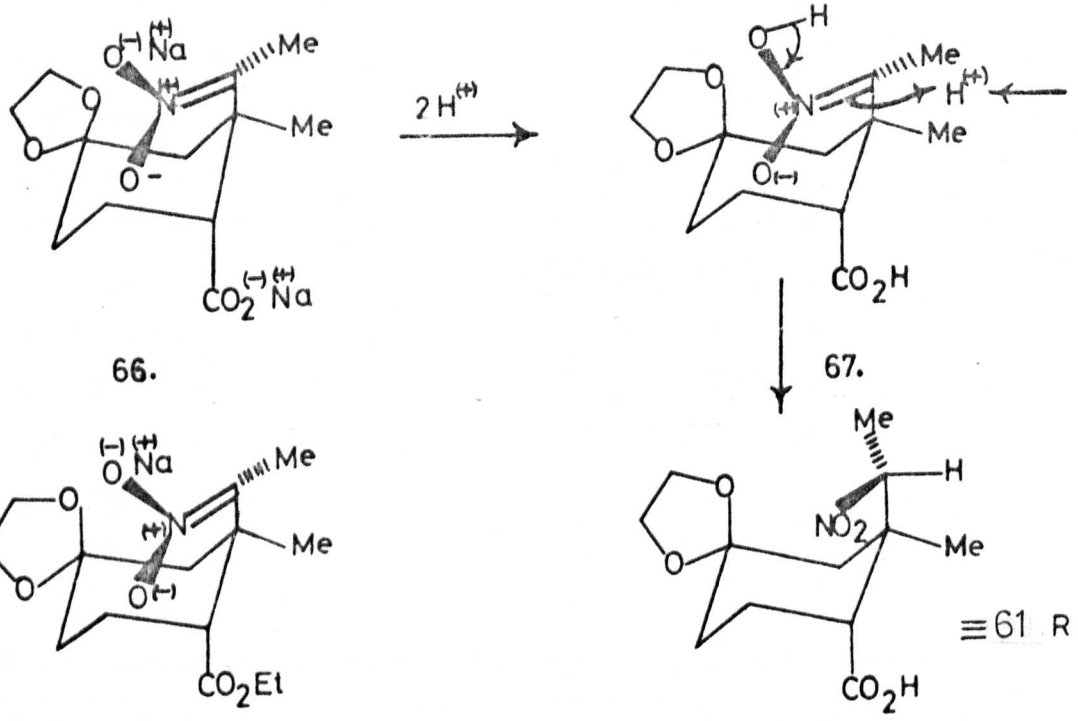
Another series of quenching reactions that was studied was on the dianions of nitro-acids, e.g. (59) and (60). It has already been shown (chapter 1) that alkaline hydrolysis of nitro-ester (13) gave the acid (57) (50%) with the same relative configuration as the nitro-ester (12S). The acid (59) with the opposite configuration was available from the (R) t-butyl ester (58) by mild acid hydrolysis. When it was converted into its dianion with excess sodium hydride in dimethyl formamide and quenched with 5% acetic acid, the acid obtained (90%) was (57) (95% (S)). Further, if a 50/50 mixture of R and S acids was treated similarly, the product isolated (80%) consisted of the acid (57) (90% (S)). These results show that the kinetic control of protonation in this case is in the opposite sense to protonation of the ester anions, in which case the (R) isomers are obtained.

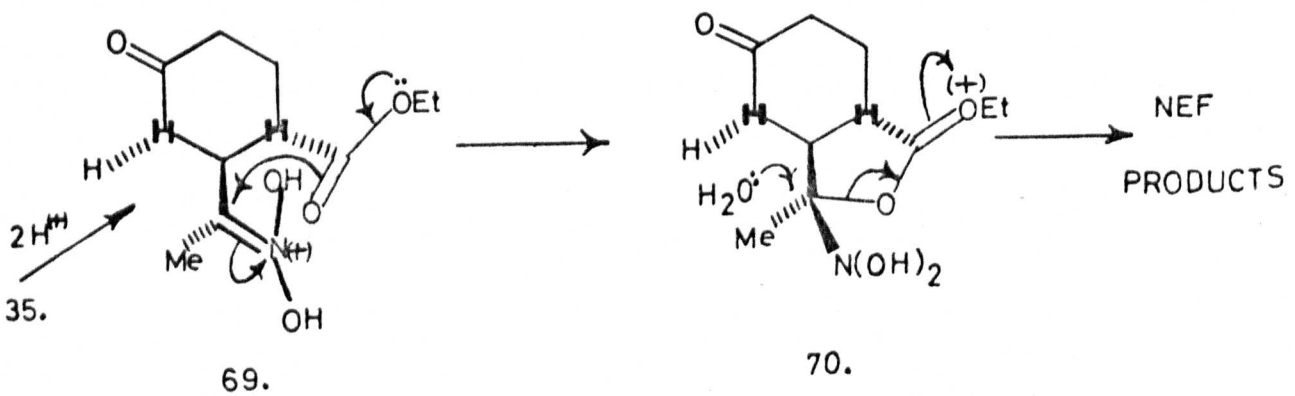
If the ketal ester (26 R) was refluxed for 4 hours with methanolic sodium hydroxide, a mixture of isomeric ketal acids (60) (60% (R)) was obtained (80%). This is in marked contrast to the alkaline hydrolysis of keto-ester (13). If the mixture of isomers (60) was now epimerised as usual, the product (61) consisted of 90% (R) isomer as shown by ethylation to give (26) or acid hydrolysis to give the keto-acid (59).

These results are rationalised as follows. Firstly, the dianion (62) will be protonated on the nitro-anion to give the nitronic acid (63) which, as argued before, maintains the conformation of the nitro-anion. This acid must have an appreciable lifetime, as in the alkaline hydrolysis of (13) the mixture is brought to pH 9 and extracted with ether. Only then is it acidified to pH 3. A second protonation of (63) will take place on the carboxyl anion to give (64). This now has a proton ideally situated to tautomerise the nitronic acid via a six-membered transition state to give (65) and hence, (57) with the S configuration. This intramolecular attack would be much faster than intermolecular attack.

Secondly, the fact that the ketal acid (60) gives the product of intermolecular attack rather than intramolecular, is explained by assuming a conformation of the anion in which backside protonation can no longer take place, e.g. (66). The nitro-anion is a less bulky substituent than the nitro-


62.
63
64.
65.
57.


66.
67.
68.
≡61 R

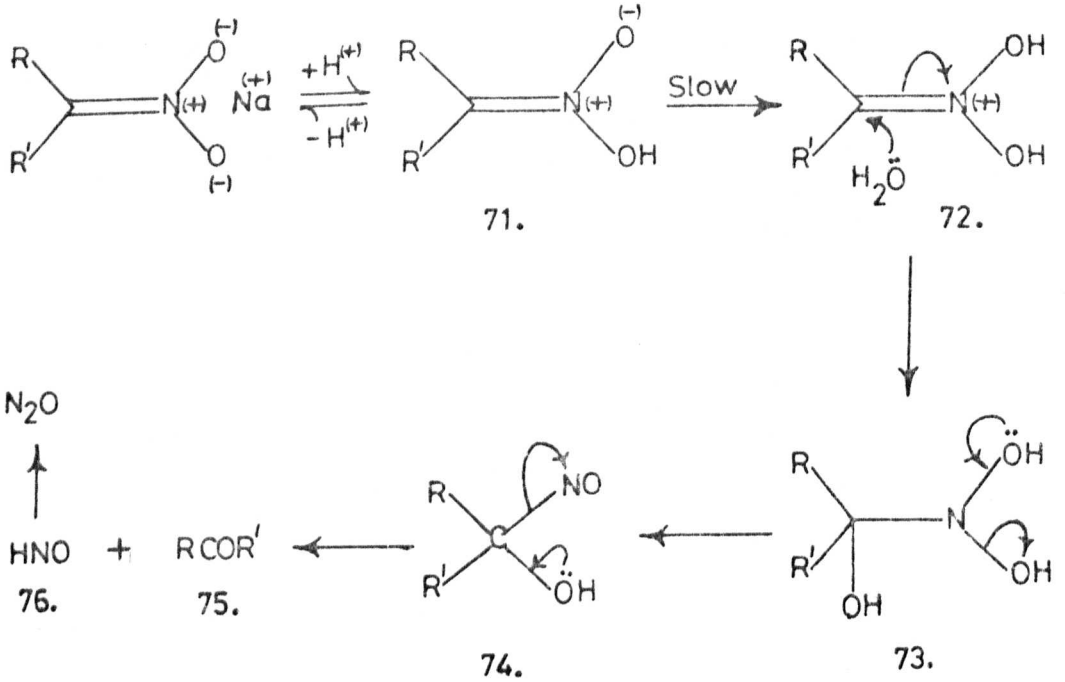

35.
69.
70.
NEF
PRODUCTS

group and possibly has a smaller A value than the methyl group. The conversion of the carbonyl group of (13) into the ketal (26) introduces a 1,3 axial-axial interaction with the methyl group. Therefore, in the dianion, the most stable conformation is (66) with the nitro-anion axial (and conformationally rigid). Protonation gives the nitronic acid (67) which cannot be protonated by the carboxyl group and hence the nitro-compound (61R) is formed by intermolecular protonation from the least hindered side. Some evidence for this hypothesis could be gained by looking at the N.M.R. of the ketal-ester anion (68) in which the deshielding caused by the nitro-anion might affect different protons than in the keto-ester anion (40).

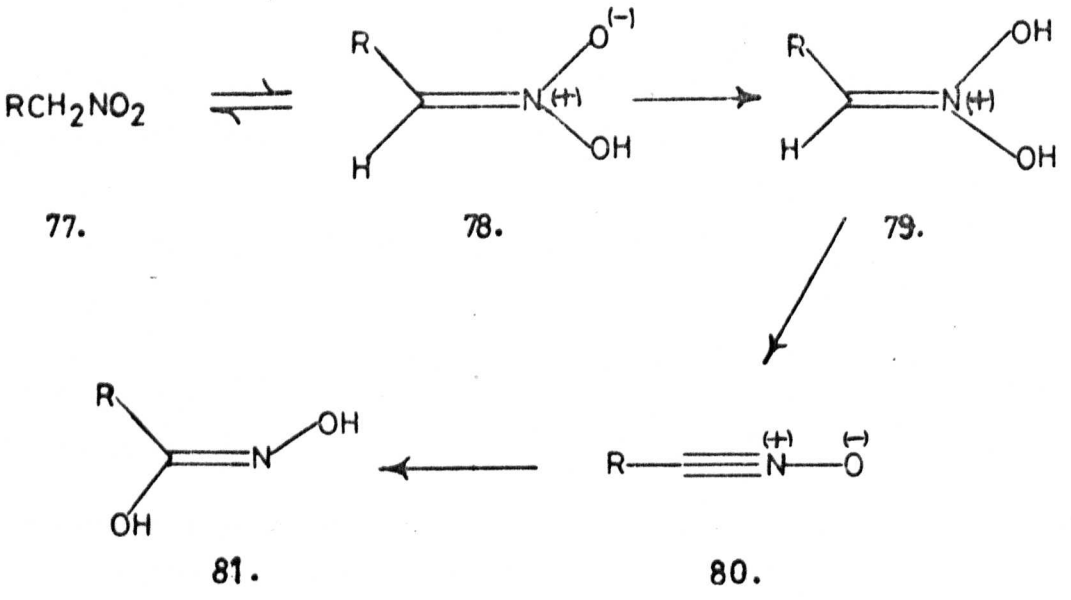
In chapter 2 it was noted that the Nef reaction on the dianion of the nitro-acid (57) did not occur and that the product was the starting nitro-acid. This result adds strong evidence in favour of the backside attack mechanism. It is important to note that firstly, the conditions used in this attempted Nef reaction were identical to those used for the keto-ester nitro-anion (40) with which the Nef reaction was successful and secondly, that the dianion is definitely formed because identical conditions for salt formation to those in which (59) was epimerised to (57), were used. It was also noted in chapter 2 that the nitro-anion (40) gave an unexpectedly high yield in the Nef reaction, for such a highly hindered compound. This could be explained by a similar backside participation of the carbethoxy group in (69) to give the cyclic intermediate (70) which then gives products of the Nef reaction.

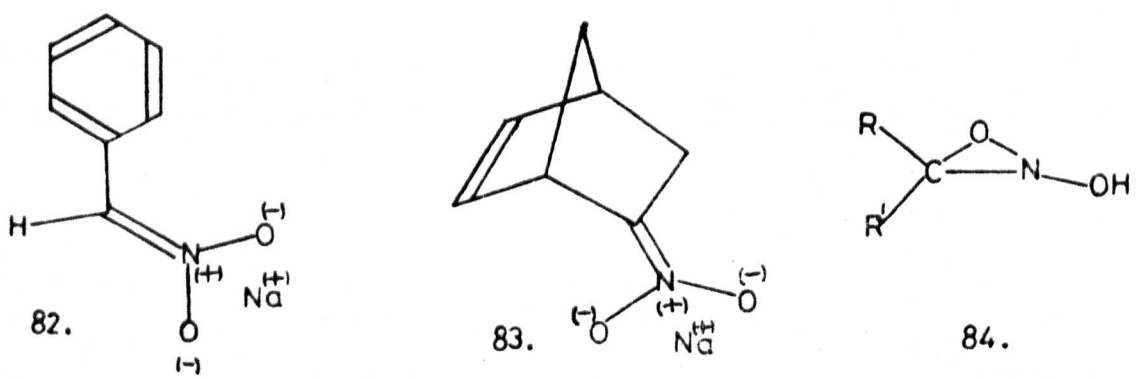
The mechanism of the Nef reaction has been reviewed[46] but at the moment there are two conflicting views. Scheme IV shows the most widely accepted view. It has been shown[66] kinetically that the slow step involves a molecule of nitronic acid (71) and a proton, the product probably being the protonated nitronic acid (72). Attack by water gives (73) which eliminates water to give the hydroxy-nitroso compound (74). This latter intermediate accounts for the transient blue colour which always accompanies the Nef reaction. Elimination of hyponitrous acid (76) which decomposes to nitrous oxide, gives the ketone (75). The conflict over the mechanism stems from the similarity of the Meyer reaction[67] (Scheme V) to the Nef reaction with

SCHEME IV



SCHEME V



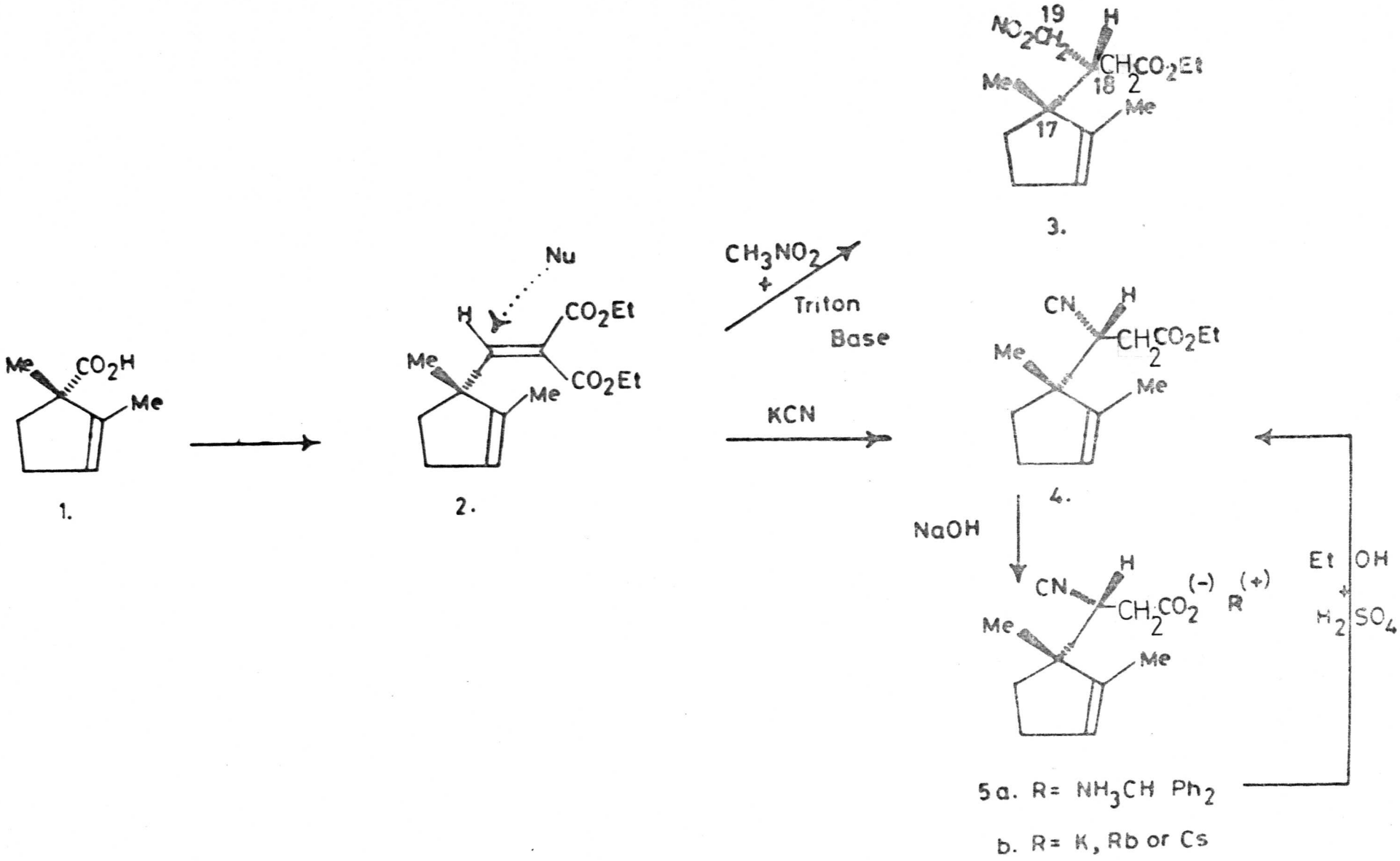


primary nitro-anions. Here a primary nitro-compound (rather than its anion) is converted, by heating with concentrated sulphuric acid, to the hydroxamic acid (81) via the nitronic acid (78), the protonated nitronic acid (79) cf. (67) and the nitrile oxide (80). It can be seen that the protonated nitronic acids (79) and (72) are common intermediates in both reaction mechanisms and there appears to be no reason why they should react differently in the two schemes. Kornblum[68] argues that acid strength is the most important factor as he could decompose primary nitronic esters (trapped nitronic acids) selectively to aldehydes or hydroxamic acid by varying the acid strength. A Nottingham group,[69] however, argues that in the Nef reaction the nitro-anion can react directly with a hydroxonium ion to give (73) without going through the Meyer intermediate. This problem remains unsolved and some work is being done in these laboratories to clarify the position, working on the idea that three-membered hererocycles, e.g. (84) may be important intermediates. The crucial point in this case is where does the oxygen of the carbonyl group come from - the nitro-group or the medium? Some ^{18}O labelling experiments are projected. It should be pointed out that the side products in the Nef reaction are numerous and Noland[70] has suggested that the formation of ketone (or aldehyde) may be the result of many, rather than one, mechanism.

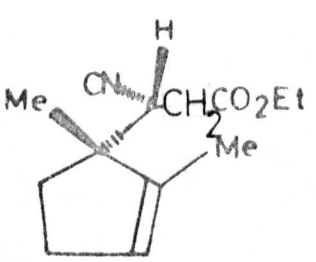
Important to the failure of the nitro-anion (57) in the Nef reaction are other cases which fail. It has been found[61] that resonance stabilised nitro-anions, e.g. (82) do not give aldehydes but nitro-compounds. The norbornene anion (83) also fails[71] whereas the norbornane derivative gives norbornanone. This is thought to be due to homoallylic π-participation. Neither of these are really similar to the case in point but it does seem that if protonation on carbon (to give the nitro-compound) takes place at a similar rate to protonation at oxygen (to give the nitronic acid) then the Nef reaction fails.

The present hypothesis for the failure of (57) is that as both mechanisms for the Nef reaction require attack of a solvent molecule at the trigonal carbon of the nitro-centre, this is much slower than protonation of the nitronic acid from the backside by the carboxyl group to give (57). When an ester group is present, this cannot take place. Attack by solvent on (69) would, however,

be slow, and appreciable tautomerisation to the nitro-compound would be expected unless this was prevented by neighbouring group participation of the carbethoxy group via (70) or some other effect.

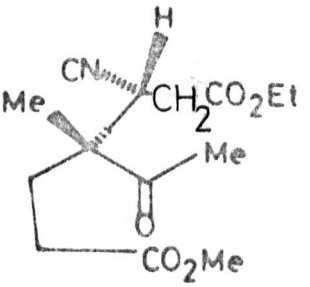

Me
CO2H
Me
1.
Nu
H
CO2Et
Me
CO2Et
Me
2.
CH3NO2
+
Triton
Base
KCN
19
NO2CH2
H
CH2CO2Et
18
2
Me
Me
17
3.
CN
H
CH2CO2Et
Me
Me
4.
NaOH
CN
H
CH2CO2
(-)
R
(+)
Me
Me
5a. R= NH3CH Ph2
b. R= K, Rb or Cs
Et OH
+
H2SO4

SCHEME 1



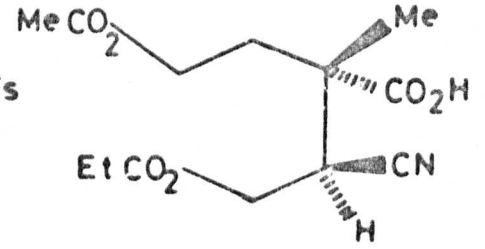
4.

O_3



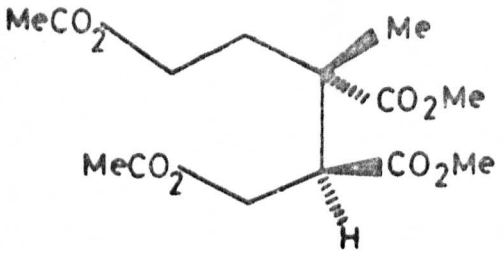
6.

NaOBr

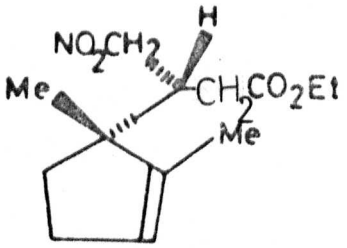


7.

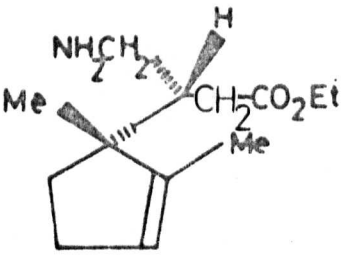
Hydrolysis



8.

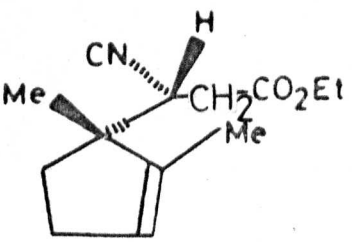


3.



9.

NiO_2



4.

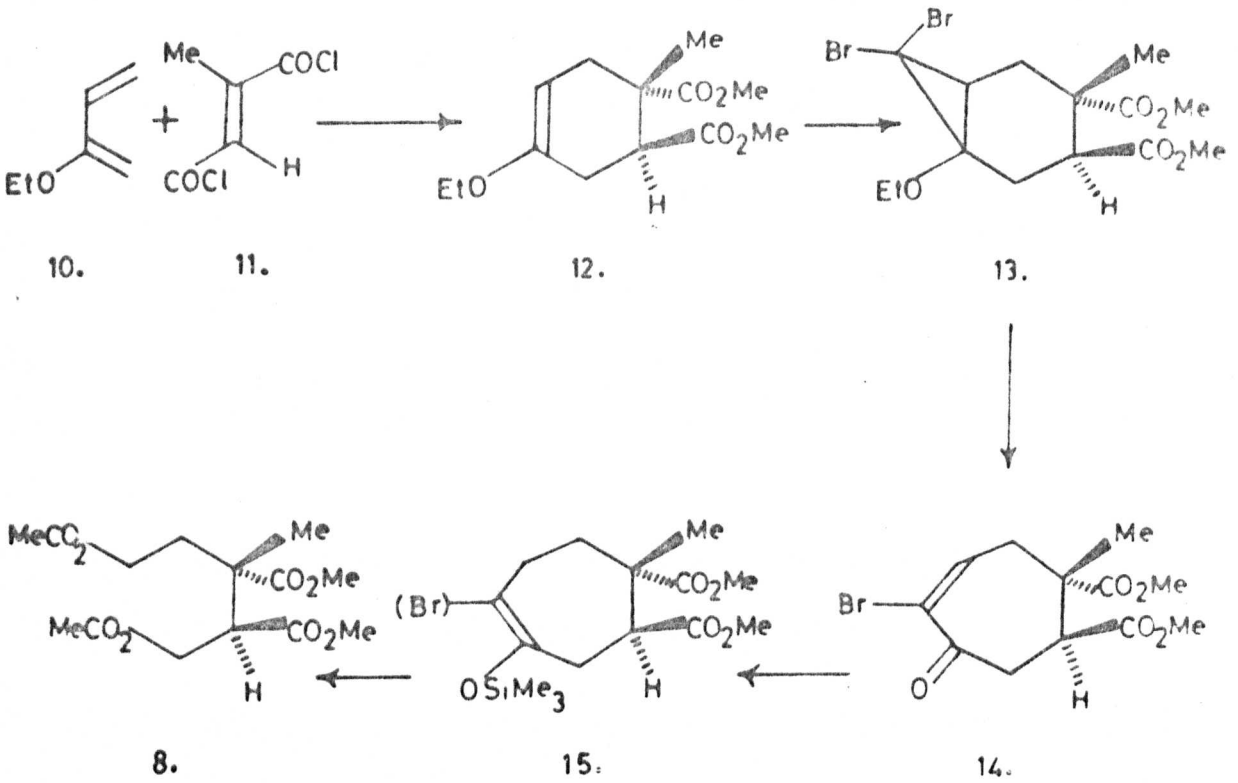
CHAPTER 4

The work described in the previous chapters dealt mainly with aspects of the ring A precursor and it remains to describe here the state of the ring D precursors (3) and (4). These have been prepared[72] by Michael additions to (2), obtained from (1) which has been resolved[72] into its enantiomers. Although two diastereomers could be formed in these additions, both (3) and (4) seem to be single isomers. Models show that the incoming nucleophile would prefer to attack the double bond at the face opposite to the ring tertiary methyl group as shown in (2). Thus, (3) and (4) are predicted to have the relative configurations shown, which happen to correspond to positions 17 and 18 of vitamin B_{12} (see 3).

It was decided initially to prove this relative configuration by X-ray crystallography. Cornforth could hydrolyse[72] (4) using sodium hydroxide under fairly vigorous conditions and convert the acid obtained into its well crystalline benzhydrylamine salt (5a). It needed to be proved that no epimerisation had occurred in this reaction. The benzhydrylamine salt (5a) was ethylated with ethanol/sulphuric acid to give a product with an N.M.R. spectrum almost identical to that of (4) and with an identical I.R. spectrum. It was thus concluded that (5a) had the same relative configuration as (4). (5a) was converted[73] into its potassium, rubidium or cesium salts which were crystalline but exceedingly delequescent. This, along with other factors, led to this approach being abandoned in favour of a degradative method.

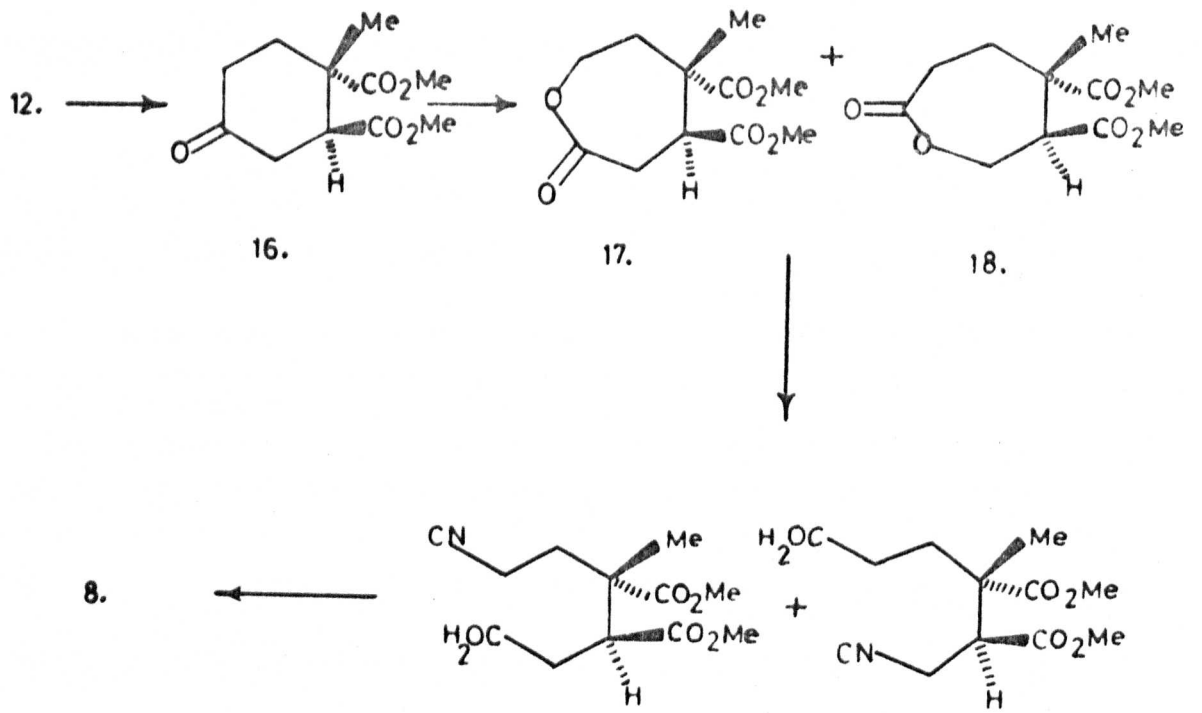
A possible degradative route is shown in Scheme I. Ozonolysis of (4) could eventually lead to (6) which would undergo a hypohalite oxidation to (7). Prolonged acidic hydrolysis followed by treatment with diazomethane would give the trans-tetramethyl ester (8). This route also requires that firstly, the nitro-compound (3) can be unambiguously correlated with the cyano-compound (4) and that secondly, both the cis and trans-tetramethyl esters, e.g. (8) can be prepared by another route. The first problem presents some difficulty. A suggested procedure is to reduce the nitro group to the

SCHEME II



10. 11. 12. 13. 14. 15. 8.

SCHEME III



amine followed by oxidation with nickel peroxide.[74] It was felt that the independent route to (8) should be perfected before the above degradation of (4) was attempted, to conserve material.

Ideas for the synthesis of the cis and trans-tetramethyl esters, e.g. (8) are outlined in Schemes II and III. In Scheme II the starting point is the enol-ether (12). This has been prepared[75] by the Diels-Alder addition of 2-ethoxy-butadiene (10) to dimethyl-mesaconate in a sealed tube at 200°C. Use of mesaconyl chloride (11) dispenses[76] with the sealed tube and as a further improvement, it is proposed to investigate the possibility of catalysis by Lewis acids, e.g. stannic chloride. The cis-isomer of (12) would be obtained from the known[75] addition product of 2-ethoxy-butadiene and citraconic anhydride by opening of the anhydride with methoxide and methylation of the half-ester obtained. The enol-ethers would then be treated with dibromocarbene to give the adduct (13), followed by treatment with silver ions to give the 7-ring ketone (14), a reaction for which there is ample analogy.[77] Reduction with sodium in liquid ammonia[78] and trapping the enolate anion with trimethyl-silyl chloride would give (15) which may or may not contain bromine. Ozonolysis of (15) would eventually give (8). Thus far only the starting compounds have been prepared.

In Scheme III both the cis and trans-ketones, e.g. (16) have been prepared.[75] Treatment with pertrifluoracetic acid[79] would give a mixture of the 7-membered ring lactones (17) and (18) which could be opened with hydrogen bromide. There is some danger that (18) may epimerise in this reaction. Treatment of the mixture of bromides with potassium cyanide in dimethyl sulphoxide would give a mixture of (19) and (20) which, after hydrolysis amd methylation, would give the single product (8). This route has not been tried as yet, although the starting ketones have been prepared.

These reactions, which open up a 6-membered ring with the introduction of an extra carbon atom to give a propionic and an acetic acid side chain, are important for the overall synthesis of vitamin B_{12}. Previously this was to be done by a rather violent cleavage of isoxazoles and a milder yet specific process needed to be found.

EXPERIMENTAL

Melting Points (M.P.)	: Melting points were taken on a Reichert heated microscope stage and are uncorrected.
Infra-Red Spectra (I.R.)	: I.R. spectra were recorded with a Perkin-Elmer 257 grating machine. Spectra were taken with 0.25 mm cells in carbon tetrachloride unless otherwise stated. The maxima are designated as w (weak), mw (medium weak), m (medium), ms (medium strong), s (strong).
Ultra-Violet Spectra (U.V.)	: U.V. spectra were recorded with a Unicam SP800 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 either with a Perkin-Elmer R 10 (60 Mc/s) or a Perkin-Elmer R 12 (60 Mc/s). The reference signal was that of tetramethylsilane (T.M.S.) $\tau = 0$, and solutions in carbon tetrachloride were used unless otherwise stated. The peaks are designated by the chemical shift (τ) in p.p.m. followed, in brackets, by the multiplicity s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), the spin-spin coupling constant (J) in c.p.s. and the integration (H).
Mass Spectra (M.S.)	: M.S. spectra were run by the University of Hull service on an A.E.I., MS 902. 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's were run on a Honeywell F and M using either a 2 ft, 10% SE 30 column or a 6 ft, 10% E 301 column with column temperatures of 175°C or 200°C. Traces were calibrated, if necessary, with known mixtures.
Thin Layer Chromatography (T.L.C.)	: Qualitative T.L.C's were taken using microscope slides dipped in a suspension of silica gel PF 254 (Merck, U.V. sensitive) or basic alumina G (Merck) in chloroform. Also used were large plates 5 x 20 cm or 20 x 20 cm.

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 when 200 mg or more of material was available. For smaller quantities 20 x 20 cm. plates and manual application was used.

Column Chromatography : This was carried out using columns of varying dimensions and 60 - 120 mesh silica gel B.D.H.

Analysis : This was carried out by the Alfred Bernhardt (W.Germany) microanalysis service.

Sodium hydride was supplied by B.D.H. as a 50% dispersion in oil and was washed well with pentane in a dry box before use.

CHAPTER 1

Preparation of Hagemann's Ester (1) by a Literature Method[32]

To ethyl acetoacetate (540 gm, 527 ml, 3.6 moles) was added paraformaldehyde (60 gm, 2 moles) and piperidine (20 ml) as catalyst. The mixture was shaken, allowing the temperature to rise to 50°C, and then keeping it below 70°C by immersion in an ice-bath. When the reaction had subsided and had stood for 30 minutes at room temperature and refluxed for 1 hour, the water was removed in vacuo at 80°C. The crude material was then added to sodium ethoxide (46 gm, sodium in 1600 ml dry ethanol) at room temperature, refluxed for 2 hours with vigorous stirring and the solvent completely removed in vacuo at 80 - 100°C. Water (1 litre) and glacial acetic acid (140 ml) were added to the gel with vigorous stirring and the whole stirred for 30 minutes at room temperature. The layers were separated, the aqueous extracted with ether (3 x 100 ml) and the total organic layer shaken with solid potassium bicarbonate, washed with saturated sodium bicarbonate (3 x 100 ml) and dried ($MgSO_4$). Removal of ether in vacuo followed by fractionation and redistillation gave an oil (350 gm, 55%).

B.P.	: 76/80°C (0.1 m.m.), Lit. 142/144°C (15 m.m.)
N.M.R.	: τ = 4.2 (q, 1, 1H), 5.82 (q, 7, 2H), 6.78 (t, 3, 1H), 7.6 - 7.9 (m, 4H), 8.0 (d, 1, 3H), 8.74 (t, 7, 3H)
I.R. (film)	: cm^{-1} = 2985^m, 1730^s, 1672^s, 1635^m, 1380^m, 1342^m, 1309^m, 1250^s, 1185^s, 1096^w, 1035^m, 856^w
U.V.	: 234n.m. / 1.35×10^4

Michael Addition of Nitroethane to Hagemann's Ester (1)

Hagemann's ester (150 gm, 0.825 mole), nitroethane (150 gm, 2.2 moles) and benzyl-trimethylammonium ethoxide[28] (175 ml of 1.47 m.mole/ml solution in ethanol) were stirred under nitrogen at 40°C for 4 days. Ether (500 ml) was added and the organic layer washed with N-hydrochloric acid (3 x 100 ml), N-sodium hydroxide (3 x 100 ml), brine (2 x 100 ml), dried ($MgSO_4$) and concentrated in vacuo to give a crude residue (150 gm). This was fractionated (0.1 m.m.) as follows.

1. 100 - 120°C 60 gm (Hagemann's ester)
2. 120 - 145°C 8 gm (1 + 3)
3. 145 - 155°C 72 gm

On standing (or seeding) fraction (3) and then repeatedly treating with pentane/ether with cooling, a crystalline material (2b) (29 gm, 42%) was obtained. This was recrystallised from pentane ether (3x).

M.P. : 90 - 91°C

N.M.R. : τ = 5.04 (q, 7, 1H), 5.83 (q, 7, 2H), 7.1 - 7.95 (m, 7H), 8.52 (d, 7, 3H), 8.69 (t, 7, 3H), 8.85 (s, 3H)

I.R. (CH_2Cl_2) : cm^{-1} = 2900^m, $1710-1720^s$, 1544^s, 1353^m, 1194^s, 1114^m, 1034^s, 865^w

(nujol) : cm^{-1} = 1730^s, 1708^s + well-resolved finger-print region

U.V. : 282 n.m. / 69 + end absorption

M.S. : m/e = 257 (2), 212 (73), 211 (35), 183 (60), 181 (72), 153 (40), 137 (100), 114 (54), 109 (80), 95 (74)

ANALYSIS : %

C	H	N	
56.08	7.48	5.41	Found
56.02	7.44	5.44	Calc. for $C_{12}H_{19}NO_5$

The mother liquor gave a viscous oil (2a) (43 gm, 58%) on removal of solvent.

N.M.R. : τ = 5.33 (q, 7, 1H), 5.81 (q, 7, 2H), 7.1 - 7.9 (m, 7H), 8.44 (d, 7, 3H), 8.69 (t, 7, 3H), 8.91 (s, 3H)

Preparation of Nitro-Acid (3) by Alkaline Hydrolysis of (2)

Either fraction (3) or isomer (2a) (from the previous reaction) (5 gm, 0.02 mole) were shaken at room temperature with 2N-aqueous sodium hydroxide. After 2 hours the oil had dissolved and the dark red mixture was brought to pH 9 by adding dry ice and the solution extracted with ether. The aqueous layer was then brought to pH 1 with N-hydrochloric acid and the cloudy mixture left overnight at 0°C. A yellow crystalline solid was precipitated (1.5 gm, 34%) which was recrystallised from ethyl acetate

(3x) to give plates.

M.P. : 154°C (dec.)

N.M.R. (CD_3OD) : τ = 4.80 (q, 7, 1H), 7.0 - 7.3 (m, 1H), 7.4 - 8.0 (m, $\simeq$ 6H), 8.47 (d, 7, 3H), 8.82 (s, 3H)

I.R. (nujol) : cm^{-1} = 1705^{s}, 1544^{s}, 1333^{m}, 1300^{mw}, 1272^{w}, 1250^{s}, 1232^{mw}, 1221^{m}, 1180^{w}, 1120^{w}, 1058^{w}, 1020^{w}, 930^{s}, 882^{w}, 868^{w}

(H.C.B.D.) : cm^{-1} = $3,200 - 2,300^{m}$ (broad)

U.V. : 284n.m./71.5 + strong end absorption

M.S. : 229 (2), 183 (36), 181 (25), 155 (60), 109 (64), 95 (92), 55 (94), 41 (100)

ANALYSIS : %

C	H	N	
52.11	6.60	5.98	Found
52.39	6.62	6.11	Calc. for $C_{10}H_{15}NO_5$

Esterification of Nitro-Acid (3) with Ethanol/Sulphuric Acid

The nitro-acid (210 mg, 0.92 m.mole) was dissolved in 4% concentrated sulphuric acid/ethanol and left for 4 days at room temperature after which time the mixute was poured into water and made alkaline with sodium carbonate. Extraction with ether, drying the ether layer ($MgSO_4$) and concentration in vacuo gave a crystalline compound (45 mg, 20%).

N.M.R. : τ = 5.03 (q, 7, 1H), 5.83 (q, 7, 2H), 7.1 - 7.9 (m, $\simeq$ 7H), 8.50 (d, 7, 3H), 8.7 (t, 7, 3H), 8.84 (s, 3H)

Acidification of the alkaline layer with N-hydrochloric acid and extraction with ethyl acetate (2 x 50 ml), drying the organic layers ($MgSO_4$) and removal of solvent in vacuo gave a crystalline residue (145 mg, 70%) which was starting material by I.R.

Esterification of the Acid (3) with Meerwein's Reagent

Recrystallised nitro-acid (200 mg, 0.87 m.mole) was dissolved in 5% sodium bicarbonate (25 ml) and triethyloxonium fluoroborate (Fluka, 1.5 gm in 100 mg portions) was added, the pH being maintained at 8 as far as possible with extra bicarbonate. The mixture was extracted with ether (2 x 50 ml) and the ether layers washed with saturated sodium bicarbonate, dried ($MgSO_4$) and the solvent removed in vacuo to give a crystalline compound (100 mg, 45%) which had the same T.L.C. and N.M.R. (except for one impurity peak) as the ethyl ester (2b).

Attempted Improvement of the Hydrolysis of Nitro-Ester (2)

(a) Pure crystalline nitro-ester (2b) (500 mg, 2 m.moles) was shaken with a mixture of dioxan (3 ml) and 2N-sodium hydroxide (3 ml) until dissolved. After 10 minutes the mixture was extracted with ether (2 x 20 ml). The ether layer, after drying ($MgSO_4$) and removal of solvent in vacuo, gave a residue (40 mg) which had 4 components (T.L.C., SiO_2, CH_2Cl_2). The aqueous layer was acidified (green colour) and extracted with dichloromethane (3 x 25 ml). The organic layer was dried ($MgSO_4$) and removal of solvent in vacuo gave a residue (502 mg) which had one main component. Preparative T.L.C. of this residue (silica gel, 20 : 1 dichloromethane/ethyl acetate) gave an oil (60 mg).

N.M.R. : τ = 5.8 (q, 7, 2H), 6.65 (q, 5 and 10, 1H), 7.3 - 7.9 (m, 6H), 7.77 (s, 3H), 8.73 (t, 7, 3H), 8.74 (s, 3H)

I.R. : no band at 1550 cm^{-1}

If the reaction was allowed to go on for longer ($\frac{1}{2}$ hour) numerous products were obtained (T.L.C.).

(b) Potassium t-butoxide in DMSO/water[29] [5 ml of (0.5 gm in 15 ml DMSO) + 2 drops water] was added dropwise to pure crystalline nitro-ethyl ester (2b) (120 mg, 0.5 m.mole) in DMSO (2 ml). After 10 minutes the mixture was poured into water (25 ml) and extracted with ether. The aqueous layer was acidified, extracted with dichloromethane (2 x 25 ml) and the organic layers washed with water (2 x 25 ml), dried ($MgSO_4$) and the solvent removed in vacuo. The resultant oil (85 mg.) had many components (T.L.C.).

Preparation of 3-Carbethoxy-Hepta-2,6-Dione (7)

The method described by Heneka[36] was used. Methyl-vinyl-ketone (Koch-Light; freshly dried and distilled[80], 100 gm, 1.4 mole) was added dropwise with stirring to a mixture of ethylacetoacetate (250 gm, 1.6 moles) and sodium methoxide solution (10 ml of a solution of 23 gm sodium in 400 ml methanol) cooled at 0°C, keeping the reaction temperature below 20°C. After addition the mixture was left at room temperature overnight, diluted with dichloromethane (250 ml) and washed with N-hydrochloric acid (2 x 50 ml). Drying ($MgSO_4$) and removal of solvent in vacuo left a residue which gave an oil (230 gm, 81%) on fractionation.

B.P. : 100 - 102°C (0.1 m.m.), Lit. 127 - 129°C (4.5 m.m.)

N.M.R. : τ = 5.86 (q, 7, 2H), 6.59 (t, 7, 1H), 7.62 (t, 7, 2H), 7.85-7.95 (2s, 6H), 8.0 (q, 7, 2H), 8.75 (t, 7, 3H)

I.R. : cm^{-1} = 3420^{w}, 2980^{mw}, 1745^{ms}, 1720^{s}, 1445^{mw}, 1412^{mw}, 1358^{m}, 1238^{m}, 1150^{m}, 1095^{mw}, 1025^{mw}

U.V. : 249n.m. / 3.25×10^{2}

Preparation of 3-Carbomethoxy-Hepta-2,6-Dione (21)

This was prepared as above from methyl-vinyl-ketone (80 gm, 1.2 mole) and methyl acetoacetate (B.D.H., 116 gm, 1 mole) to yield an oil (140 gm, 80%).

B.P. : 112 - 120°C (0.2 m.m.)

N.M.R. : τ = 6.29 (s, 3H), 6.55 (t, 7, 1H), 7.61 (t, 7), 7.82, 7.93 (2s, 6H), 7.98 (q, 7).

I.R. : cm^{-1} = 3420^{w}, 3000^{w}, 2955^{mw}, 1750^{ms}, 1721^{s}, 1435^{m}, 1410^{mw}, 1358^{ms}, 1240^{m}, 1150^{ms}

U.V. : 257n.m. / 2.53×10^{2}

M.S. : m/e = 186 (10), 155 (45), 144 (100), 139 (38), 115 (50), 112 (60), 111 (55), 97 (90), 94 (100), 58 (55), 55 (70)

ACC.MASS : m/e = 186.0890 [186.0892 = $C_9H_{14}O_4$]

Preparation of 3-Carbo-t-Butoxy-Hepta-2,6-Dione (22)

Methyl-vinyl-ketone (dried, distilled, 35 gm, 0.5 mole) was added dropwise with stirring to a mixture of t-butyl-acetoacetate (Emmanuel, 71 gm, 0.45 mole) and sodium methoxide (5 ml of a solution of 1 gm sodium in 50 ml ethanol) cooled at 0°C. There was a white coagulated precipitate present after addition and the temperature of the reaction did not rise. The mixture showed incomplete conversion to product (G.L.C.) after standing at 35°C overnight and further methoxide (2.5 ml) was added to complete the reaction. (In subsequent reactions more base was added from the start). The mixture was diluted with dichloromethane (100 ml), washed with N-hydrochloric acid (2 x 100 ml), dried ($MgSO_4$) and the solvent removed in vacuo to leave a residue (80 gm) which gave an oil (73 gm, 72%) on fractionation.

B.P. : 110 - 116°C (0.1 m.m.)

N.M.R. : τ = 6.69 (t, 7, 1H), 7.63 (t, 7), 7.84, 7.93 (2s, 6H), 8.03 (q, 7), 8.55 (s, 9H)

I.R. : cm^{-1} = 3420^{w}, 3005^{w}, 2982^{m}, 2935^{mw}, 1740^{ms}, 1720^{s}, 1370^{ms}, 1358^{m}, 1280^{mw}, 1245^{m}, 1140^{s}

U.V. : 258n.m./2.46 x 10^{2}

M.S. : m/e = 228 (1), 172 (26), 154 (36), 112 (53), 57 (100), 44 (80), 43 (98)

ACC.MASS : m/e = 228.1359 [228.1361 = $C_{12}H_{20}O_4$]

Side Reaction Giving (24) and (25)

Methyl-vinyl-ketone (dried and distilled, 7 gm, 0.1 mole) was added dropwise with stirring to a mixture of t-butyl-acetoacetate (10 gm, 0.07 mole) and sodium methoxide (100 mg) in methanol (2 ml) cooled at 0°C. The temperature only rose slightly, but on warming, an uncontrollable reaction took place. The viscous reaction mixture was diluted with ether (100 ml), washed with dilute sulphuric acid (2 x 50 ml), dried ($MgSO_4$), and removal of ether in vacuo left a residue (11.9 gm) which gave a viscous oil (8 gm) on fractionation.

B.P. : 133°C (0.05 m.m.)

N.M.R. : τ = 6.4 (s, 1H removed by D_2O), 8.5, 8.56 (2s unequal intensity, 0H), 8.88, 9.1 (2s unequal intensity, 3H) plus other peaks

I.R. (film) : cm^{-1} = 3500^{m} broad, 2990^{ms}, 2940^{m}, 1705^{s} broad, 1455^{mw}, 1430^{mw}, 1390^{mw}, 1368^{ms}, 1310^{mw}, 1245^{ms}, 1150^{s}, 925^{w}, 845^{m}

G.L.C. : 2 peaks ratio 4:1 (200°C)

Preparation of Hagemann's Ester (1) by a New Method

The dione (7) (280 gm, 1.4 mole) was mixed with acetic acid (50 gm, 0.84 mole) and pyrrolidine (30 gm, 0.42 mole) was added dropwise with stirring and cooling at 0°C. The mixture was then heated under reflux at 80°C for ½ hour after which there was complete disappearance of starting material (by G.L.C.). The cloudy, red solution was cooled, diluted with ether (200 ml) and washed with N-hydrochloric acid (3 x 50 ml), N-sodium hydroxide (3 x 50 ml), brine (3 x 50 ml), dried ($MgSO_4$) and the solvent

removed in vacuo. Fractionation gave an oil (200 gm, 75%) B.P. 86 - 87°C/ 0.2 m.m. which was over 95% pure by G.L.C. and had an identical R_T to a sample of known Hagemann's ester.

N.M.R. : τ = 4.2 (q, 1, 1H), 5.48 (q, 7, 2H), 6.78 (t, 3, 1H), 7.6 - 7.9 (m, 4H), 8.0 (d, 1, 3H), 8.74 (t, 7, 3H)

I.R. (film) : cm^{-1} = 2983^{m}, 1728^{s}, 1672^{s}, 1633^{m}, 1444^{m}, 1380^{ms}, 1343^{ms}, 1309^{ms}, 1281^{m}, 1250^{s}, 1185^{s}, 1160^{ms}, 1098^{mw}, 1035^{m}, 880^{mw}, 858^{mw}

U.V. : 234 n.m. / 1.35×10^4

Preparation of Methyl-Hagemann's Ester (23)

The dione (21) (80 gm, 0.5 mole) was treated, as above, with acetic acid (20 ml, 0.33 mole) and pyrrolidine (10 gm, 0.14 mole) to give, after fractionation, an oil (53 gm, 72%). G.L.C. showed one main component (85 - 90%) with the same R_T as Hagemann's ester (1).

B.P. : 86 - 90°C (0.2 m.m.)

N.M.R. : τ = 4.18 (q, 1, 1H), 6.29 (s, 3H), 6.74 (t, 3, 1H), 7.6 - 7.85 (m, 4H), 8.0 (d, 1, 3H)

I.R. : cm^{-1} = 2955^{m}, 1740^{s}, 1680^{s}, 1632^{mw}, 1435^{m}, 1379^{mw}, 1332^{mw}, 1308^{w}, 1241^{m}, 1190^{ms}, 1158^{ms}, 1030^{mw}

U.V. : 233 n.m. / 1.27×10^4

M.S. : m/e = 168 (54), 140 (47), 125 (34), 112 (100), 109 (75), 97 (34), 81 (32)

ACC MASS : m/e = 168.0788 [168.1786 = $C_9H_{12}O_3$]

Preparation of t-Butyl Hagemann's Ester (9)

The diketo-ester (21) (75 gm, 0.33 mole) was treated as above with glacial acetic acid (4.5 gm, 0.075 mole) and pyrrolidine (5.0 gm, 0.07 mole) to give an oil (52 gm, 76%) on fractionation, which was approximately 90% pure by G.L.C. Refractionation gave a purer sample.

B.P. : 94°C (0.1 m.m.)

N.M.R. : τ = 4.21 (q, 1, 1H), 6.84 (t, 3, 1H), 7.6 - 7.85 (m, 4H), 8.0 (d, 1, 3H), 8.52 (s, 9H)

I.R. (film)	: cm^{-1} = 2982^{ms}, 2942^{m}, 1624^{s}, 1674^{s}, 1632^{m}, 1395^{m}, 1372^{ms}, 1346^{m}, 1311^{m}, 1283^{m}, 1252^{ms}, 1214^{m}, 1150^{s}, 1033^{mw}, 846^{m}
U.V.	: 234.5n.m. / 1.57×10^{4}
M.S.	: m/e = 210 (1), 156 (22), 137 (20, 110 (23), 109 (30), 57 (100)
ACC MASS	: m/e = 210.1247 [210.1255 = $C_{12}H_{18}O_3$]

Preparation of Ethyl-Hagemann's Ester in Improved Yield

The dione (7) (210 gm, 1.1 mole) was refluxed with a mixture of glacial acetic acid (20 gm, 0.33 mole), pyrrolidine (8.0 gm, 0.11 mole) and 90% methanol/water (440 ml) following the reaction by G.L.C. After 2 hours the reaction was complete and the methanol removed in vacuo. The residue was dissolved in ether (350 ml) and washed with N-hydrochloric acid (3 x 100 ml), dilute potassium carbonate (3 x 100 ml), dried ($MgSO_4$) and the ether removed in vacuo to give a reddish oil (150 gm) which was more than 90% pure by G.L.C. The acid layer from above was re-extracted with dichloromethane to yield another 10 gm of Hagemann's ester (83% overall). The residue (25 gm) in the acid layer was obtained by extraction with dichloromethane at pH 9 as a deep red solid.

Preparation of Ethyl-iso-Hagemann's Ester (26b)

The method described by Heneka[36] was used. The dione (7) was dissolved in dry benzene (50 ml) and the mixture saturated with dry hydrogen chloride (cylinder) at 0°C (green solution). It was stoppered tightly and left overnight at 0°C, after which time a yellow oily layer containing white crystals had separated from the mother liquor. The crystals were filtered off and the filtrate poured on to ice. The benzene layer was thoroughly shaken with sodium carbonate, dried ($MgSO_4$) and the solvent removed in vacuo to yield an oil (19 gm) which consisted of three components by G.L.C. The major one had an R_T identical to Hagemann's ester, whilst one of the others was identical to 3-methyl-cyclohex-2-enone. The oil (which fumed) was heated with excess N,N-dimethylaniline at 140°C for 2 hours, followed by cooling, pouring on to ice and acidifying with 2N-sulphuric acid. The mixture was extracted with ether (3 x 100 ml), the ether layers dried ($MgSO_4$) and solvent removed in vacuo

to leave a residue which fractionated to give an oil (7.3 gm, 40%).

B.P. : 90°C (0.1 m.m.). Lit. 119 - 120°C (3.5 m.m.)

N.M.R. : τ = 4.21 (q, 1, 1H), 5.85 (q, 7, 2H), 6.86 (m, 1H), 7.5 - 7.9 (m, 4H), 8.03 (broadened s, 3H), 8.74 (t, 7, 3H)

I.R. : cm^{-1} = 2980^{mw}, 2940^{mw}, 1740^{s} 1680^{s}, 1636^{mw}, 1380^{m}, 1372^{m}, 1355^{mw}, 1308^{ms}, 1284^{mw}, 1246^{mw}, 1210^{m}, 1172^{s}, 1152^{ms}, 1093^{mw}, 1030^{m}, 882^{mw}

U.V. : 235.5n.m. / 1.37×10^{4}

The white crystals obtained were washed with cold benzene to give .75 gm (4%). Although unstable (darkened and fumed in air) they could be recrystallised (3x from acetone/hexane) to give fine needles which were kept at -20°C.

M.P. : 90°C (dec. with effervescence)

N.M.R. (CD_3OD) : τ = 7.2 - 8.2 (m, $\sim$ 6H), 8.3 (s, 3H)

(d^6DMSO) : τ = 1 (broad $\sim$ 2.5H, rapidly exchanged with D_2O), 7.2 (s, 2H), 7.5 - 8.0 (m, 4H), 8.3 (s, 3H)

[This N.M.R. changed rapidly with the evolution of a gas to give an infinity spectrum

τ = 4.18 (s, 1H), 7.5 - 7.9 (m, $\sim$ 6H), 8.03 (s, $\sim$ 3H)]

I.R. : cm^{-1} = $3400 - 2300^{m}$ (broad), 1655^{s}, 1592^{s} (broad), 1445^{s}, 1413^{mw}, 1382^{mw}, 1338^{mw}, 1323^{m}, 1292^{ms}, 1225^{s}, 1154^{mw}, 1125^{mw}, 1080^{mw}

(Nujol) : cm^{-1} = 1660^{s}, 1595^{s}, 1378^{ms}

U.V. : 250n.m. / 4.65×10^{3} [treatment with 1 drop N-NaOH gave a new spectrum 234n.m. / 7.8×10^{3}]

M.S. : m/e = 192 (8), 190 (18), 174 (27), 172 (41), 148 (22), 146 (33), 111 (47), 95 (59), 82 (100), 68 (77), 55 (153), 44 (180)

ACC.MASS : m/e = 190.0386 [190.6396 = $C_8H_{11}O_3Cl^{35}$]

Structural Evidence for Crystals

Diazomethane[81] (.31 gm, in 30 ml ether) was added to the recrystallised compound (240 mg, 1.25 m.mole) cooled in a flask at -20°C.

The crystals dissolved with effervescence and the excess diazomethane was decomposed after 5 minutes with glacial acetic acid at -10°C. The solvents were removed in vacuo (freeze drier) and the resultant oily residue (260 mg, 100%) had the following N.M.R. : τ = 6.23 (s, 3H), 7.48 (s, 2H), 7.23 - 8.1 (m, 4 - 5H), 8.34 (s, 3H).

This residue (250 mg) in methanol was treated with sodium methoxide solution (100 mg/5 ml MeOH), following the reaction by the increase in absorption at 234 n.m., which ceased to change after 1 hour at room temperature. The mixture was acidified (N-hydrochloric acid) and extracted with dichloromethane to yield a residue (210 mg, 100%), after drying ($MgSO_4$) and removal of solvent in vacuo.

N.M.R. : τ = 4.18 (broadened s, 1H), 6.32 (s, 3H), 6.77 (m, 1H), 7.5 - 7.9 (m, 4H), 8.02 (s, 3H)

I.R. : cm^{-1} = 2955^{mw}, 1748^{s}, 1680^{s}, 1638^{mw}, 1435^{m}, 1380^{mw}, 1360^{mw}, 1310^{m}, 1210^{mw}, 1190^{mw}, 1170^{ms}, 1153^{ms}, 1078^{w}, 1025^{mw}, 880^{w}

Preparation of Methyl-iso-Hagemann's Ester (26a)

This was prepared in a similar manner to the ethyl-ester (26b) from the dione (21) (5 gm, 0.027 mole) to yield, after fractionation, an oil (2 gm, 40%).

B.P. : 85 - 90°C (0.1 m.m.)

N.M.R. : τ = 4.18 (broad a, 1H), 6.32 (s, 3H), 6.76 (m, 1H), 7.51 - 7.9 (m, 4H), 8.03 (s, 3H)

I.R. : cm^{-1} = 2956^{mw}, 1747^{s}, 1680^{s}, 1636^{mw}, 1435^{m}, 1380^{mw}, 1360^{mw}, 1310^{s}, 1210^{mw}, 1190^{mw}, 1170^{ms}, 1154^{ms}, 1080^{w}, 1026^{mw}, 880^{mw}

U.V. : 235 n.m. / 1.3×10^4

Preparation of Enamine (40b)

(a) The dione (7) (20 gm, 0.1 mole) was treated with pyrrolidine (7.4 gm, 0.11 mole). There was an exothermic reaction and the mixture turned yellow, finally solidifying. The residue was dissolved in N-hydrochloric acid extracted with ether. After drying the ether layer ($MgSO_4$) and removal of solvent in vacuo, there was a residue (0.5 gm, 2.5%) which was mainly starting material (G.L.C.).

The acidic aqueous layer was made alkaline (saturated sodium carbonate) and the precipitated solid filtered and pumped dry (21 gm, 85%). Extraction of the mother liquor gave another 2 gm of material. Recrystallisation (3x from hexane) gave yellow plates which discoloured in air.

M.P. : 71 - 71.5°C

(b) The above preparation was repeated using Hagemann's ester (1) under identical conditions to give a yellow crystalline solid (85%).

M.P. : 71°C

N.M.R. :

	(a)	(b)
τ =	5.58 (s, 1H)	5.59 (s, 1H)
	5.98 (q, 7, 2H)	5.98 (q, 7, 3H)
	6.77 (m, 4H)	6.78 (m, 4H)
	7.53 - 7.83 (m, 4H)	7.53 - 7.80 (m, 4H)
	7.89 (s, 3H)	7.9 (s, 4H)
	8.77 (t, 7, 3H)	8.78 (t, 7, 3H)

I.R. : cm^{-1} =

(a)	(b)
3058^{w}	3060^{w}
2985^{s}	2986^{s}
2888^{ms}	2890^{ms}
2842^{ms}	2850^{ms}
1675^{s}	1678^{s}
1613^{m}	1613^{m}
1480^{s}	1480^{s}
1460^{ms}	1460^{ms}
1350^{s}	1350^{s}
1320^{mw}	1319^{mw}
1280^{s}	1280^{s}
1268^{s}	1268^{s}
1200^{s}	1200^{s}
1108^{s}	1109^{s}
1073^{s}	1075^{s}

+ other bands all corresponding.

Analytical N.M.R. : τ = 5.53 (3, 1H), 5.92 (q, 7, 2H), 6.72 (m, 4H), 7.48 - 7.78 (m, 4H), 7.86 (s, 3H), 7.94 - 8.18 (m, 4H), 8.73 (t, 7, 3H)

Analytical I.R. : cm^{-1} = 2983^{ms}, 2883^{ms}, 2860^{ms}, 1683^{s}, 1615^{m}, 1520^{s}, 1485^{s}, 1465^{m}, 1394^{mw}, 1353^{ms}, 1323^{mw}, 1283^{s}, 1270^{s}, 1205^{s}, 1111^{s}, 1085^{s}, 942^{w}, 895^{w}

U.V. : 386n.m. / 3.16×10^4

M.S. : m/e = 235 (98), 206 (15), 190 (42), 166 (100)

ACC MASS : m/e = 235.1561 (235.1572 for $C_{14}H_{21}NO_2$)

Preparation of Enamine (40a)

(a) This was prepared using identical conditions to those above from dione (21) (5 gm, 0.027 mole) and pyrrolidine (2 gm, 0.028 mole) to yield a yellow crystalline solid (6 gm, 96%).

(b) A similar preparation using methyl-Hagemann's ester (23) (5 gm, 0.03 mole) and pyrrolidine (2.2 gm, 0.031 mole) gave a yellow crystalline solid (5.8 gm, 97%) identical to that from (a) by N.M.R. and I.R. Recrystallisation (hexane 3x) gave yellow plates which discoloured in air.

M.P. : 85°C

N.M.R. : τ = 5.54 (s, 1H), 6.41 (s, 3H), 6.72 (m, 4H), 7.5 - 7.8 (m, 4H), 7.88 (s, 3H), 7.93 - 8.18 (m, 4H)

I.R. : cm^{-1} = 3060^{w}, 2980^{ms}, 2958^{ms}, 2885^{m}, 2855^{m}, 1683^{s}, 1615^{m}, 1518^{s}, 1483^{s}, 1460^{m}, 1430^{s}, 1375^{m}, 1353^{ms}, 1320^{mw}, 1285^{s}, 1272^{s}, 1210^{s}, 1185^{s}, 1113^{s}, 1085^{s}, 975^{w}, 885^{mw}

U.V. : 386n.m. / 3.07×10^4

M.S. : m/e = 221 (66), 206 (15), 190 (42), 162 (100)

ANALYSIS : %

C	H	N	
70.54	8.58	6.29	Found
70.55	8.65	6.33	Calc. for $C_{13}H_{19}NO_2$

Preparation of Enamine (40c)

(a) The dione (22) (5 gm, 0.026 mole) was treated with pyrrolidine (2 gm, 0.027 mole) as above to give a yellow crystalline solid (6 gm, 95%).

(b) The Hagemann's ester (9) (5 gm, 0.027 mole) was similarly treated with pyrrolidine (2.2 gm, 0.031 mole) to yield a yellow crystalline solid (6 gm, 92%).

The products were identical by N.M.R. and I.R. Recrystallisation (3x from hexane) gave yellow needles which decolourised in air.

M.P. : 79 - 80°C

N.M.R. : τ = 5.58 (s, 1H), 6.72 (m, 4H), 7.55 - 7.8 (m, 4H), 7.93 (s, 3H), 7.93 - 8.2 (m, 4H), 8.55 (s, 9H)

I.R. : cm^{-1} = 3060^{w}, 2980^{ms}, 2940^{mw}, 2880^{mw}, 2860^{mw}, 1680^{s}, 1613^{mw}, 1522^{s}, 1485^{s}, 1455^{m}, 1430^{m}, 1390^{m}, 1368^{ms}, 1352^{ms}, 1320^{w}, 1295s, 1280^{s}, 1250^{mw}, 1220^{s}, 1168^{s}, 1113^{s}, 1080^{ms}, 940^{w}, 898^{w}

U.V. : 383 n.m. / 2.44×10^{4}

M.S. : m/e = 263 (46), 206 (100), 190 (43), 162 (93)

ANALYSIS : %

C	H	N	
72.83	9.45	5.46	Found
72.96	9.57	5.32	Calc. for $C_{16}H_{25}NO_2$

Hydrolysis of Enamine (40b)

1. The enamine (1.2 gm) was refluxed with 2N-hydrochloric acid for 1 hour under nitrogen. This was then extracted with ether (which gave 100 mgs material) and was then made alkaline with saturated sodium carbonate. Extraction with dichloromethane, drying the dichloromethane layer ($MgSO_4$) and removal of solvent in vacuo gave a residue (1 gm, 83%) which was starting material (N.M.R., I.R.).

2. Shaking 1 gm with 70% acetic acid at room temperature for $2\frac{1}{2}$ days gave over 95% recovery of starting material.

3. The enamine (0.5 gm) was refluxed under nitrogen for 40 mins., with 98% acetic acid/water. Work-up as in 1. above gave over 85% recovery of starting material.

Mechanistic Experiments

(a) 3-carbomethoxy-hepta-2,6-dione (21) (100 mg, 0.57 m.mole) was dissolved in tetradeuteromethanol (0.5 ml) and the N.M.R. spectrum taken. Pyrrolidine (40 mg, 0.57 m.mole) was added with a syringe, the solution vigorously shaken and the N.M.R. run continuously. After 8 spectra ($\simeq$ 15 minutes) all the pyrrolidine had been used up and a further 1 drop added. An infinity spectrum after 24 hours was taken and also a spectrum of pyrrolidine in methanol.

N.M.R. spectra :

1. Pyrrolidine/methanol : τ = 6.98 - 7.25 (m, 4H), 8.1 - 8.4 (m, 4H)
2. Dione in CD_3OD : τ = 6.25 (s), 6.35 (t, 7), 7.51 (t, 7), 7.78, 7.88 (2s of equal intensity), 8.05 (t, 7)
3. Immediately after addition : τ = 5.34 (s, CD_3OH), 6.28 (s), 6.98 - 7.3 (m), 7.51 (t), 7.78, 7.89 (2s unequal intensity), 8.0 - 8.4 (m), 8.68, 8.74 (2s unequal intensity)
4. 2nd run (after 1 minute) : τ = 6.29 (s), 6.39 (s), 6.74 (m), 7.10 (m), 7.44 - 7.73 (broad m), 7.84 (broad s), 7.90 (s), 7.95 - 8.44 (m), 8.68, 8.74 (2s unequal intensity)
5. After all pyrrolidine used : τ = 5.32 (s), 6.25 (s, small), 6.35 (s), 6.7 (m), 7.55 (broad s), 7.8 (s), 7.94 - 8.22 (m), 8.68, 8.74 (2s unequal intensity)
6. Infinity : τ = 5.32 (s), 6.39 (s), 6.68 (m), 7.55 (m), 7.8 (s), 7.94 - 8.18 (m)

(b) Treatment of Methyl acetoacetate with Pyrrolidine

Methyl acetoacetate (100 mg), dissolved in tetradeuteromethanol (0.5 ml), was treated with excess of pyrrolidine in an N.M.R. tube. After 15 minutes there was no further change in the N.M.R.

: τ = 5.55 (s, 1H), 6.42 (s, 3H), 6.75 (m, 4H), 7.58 (s, 3H), 7.90 - 8.18 (m, 4H) + pyrrolidine protons.

Michael Addition of Nitroethane to Hagemann's Ester in Aprotic Solvents

Ethyl Hagemann's ester (5 gm, 0.028 mole), nitroethane (B.P. 113°C) (5 gm, 0.072 m.mole) and potassium t-butoxide (1.3 gm, 0.0117 mole) in DMSO (dried over calcium hydride, 6 ml) were stirred under nitrogen at

40°C. Samples (1 ml) were taken out at intervals, acidified with N-hydrochloric acid, extracted (dichloromethane) and the solvent removed in vacuo. 1 μl samples were analysed by G.L.C. at 150°C, the ratio of the peaks being determined by weighing.

Time (hours)	Ratio Hagemann's/Nitro
19.5	2.5 : 1
44.5	2.2 : 1
49	1.7 : 1
68	1.5 : 1
∞	1.5 : 1

The equilibrium mixture was an approximately 50/50 mixture when compared with a calibration mixture of known composition.

Michael Additions to the Three Hagemann's Esters

1. Methyl Hagemann's ester (redistilled 10 gm, 0.06 mole), nitroethane (10 gm, 0.138 mole) and benzyl-trimethylammonium methoxide (9.0 ml of a 1.98 m.mole/ml solution in methanol) were heated with stirring, under nitrogen at 40°C. The reaction was followed by removing samples (2.5 ml) at intervals of 1 day. These were acidified with N-hydrochloric acid, extracted with dichloromethane, the dichloromethane dried ($MgSO_4$) and the solvent removed in vacuo. 5 μl samples were then analysed by G.L.C. Calibration with an equimolar mixture of ethyl Hagemann's ester and ethyl nitro-compound allowed the relative concentration of starting material and product to be determined. The reaction showed no further progress after about 94 hours when there was (by peak-height analysis) 40% of Michael adduct. Working-up the total reaction mixture as were the sample and pumping on the freeze drier, gave a viscous red oil (11 gm, ~85%).

N.M.R. : τ = 4.18 (q,1,.45H), 5.05, 5.35 (2q ratio 40:60, 7, .55H), 4.28 (s, 3H) + other peaks

2. Ethyl Hagemann's ester (10 gm, 0.055 mole), nitroethane (10 gm, 0.0138 mole) and benzyl-trimethylammonium ethoxide (11.5 ml of a 1.47 m.mole/ml

of a solution in ethanol) were stirred and followed exactly as in 1. The reaction was over in 94 hours and work-up gave a viscous red oil (11 gm, $\simeq$ 85%).

N.M.R. : τ = 4.18 (q, 1, .45H), 5.05, 5.35 (2 q ratio 40:60, 7, .55H), 5.82 (q, 7, 2H)

3. t-Butyl Hagemann's ester (redistilled 10 gm, 0.048 mole), nitroethane (10 gm, 0.0138 mole) and benzyl-trimethylammonium-t-butoxide (11.6 ml of 1.38 m.mole/ml solution in t-butanol) were stirred and followed as in 1. Work-up gave a viscous red oil (10.5 gm, $\simeq$ 85%) which was a 40:60 mixture of Michael adduct and starting ester (G.L.C.).

Preparation of t-Butyl Nitro-Compound (8) on a Large Scale

t-Butyl Hagemann's ester (9) (redistilled 48 gm, 0.23 mole), nitroethane (48 gm, 0.66 mole) and benzyl-trimethylammonium t-butoxide (60 ml of a 1.38 m.mole/ml solution in t-butanol) were heated with stirring under nitrogen, at 40°C for 4½ days. The mixture was cooled, diluted with ether (500 ml) and washed with N-hydrochloric acid (3 x 100 ml), N-sodium hydroxide (3 x 100 ml), brine (3 x 100 ml), dried (Na_2SO_4) and concentrated to give a crude residue (53 gm). This was fractionated (0.1 m.m.) to give

1. 96 - 110°C 30 gm pure starting material
2. 156 - 160°C 18 gm

N.M.R. (fraction 2) : τ = 4.97, 5.26 (2q ratio 40:60, 7, 1H), 8.42, 8.47 (2d, 7, 3H), 8.50 (s, 9H), 8.86, 8.90 (2s, 3H)

Standing at 0°C overnight followed by treatment with pentane/ether gave a crystalline compound (9 gm, 50%) which was recrystallised (3x pentane/ether) to give needles.

M.P. : 94.5°C

N.M.R. ($CDCl_3$) : τ = 5.21 (q, 7, 1H), 7.1-7.95 (m, 7H), 8.83 (d, 7, 3H), 8.48 (s, 9H), 8.86 (s, 3H)

I.R. : cm^{-1} = 2940^{mw}, 1720^{s} (doublet), 1553^{s}, 1458^{mw}, 1390^{m}, 1371^{ms}, 1342^{mw}, 1300^{m}, 1149^{s}, 1105^{mw}

U.V. : 282 n.m. / 78.5 + end absorption

M.S. : m/e = 285 (0.002), 270 (0.004), 211 (19), 183 (18), 181 (15), 165 (10), 155 (11), 153 (10), 137 (13), 109 (10), 95 (15), 69 (11), 57 (100), 55 (19), 41 (26)

ANALYSIS : %	C	H	N	
	59.08	8.05	4.91	Found
	58.93	8.13	4.91	Calc. for $C_{14}H_{23}NO_5$

The mother liquor still contained some of the crystalline material by N.M.R.

Hydrolysis of the t-Butyl Ester (9)

1. The t-butyl-nitro ester (150 mg) was left in trifluoroacetic acid in an N.M.R. tube for 1 week. There was no change in the intensity of the peak at 8.37 τ.

N.M.R. (CF_3COOH) : τ = 5.01 (q, 7, 1H), 6.86 (q, 6 and 8, 1H), 7.15 - 7.8 (m, 6H), 8.27 (d, 3H), 8.37 (s, 9H), 8.73 (s, 3H)

2. The t-butyl ester (150 mg, 0.53 m.mole) was dissolved in benzene (1 ml) and para-toluene-sulphonic acid (4 mg, 5%) added. The mixture was refluxed and the N.M.R. taken (after cooling) at intervals of 1 hour. After 11 hours the peak at 8.72 τ had disappeared and the benzene was removed in vacuo to yield 110 mg (92%) of material.

N.M.R. (d^6 Acetone) : τ = 5.03 (q, 7, 1H), 6.8 - 7.8 (m, ~ 7H), 8.33 (d, 7, 3H), 8.90 (s, 3H)

[The N.M.R. (d^6 Acetone) of the acid obtained by alkaline hydrolysis of 2 was τ = 4.88 (q, 7, 1H), 6.9 - 7.9 (m, ~ 7H), 8.47 (d, 7, 3H), 8.84 (s, 3H)].

CHAPTER 2

Nef Reaction of Nitro-Ethyl Compound (3a) (liquid isomer)

The liquid nitro-ethyl ester (10 gm, 0.045 mole) was dissolved in absolute ethanol (50 ml) and a solution of sodium ethoxide in ethanol (0.0455 mole in 12 ml) was added. After 15 minutes at room temperature, the deep red solution was added very slowly, dropwise with good stirring at $0^{o}C$ to 17N-sulphuric acid (100 ml). After addition ($\frac{3}{4}$ hour) the mixture was diluted with water (200 ml) and extracted with dichloromethane (2 x 200 ml). The combined dichloromethane layers were dried ($MgSO_4$) and the solvent removed in vacuo to give a residue (7.75 gm) which was one main component with no starting material (T.L.C.) A further extraction of the aqueous layer with dichloromethane gave 0.4 gm of material and in subsequent preparations the ethanol was removed in vacuo before extraction.

Chromatography (230 gm, silica gel) gave an oil (6.2 gm, 70% 5:1 CH_2Cl_2/ethyl acetate) which was homogeneous by T.L.C. This was sublimed at 0.01 m.m. on to a cold finger to give a colourless viscous oil.

N.M.R.	: τ = 5.81 (q, 7, 2H), 6.67 (q, 5 and 10, 1H), 7.3-8.0 (m, 6H), 7.78 (s, 3H), 8.72 (t, 7, 3H), 8.75 (s, 3H)
I.R. ($CHCl_3$)	: cm^{-1} = 2980^{m}, 1715^{s}, 1375^{mw}, 1358^{m}, 1328^{w}, 1302^{mw}, 1178^{m}, 1160^{m}, 1118^{mw}, 1098^{w}, 1033^{m}, 965^{w}
U.V.	: 287n.m./71.5
M.S.	: m/e = 226 (20), 184 (34), 183 (36), 181 (48), 154 (24), 151 (26), 111 (24), 110 (100), 109 (52), 85 (24), 81 (22), 55 (45), 43 (110)
ACC.MASS	: 226.1208 (226.1205 for $C_{12}H_{18}O_5$)

ANALYSIS :

% C	H	
63.90	7.98	Found
63.70	8.02	Calc. for $C_{12}H_{18}O_4$

Hydrolysis of the Diketo-Ethyl Ester (4a)

The pure product (4a) from above (0.890 gm, 4 m.moles) was refluxed

with a mixture of 2N-sulphuric acid (20 ml) and dioxan (10 ml) for 36 hours under nitrogen. The pH was brought to 8 (bicarbonate) and the mixture extracted with ether. N-hydrochloric acid was added until the pH was 1 and the mixture extracted with ethyl acetate (2 x 75 ml). The combined ethyl acetate layers were dried ($MgSO_4$) and the solvent removed in vacuo to give a crystalline residue (540 mg, 70%). Recrystallisation from ethyl acetate (3x) gave plates.

M.P. : 158°C

N.M.R. (CD_3OD) : τ = 6.5 (q hidden by solvent), 7.2 - 8.0 (m, 6H), 7.76 (s, 3H), 8.77 (s, 3H)

I.R. (Nujol) : cm^{-1} = $3250-2200^{m}$ (broad), 1716^{s}, 1705^{s} (Sh), 1693^{s}, 1420^{m}, 1322^{mw}, 1309^{w}, 1283^{mw}, 1252^{m}, 1225^{mw}, 1208^{mw}, 1166^{w}, 1134^{w}, 1120^{mw}, 1066^{w}, 1020^{w}, 1012^{w}, 972^{w}, 963^{w}, 945^{w}, 926^{w}, 895^{w}, 760^{w}

I.R. (Nujol from CD_3OD) : cm^{-1} = 2225^{m}, 2090^{m}, 1715^{s} (Sh), 1690^{s}, 1415^{m}, 1356^{m}, 1288^{m}, 1260^{m}, 1225^{m}, 1206^{m}, 1165^{mw}, 1133^{w}, 1119^{m}, 1050^{m}, 1019^{m}, 970^{mw}, 959^{mw}, 922^{m}, 885^{w}, 760^{w}

U.V. : 287 n.m. / 60

M.S. : m/e = 198 (5), 170 (16), 155 (17), 154 (14), 152 (14), 141 (18), 127 (13), 111 (12), 110 (42), 85 (40), 84 (24), 81 (17), 68 (13), 67 (11), 55 (19), 43 (100), 41 (18)

ACC.MASS : m/e = 198.0901 (198.0892 for $C_{10}H_{14}O_4$)

ANALYSIS :

C	H	
60.32	7.14	Found
60.59	7.12	Calc. for $C_{10}H_{14}O_4$

Nef Reaction of Nitro-Ethyl Ester (3a) (crystalline isomer)

The crystalline ester (3a) (500 mg, 1.95 m.mole) was treated with sodium ethoxide (2 m.moles) in ethanol (6 ml) and added to 17N-sulphuric acid (25 ml) as for the Nef reaction on the liquid isomer. An oil (300 mg, 70%) was obtained which was identical to (4a) by T.L.C.

N.M.R. : τ = 5.80 (q, 7, 2H), 6.68 (q, 5 and 10, 1H) 7.3 - 8.0 (m, 6H), 7.79 (s, 3H), 8.72 (t, 7, 3H), 8.76 (s, 3H)

Hydrolysis of the Diketo-Ester Obtained from Crystalline (3a)

The product from the above reaction (200 mg, 0.95 m.mole) was refluxed with a mixture of 2N-sulphuric acid (5 ml) and dioxan (3 ml) for 24 hours under nitrogen. It was worked-up as for the acid (4b) to yield a crystalline compound (150 mg, 86%) which had M.P. 156°C after re-crystallisation (1x) from ethylacetate.

N.M.R. (CD_3OD) : τ = 6.50 (q, hidden), 7.2 - 8.0 (m, 6H), 7.75 (s, 3H), 8.76 (s, 3H)

I.R. (Nujol of N.M.R. residue) : cm^{-1} = 2225^{m}, 2090^{m}, 1714^{s} (Sh), 1690^{s}, 1416^{m}, 1356^{m}, 1288^{m}, 1260^{m}, 1226^{m}, 1207^{m}, 1165^{mw}, 1131^{w}, 1118^{m}, 1049^{m}, 1020^{m}, 970^{mw}, 959^{mw}, 922^{m}, 885^{w}, 760^{w}

Equilibration of the Liquid Diastereomer of the Nitro-Ethyl Ester (3a)

The liquid nitro-ethyl ester (100 mg, 0.4 m.mole containing 5% of epimer) was dissolved in carbon tetrachloride (0.4 ml) and trimethylamine (0.1 ml) added at -10°C in an N.M.R. tube. The tube was sealed and allowed to warm up to the temperature of the N.M.R. probe (35°C). The spectrum was taken at day intervals for 2 weeks.

N.M.R. initial : τ = 5.32 (q, 7), 5.81 (q, 7), 6.6 - 7.8 blocked 8.44 (d, 7), 8.70 (t, 7), 8.91 (s)

+ 5% : τ = 5.03 (q, 7), 8.52 (d, 7), 8.85 (s)

N.M.R. after 2 weeks : τ = 5.00, 5.28 (2q, 7, equal intensity), 5.77 (q, 7), 8.42, 8.49 (2d, 7, equal intensity), 8.83, 8.91 (2s, equal intensity)

Attempted Nef Reaction on Nitro-Acid (3b)

Sodium hydride (150 mg, 6 m.mole) was added to pure recrystallised nitro-acid (185 mg, 0.83 m.mole of acid from alkaline hydrolysis) in dimethyl-formamide (dried, 5 ml). After stirring (10 mins.) the mixture was added slowly dropwise with stirring to 17N-sulphuric acid (25 ml) at 0°C. Dilution with water (150 ml) and extraction with ethylacetate (4 x 50 ml), drying the organic layers ($MgSO_4$) and removal of solvent in vacuo gave a crystalline compound (180 mg) containing dimethylformamide (10 mg) (by N.M.R. integration), thus giving a recovery of 92%.

N.M.R. (d^6 Acetone) : τ = 4.78 (q, 7, 1H), 7.2 - 7.8 (m), 8.45 (d, 7, 3H), 8.82 (s, 3H)

Degradation of Isoxazole (7)

The crude isoxazole (Cornforth) was sublimed at 160°C and 0.1 m.m. to give crystals

M.P.	: 209°C
N.M.R. (d^5 pyridine)	: τ = 1.38 (s, 1H), 5.4 (d, 2AB, 1H). 5.68 (d, 2AB, 1H), 6.97 (s, 2H), 7.0-7.4 (m, 3H), 8.88 (s, 3H)
I.R. (Nujol)	: cm^{-1} = 3190^m, 3100^w, 1720^s, 1665^s, 1623^w, 1446^m, 1402^w, 1330^{mw}, 1306^{mw}, 1270^m, 1249^m, 1230^w, 1211^w, 1199^{mw}, 1168^m, 1138^m, 1084^w, 947^w, 940^w, 913^w, 905^w, 850^m
U.V.	: 224n.m. / 1.28×10^4
M.S.	: m/e = 204 (100), 189 (43), 161 (14), 146 (11), 144 (19), 134 (12), 123 (17)

The sublimed isoxazole (50 mg, 0.25 m.mole) was dissolved in methanol (5 ml) and a solution of sodium methoxide (100 mg) in methanol (2 ml) was added. The reaction was monitored by sampling, diluting with methanol and running a U.V., following the decrease in absorption at 224n.m. and the increase at 264n.m. After 18 hours no more change was observed and the solution was acidified with N-hydrochloric acid, the methanol removed in vacuo, the residue diluted with water (50 ml) and extracted with ethylacetate (3 x 25 ml). The organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to leave a gummy residue (55 mg).

I.R. (Nujol)	: cm^{-1} = 3450^m (broad), 2200^w, 1680^s

This residue was dissolved in a mixture of dioxan (20 ml) and 10%-hydrochloric acid and the mixture refluxed for 3 days under nitrogen. After cooling, it was made alkaline with sodium carbonate and extracted with ethylacetate (2 x 20 ml). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to give a residue (20 mg) which had no peaks at 3450 or 2200 in the I.R.

The alkaline aqueous layer was made acid (N-hydrochloric) and extracted with ethylacetate (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to give a residue (30 mg). This

residue was treated with 3% HCl/methanol overnight and the solvents removed in vacuo to give an oil (35 mg). This had six components by T.L.C. Preparative T.L.C. (silica gel 10:1 CH_2Cl_2 / ethylacetate 1x) allowed the separation of a fairly pure component (7 mg) with an R_f identical to authentic methyl-keto ester (10). The I.R., however, was substantially different.

Hypobromite Oxidation of the Keto-Acid (4b)

An alkaline hypobromite solution was made according to a literature[50] procedure and contained 0.57 m.mole/ml by titration. The recrystallised acid (4b) (50 mg, 0.25 m.mole) was converted into its salt with aqueous sodium hydroxide (10 mg., 0.25 m.mole) and sodium hypobromite solution (1.32 ml, 0.75 m.mole) added at 0°C with stirring. The mixture was allowed to warm up to room temperature and stirred for 15 mins. Acidification with N-hydrochloric acid, extraction with ethylacetate (3 x 25 ml), drying the organic layer and removal of solvent in vacuo gave a residue (45 mg, 90%) which was treated with methanolic hydrogen chloride for 2 days. Removal of solvent in vacuo gave an oil (50 mg) which was a complex mixture of at least six components by T.L.C.

Hypobromite Oxidation of the N,N-Dimethylhydrazone of the Diketo-Ester (4a) and Degradation to the Dimethyl-Ester (16)

Purified keto-ester (4a) (1 gm, 4.4 m.mole) was mixed with unsym-dimethylhydrazine (Koch-Light B.P. 63°C, 300 mg, 5 m.moles) and an exothermic reaction took place (water droplets). After 15 mins the water and any excess hydrazine were removed by pumping in vacuo for two days to give an oil (1.22 gm, 103%). This showed two components by T.L.C., one very polar and one with a similar R_f to starting ketone.

N.M.R. : τ = 5.83 (q, 7, $\simeq$ 2H), 5.81 (q, $\simeq$ 20% of 5.83), 6.8-7.0 (m, $\simeq$ 2H), 7.61 (s), 7.63 (2s, 1 c.p.s. apart), 7.78 (s, $\simeq$ 3H), 8.76 (t, 3H), 8.75 (t, $\simeq$ 20% of 8.76), 8.82 (s, 3H)

I.R. ($CHCl_3$) : cm^{-1} = 2990^{ms}, 2962^{ms}, 2915^{m}, 2870^{m}, 2830^{mw}, 2784^{mw}, 1725^{s}, 1709^{s}, 1642^{mw}, 1471^{m}, 1455^{m}, 1390^{w}, 1378^{m}, 1360^{m}, 1330^{w}, 1310^{mw}, 1268^{s}, 1163^{m}, 1120^{w}, 1110^{mw}, 1035^{m}, 980^{mw}, 898^{w} 862^{w}

Without purification the hydrazone was dissolved in dioxan (30 ml) and, after cooling to 0°C, alkaline hypobromite (15.5 ml, 15 m.mole) was added dropwise with stirring. The mixture was left for ½ hour at 0°C and then ½ hour at room temperature. N/10 thiosulphate (10 ml) was added and the mixture acidified to pH 6 with N-hydrochloric acid. After addition of dioxan (50 ml), refluxing with excess methyl iodide (5 ml) for 1½ hours and concentration to 25 ml in vacuo, the mixture was made alkaline with sodium bicarbonate and extracted with dichloromethane (2 x 50 ml). The combined dichloromethane layers were dried and solvent removed in vacuo to give a residue (250 mg) which was mainly starting keto-ester (4a) by T.L.C.

The alkaline aqueous layer was acidified with 10% hydrochloric acid, extracted with ethylacetate (3 x 50 ml) and the ethylacetate layer dried ($MgSO_4$), the solvent removed in vacuo to give a residue (300 mg). Evaporation of the aqueous layer to dryness and extraction with ethylacetate (2 x 50 ml) gave a residue (230 mg). The two residues combined (530 mg) had a T.L.C. showing 3 components. Overall mass recovery was 78%.

The acidic residues (530 mg) were dissolved in a mixture of dioxan (10 ml) and 2N-sulphuric acid (10 ml) and refluxed for 24 hours under nitrogen. After cooling, the mixture was extracted with ethylacetate (3 x 50 ml), the organic layers dried ($MgSO_4$) and the solvent removed in vacuo to give a residue (220 mg). This residue was dissolved in 3% hydrogen chloride/methanol and left for 2 days at room temperature. The methanol was removed in vacuo to give an oil (200 mg) which showed two spots of approximately equal intensity by T.L.C. The two components were separated by preparative T.L.C. (silica gel 10/1, CH_2Cl_2 / ethylacetate run 3x) and each separate component was purified by one more preparative T.L.C. In this way an oil (30 mg) was obtained having an R_f and I.R. identical to the methyl keto-ester (10).

The other component was obtained as an oil (40 mg), 1 spot by T.L.C. in several solvents and identical in R_f to the authentic samples of (15) and (16).

N.M.R. : τ = 6.33 (s, 3H), 6.35 (s, 3H), 6.8 (q, 5 and 9, 1H), 7.2 - 8.0 (m, 6H), 8.81 (s, 3H)

I.R. : cm^{-1} = 2959^{ms}, 2890^{mw}, 2842^{w}, 1728^{s} (broad), 1460^{mw}, 1435^{ms}, 1423^{mw}, 1368^{m}, 1323^{mw}, 1302 (Sh), 1270 (Sh), 1246^{s}, 1165^{ms}, 1138^{m}, 1112^{m}, 1092^{w}, 1061^{w}, 1030^{mw}, 860^{s}, 692^{mw}

Preparation of Trans-Dimethyl-Ester (16)

A sample of the trans-diketo acid (Cornforth) (52 mg, 0.26 m.mole) was dissolved in 3% HCl/methanol and left for 2 days at room temperature after which time the solvent was removed in vacuo to yield an oil (50 mg) which was mainly one component by T.L.C. Preparative T.L.C. (silica gel, 10/1 CH_2Cl_2/ethylacetate run 3x) gave a colourless oil (35 mg, 63%) which was a single spot by T.L.C. in several solvents.

N.M.R. : τ = 6.33, 6.55 (2s, 3H), 6.8 (q, 5 and 9, 1H), 7.2 - 8.0 (m, 6H), 8.81 (s, 3H)

I.R. : cm^{-1} = 2959^{ms}, 2890^{mw}, 2842^{w}, 1728^{s} (broad), 1460^{mw}, 1435^{ms}, 1423^{mw} (sh), 1368^{m}, 1323^{mw}, 1302^{mw}, 1272^{m}, 1246^{s}, 1164^{ms}, 1138^{m}, 1112^{m}, 1092^{w}, 1061^{w}, 1030^{mw}, 860^{s}, 690^{mw}

Preparation of cis-Dimethyl-Ester (15)

The cis-cyano-ethyl ester (11) (Cornforth) (100 mg, 0.48 m.mole) was refluxed with a mixture of dioxan (5 ml) and 2N-sulphuric acid (5 ml) for 4 days under nitrogen. After cooling, the mixture was extracted with ethylacetate (3 x 50 ml), the organic layers dried ($MgSO_4$), the solvent removed in vacuo and the residue treated with excess of ethereal diazomethane. Decomposition of excess diazomethane with 10% acetic acid, washing the ether layer with saturated sodium bicarbonate, drying ($MgSO_4$) and removal of ether in vacuo gave an oil (65 mg) which was mainly one component by T.L.C. Preparative T.L.C. (silica gel 10/1, CH_2Cl_2/ethylacetate, run 3x) gave an oil (45 mg, 35%) which was one spot by T.L.C. in several solvents and had an identical R_f to the trans-ester (16).

N.M.R. : τ = 6.34, 6.38 (2s, 6H), 6.94 - 7.17 (m, 2H), 7.63 - 7.8 (m, 5H), 8.79 (s, 3H).

I.R. : cm^{-1} = 2959^{ms}, 2890^{mw}, 2842^{w}, 1728^{s} (broad), 1460^{m}, 1435^{ms}, 1433^{mw} (Sh), 1400^{m}, 1380^{mw}, 1365^{m}, 1309^{m}, 1230^{s}, 1193^{ms}, 1171^{ms}, 1138^{mw} 1108^{s}, 1050^{w}, 1020^{mw}, 900^{w}, 860^{s}, 691^{mw}

Preparation of Diketo-Methyl-Ester (10)

Pure diketo-acid (4b) (75 mg, 0.38 m.mole) was dissolved in 3% HCl/methanol and left for 2 days at room temperature. After this time the solvent was removed in vacuo to yield an oil (75 mg). This was one pure component by T.L.C.

I.R. : cm^{-1} = 2960^{m}, 1720^{s} (broad), 1460^{mw}, 1390^{mw}, 1360^{m}, 1330^{mw}, 1300^{mw}, 1665^{mw}, 1119^{mw}, 1100^{w} 1065^{w}, 1030^{mw}, 980^{w}, 965^{w}, 880^{w}

Preparation of Ethylene Ketal (28)

The pure diketo-ester (4a) (1.421 gm, 6.8 m.moles), purified ethylene glycol (0.5 gm, 8 m.moles), p-toluene sulphonic acid (5%) and dry benzene (50 ml) were refluxed together in a Dean and Stark water separator for 18 hours, draining the trap 3 times during the reaction. The cooled mixture was diluted with benzene (40 ml), washed with dilute aqueous potassium carbonate (2 x 50 ml), brine (2 x 50 ml), dried ($MgSO_4$) and the benzene removed in vacuo to give an oil (1.54 gm, 95%). This was sublimed on to a cold finger at 0.01 m.m. to yield an oil (1.4 gm, 87%) which solidified.

N.M.R. : τ = 5.93 (q, 7, 2H), 6.12 (s, 4H), 6.98 (q, 4 and 7, 1H), 7.91 (s, 3H), 8.79 (t, 7, 3H), 8.83 (s, 3H)

I.R. : cm^{-1} = 2979^{ms}, 2955^{ms}, 2878^{m}, 1730^{s}, 1710^{s}, 1443^{mw}, 1365^{m}, 1350^{m}, 1280^{mw}, 1178^{s}, 1122^{s}, 1107^{s}, 1070^{m}, 1042^{ms}, 943^{m}

M.S. : m/e = 270 (7), 228 (15), 227 (54), 226 (19), 225 (38), 186 (15), 185 (75), 184 (34), 183 (15), 181 (14), 156 (14), 153 (18), 141 (19), 139 (16), 113 (28), 109 (17), 99 (100), 87 (33), 86 (67), 43 (29)

ACC MASS : 270.1464 (270.0467 for $C_{14}H_{22}O_5$)

ANALYSIS :

%	C	H	
	61.97	8.20	Found
	62.20	8.05	Calc. for $C_{14}H_{22}O_5$

Degradation of Ketal (28)

The sublimed ketal (1.2 gm, 5.5 m.moles) was treated with alkaline sodium hypobromite (20 ml, 20 m.moles) with stirring at room temperature. Dioxan was added dropwise until the mixture was homogeneous. The yellow

colour faded quickly and the solution turned cloudy. After 15 mins. the pH was 8 and the mixture was warmed at 50°C for 5 mins. After cooling, the solution was made alkaline with N-sodium hydroxide and extracted with ether (2 x 50 ml), which, after drying ($MgSO_4$) and removal of solvent gave a residue (75 mg).

Acidification of the aqueous layer with N-hydrochloric acid, extraction with ethylacetate (4 x 50 ml), drying the organic layers ($MgSO_4$) and removal of solvent in vacuo gave a crystalline residue (737 mg).

N.M.R. ($CDCl_3$) : τ = 5.84 (q, 7, 2H), 6.03 (s, 4H), 6.92 (m, 1H), 8.70 (s, 3H), 8.76 (t, 7, 3H).

I.R. (CH_2Cl_2) : cm^{-1} = $3300-2400^{m}$ (broad), 2938^{ms}, 2886^{ms}, 1730^{s}, 1705^{s}, 1603^{w}, 1368^{m}, 1205^{m}, 1180^{ms}, 1116^{ms}, 1040^{m}, 968^{mw}, 946^{mw}, 870^{mw}

This residue was dissolved in a mixture of dioxan (20 ml) and 20% sulphuric acid (11 ml) and refluxed for 2 days under nitrogen. After cooling the mixture was extracted with ethylacetate (5 x 30 ml), the organic layers dried ($MgSO_4$) and the solvent removed in vacuo to give a brown solid (480 mg).

N.M.R. : τ = 6.70 (s, 2H), 6.67 (q, 5 and 9, 1H), 7.1 - 7.8 (m), 8.72 (s, 3H)

A continuous chloroform extraction on the aqueous layer gave a residue (50 mg) which was different from that above.

The former product was treated with excess of ethereal diazomethane at room temperature. The excess of diazomethane was decomposed with 10% acetic acid and the ether layer was washed with dilute aqueous potassium carbonate (2 x 25 ml), brine (2 x 25 ml), dried ($MgSO_4$) and the ether removed in vacuo to give a light yellow oil (450 mg, 40% from ketal) which was essentially one component by T.L.C. with the same R_f as (15) and (16).

N.M.R. : τ = 6.31, 6.33 (2s, 6H), 6.78 (q, 5 and 9, 1H), 7.15 - 8.05 (m, 6H), 8.78 (s, 3H) impurity at 6.03 (1H)

CHAPTER 3

Preparation of Bromo–Nitro Ketone (15) from Nitro-Isomer (12)

The recrystallised nitro-ester (M.P. 90°C, 2.8 gm, 9.911 mole) was dissolved in dimethylformamide (dried, 50 ml) and sodium hydride (0.31 gm, 0.013 mole) was added with stirring and exclusion of moisture. After ¼ hour, bromine (0.7 ml, 0.013 mole) was added dropwise at room temperature, waiting for decolourisation before addition of another drop. After addition, the red solution was stirred for ½ hour at room temperature. Dilution with water (300 ml), extraction with ether (4 x 75 ml), washing the combined ether layers with dilute thiosulphate (2 x 50 ml), water (3 x 50 ml), drying ($MgSO_4$) and removal of solvent in vacuo gave a gummy residue (2.5 gm, 75%) which crystallised to a yellow solid. In other experiments yields up to 90% were obtained. Recrystallisation (ether/pentane) gave white plates which were homogeneous by T.L.C.

M.P. : 74 - 75°C

N.M.R. : τ = 5.86 (q, 7, 2H), 7.0 (m, 1H), 7.3 - 8.1 (m, 6H), 7.72 (s, 3H), 8.57 (s, 3H), 8.70 (t, 7, 3H)

I.R. (CH_2Cl_2) : cm^{-1} = 2910^{m} (broad), 1712^{s}, 1555^{s}, 1475^{mw}, 1433^{m}, 1193^{ms}, 1116^{m}, 1034^{m}, 856^{mw}

U.V. : 283 n.m. / 94.8 + end absorption

M.S. : m/e = 337, 335 (0.1), 289, 291 (10), 245, 243 (4), 217, 215 (6), 209 (30), 183 (60), 181 (75), 163 (35), 135 (68), 114 (33), 109 (62), 107 (100), 95 (42), 93 (52), 81 (47), 67 (57), 55 (100), 53 (61), 43 (100), 41 (100)

ANALYSIS : %

C	H	N	Br	
42.91	5.62	4.10	23.97	Found
42.87	5.36	4.16	23.79	Calc. for $C_{12}H_{18}NO_5Br$

Preparation of Bromo-Nitro Ketone (15) from Nitro-Isomer (13)

The liquid nitro-ester (885 mg, 34.4 m.moles) in DMF (dry, 15 ml) with sodium hydride (100 mg, 41.7 m.moles) and bromine (0.25 ml, 46.8 m.moles)

to give a gum (1.015 gm, 88%) which crystallised to a brown solid. The N.M.R. after recrystallisation was identical to that from the previous reaction.

Preparation of Ethylene Ketal (25) from Nitro-Isomer (12)

Crystalline nitro-ester (100 mg, 0.375 m.mole) was dissolved in dry benzene (25 ml) and purified ethylene glycol (35 mg, 0.52 m.mole) added along with a crystal of p-toluene sulphonic acid. The mixture was refluxed in a Dean and Stark water separator (18 hours) under nitrogen with the exclusion of moisture. The cooled solution was washed with dilute potassium carbonate (2 x 25 ml), water (1 x 25 ml), dried ($MgSO_4$) and the solvent removed in vacuo to give a colourless oil (115 mg, 100%) which was a single component by T.L.C.

N.M.R. : τ = 5.10 (q, 7, 1H), 5.91 (q, 7, 2H), 6.13 (s, 4H), 7.73 (m, 1H), 7.9-8.4 (m, 6H), 8.55 (d, 7, 2H), 8.74 (t, 1, 3H), 8.80 (s, 3H)

Preparation of Ethylene Ketal (26) from Nitro-Isomer (13)

The liquid nitro-ester (95% pure isomer 1.00 gm, 3.89 m.moles) was dissolved in dry benzene (50 ml) and ethylene glycol (290 mg, 4.67 m.moles) along with a crystal of p-toluene sulphonic acid. The mixture was refluxed in a Dean and Stark water separator (16 hours) and worked-up as for the previous reaction to yield a brown liquid (1.072 gm, 92%) which was one component by T.L.C.

N.M.R. : τ = 5.07 (q, 7, 1H), 5.87 (q, 7, 2H), 6.13 (s, 4H), 7.65 (m, 1H), 7.9-8.4 (m, 6H), 8.48 (d, 7, 3H), 8.75 (t, 7, 3H), 8.91 (s, 3H)

M.S. : m/e = 284 (2), 271 (4), 256 (10), 255 (8), 237 (22), 199 (4), 186 (14), 140 (16), 115 (16), 99 (100), 86 (66).

Bromination of Ethylene Ketal (25)

The ketal (25) (110 mg, 0.366 m.mole) was dissolved in dry t-butanol (20 ml) under nitrogen, in dry conditions, and potassium t-butoxide (48 mg, 0.428 m.mole) was added and the mixture stirred for 15 minutes (yellow). Bromine (66 mg, 0.032 ml, 0.043 m.mole) in t-butanol (5 ml) was added dropwise with a syringe, at such a rate that the first drop had decolourised

before the next drop was added. At the end of the addition there was a white suspension. The mixture was diluted with water (50 ml), extracted with dichloromethane (3 x 25 ml), the organic layers washed with dilute thiosulphate (1 x 25 ml), with water (2 x 25 ml), dried ($MgSO_4$) and the solvent removed in vacuo to give an oil which solidified (122 mg, 88%).

N.M.R. : τ = 5.90 (q, 7, 2H), 6.10 (s, 4H), 7.3-7.6 (m, 1H), 7.65 (s, 3H), 8.0-8.4 (m, 6H), 8.42 (s, 3H), 8.72 (t, 7, 3H)

I.R. ($CHCl_3$) : cm^{-1} = 2940^{s}, 2880^{ms}, 1725^{s}, 1550^{s}, 1442^{m}, 1371^{m}, 1351^{m}, 1328^{m}, 1170^{ms}, 1135^{s}, 1100^{s}, 1015^{m}, 966^{mw}, 949^{mw}

Bromination of Ethylene Ketal (26)

The liquid nitro-ketal (602 mg, 2.00 m.moles) was dissolved in dry t-butanol (25 ml) under nitrogen and with exclusion of moisture and potassium t-butoxide (278 mg, 2.48 m.moles) was added with stirring (15 minutes). Bromine (395 mg, 0.13 ml, 1.22 eq.) in t-butanol was added as in the previous reaction and worked-up to give a gum which crystallised (635 mg, 84%) and which was one spot by T.L.C. Attempts to recrystallise from ether pentane seemed to decompose the compound and it was only partially purified.

N.M.R. : τ = 5.91 (q, 7, 2H), 6.13 (s, 4H), 7.28-7.55 (m, 1H), 7.66 (s, 3H), 8.0-8.4 (m, 6H), 8.43 (s, 3H), 8.73 (t, 7, 3H).

I.R. : cm^{-1} = 2940^{ms}, 2880^{ms}, 1725^{s}, 1550^{s}, 1442^{m}, 1371^{m}, 1351^{m}, 1328^{m}, 1170^{ms}, 1135^{s}, 1100^{s}, 1015^{m}, 966^{mw}, 949^{mw}

M.S. : m/e = 351, 349 (3), 335, 333 (2), 321, 319 (2), 280, 278 (12), 227 (70), 101 (30), 99 (100), 86 (90)

ANALYSIS %	C	H	N	Br	
	44.20	5.88	3.66	20.37	Found
	45.72	5.82	3.66	21.03	Calc. for $C_{14}H_{22}NBrO_6$

Epimerisation Reactions

S-Nitro-Ester (12)

The S-nitro-ester (M.P. 90°C 100 mg, 0.39 m.mole) was dissolved in a suspension of sodium hydride (11 mg, 0.48 m.mole) in dimethylformamide

(dry 5 ml) and the mixture stirred for 1 hour under nitrogen with the exclusion of moisture. The mixture was then added in one go to 5% acetic acid (20 ml) to ensure instantaneous quenching and stirred for 5 minutes. Dilution with water followed by extraction with ether (3 x 30 ml), washing the ether layers with dilute sodium carbonate (1 x 30 ml), water (3 x 30 ml), drying ($MgSO_4$) and removal of solvent in vacuo gave a residue (89 mg, 90%).

N.M.R. : τ = 5.33 (q, 7, 1H), 5.81 (q, 7, 2H), 7.15 - 7.35 (m, 1H), 7.5 - 8.0 (6H), 8.44 (d, 7, 3H), 8.79 (t, 7, 3H), 8.91 (s, 3H)

+ 5% of other isomer

R-Nitro-Ester (13)

The R-nitro-ester (108 mg, 0.4 m.mole) was dissolved in a suspension of sodium hydride (16 mg, 0.7 m.mole) in dimethylformamide (dry 5 ml). The mixture was stirred for $\frac{1}{4}$ hour, then quenched and worked-up as above to yield an oil (99 mg, 91%) which was mainly one spot by T.L.C. The N.M.R. was the same as starting material showing approximately 10% of the S.

R-Nitro-Ethylene-Ketal (26)

The R-ketal (26) (containing 10% S, 110 mg, 0.35 m.mole) was added to a suspension of sodium hydride (16.0 mg, 0.7 m.mole) in dimethylformamide (dry 5 ml). The suspension was stirred for 15 minutes under nitrogen with exclusion of moisture and then quenched as above. Dilution with water, extraction with dichloromethane (3 x 25 ml), washing the organic layers with water (3 x 50 ml), drying ($MgSO_4$) and removal of solvent in vacuo gave an oil (95 mg, 86%) which had an N.M.R. showing the R-ester containing 5% S.

S-Nitro-Ethylene-Ketal (25)

S-ketal (25) (122 mg, 0.4 m.mole) was added to a suspension of sodium hydride (12 mg, 0.5 m.mole) in dimethylformamide (dry 5 ml) and stirred (15 minutes) under nitrogen with the exclusion of moisture. Quenching and work-up as above gave an oil (110 mg, 90%). This had an N.M.R. which showed 60% R and 40% S ketal-esters.

Preparation and Properties of the Nitro-Anion (35)

Sodium hydride (12.7 mg, 0.55 m.mole) was placed in a clean,

dry N.M.R. tube that had been flushed out with nitrogen. The crystalline S-nitro ester (135 mg, 0.53 m.mole) was dissolved in d^6DMSO (0.5 ml) (dried over molecular sieves) in a dry box and the solution transferred to the N.M.R. tube. The reaction was allowed to proceed until frothing ceased (this could also be carried out in a vial followed by transference to the N.M.R. tube) and the N.M.R. recorded. The N.M.R. of the starting material in d^6DMSO was also recorded.

N.M.R. (starting material) : τ = 5.02 (q, 7, 1H), 5.81 (q, 7, 2H), 7.13 (q, 5 and 10, 1H), 7.5 - 8.0 (m, 6H), 8.52 (d, 7, 3H), 8.76 (t, 7, 3H), 8.91 (s, 3H)

N.M.R. (salt) : τ = 5.37 (q, 6 and 9, 1H), 5.80 (d, 13, 1H) 5.90 (q, 7, 2H), 7.5 - 8.1 (m, 6H), 8.11 (s, 3H), 8.80 (t, 7, 3H), 8.92 (s, 3H)

The salt was left for 48 hours at room temperature during which its N.M.R. was run at intervals. The main change was the increase in a peak at 4.0 τ and one at 7.95 τ. The solution was then rapidly mixed with 5% acetic acid and extracted with ether (4 x 20 ml). The combined ether layers were washed with bicarbonate (2 x 20 ml), dried ($MgSO_4$) and the solvents removed in vacuo and pumping (freeze drier) for 1 week.

N.M.R. : τ = 4.2 (s, 20%), 5.45 (q, 7, 1H), 5.83 (q, 7, 2H), 8.46 (d, 7, 3H), 8.71 (t, 7, 3H), 8.91 (s, 3H) and other peaks showing $\simeq$ 10% isomer.

Similar preparation of the salt of the R-nitro-ethyl ester gave an

N.M.R. : τ = 5.44 (q, 6 and 9, 1H), 5.98 (distorted q, 3H), 7.5 - 8.1 (m, 6H), 8.16 (s, 3H), 8.85 (t, 7, 3H), 8.96 (s, 3H)

which was almost identical to that from the S-nitro ester.

Preparation of the Sodium Salt (37) of the R-t-Butyl-Ester (36)

The salt was prepared in a similar manner to the ethyl-nitro ester from crystalline R-t-butyl ester (35) (160 mg, 0.56 m.mole) and sodium hydride (13.1 mg, 0.57 m.mole). The N.M.R. (d^6DMSO) was taken when the reaction had subsided (20 minutes).

N.M.R. (starting material) : τ = 5.25 (q, 7, 1H), 7.09 (m, 1H), 7.5 - 8.0 (m, 6H), 8.43 (d, 7, 3H), 8.54 (s, 9H), 9.0 (s, 3H)

N.M.R. (salt) : τ = 5.62 (q, 5 and 8, 1H), 6.01 (d, 13, 1H), 7.5 - 8.1 (m, $\simeq$ 6H), 8.18 (s, 3H), 8.62 (s, 9H), 8.98 (s, 3H)

Hydrolysis of R-Ketal Ester (26)

The R-ketal ester (12) (153 mg, 0.508 m.mole) was refluxed under nitrogen in 50% methanol/2N sodium hydroxide (20 ml) for 4 hours. The pH was brought to 9 with glacial acetic acid and extracted with ether. The ether layer, after drying ($MgSO_4$) and removal of solvent in vacuo, gave a residue (9 mg).

The aqueous layer was acidified to pH 3 - 4, extracted with chloroform (3 x 25 ml), the chloroform layer dried ($MgSO_4$) and solvent removed in vacuo to give a residue (110 mg, 80%).

N.M.R. : τ = 4.90 (q, 7, 0.4H), 5.00 (q, 7, 0.6H), 6.06 (s, 4H), 7.49 (m, 1H), 7.72 - 8.32 (m, 6H), 8.43 (d, 7, 1.8H), 8.51 (d, 7, 1.2H), 8.72 (s, 1.2H), 8.79 (s, 1.8H)

I.R. ($CHCl_3$) : cm^{-1} = $3400-2300^{mw}$ (broad), 2940^{m}, 2880^{m}, 1710^{s}, 1545^{s}, 1448^{mw}, 1388^{m}, 1360^{m}, 1170^{mw}, 1095^{s}, 962^{m}, 945^{m}, 866^{w}

M.S. : m/e = 273 (1), 237 (16), 199 (24), 140 (20), 99 (100), 86 (66)

Epimerisation of Ketal-Acid (60)

The acid (99.5 mg, 0.364 m.mole) was dissolved in dimethylformamide (dry 5 ml), sodium hydride (25 mg, 1.085 m.mole) added and the mixture stirred (15 minutes). It was quenched as normal and extracted with chloroform (4 x 25 ml). The combined layers were washed with water (4 x 25 ml), dried ($MgSO_4$) and solvent removed in vacuo to give a solid residue (90 mg, 90%).

N.M.R. : τ = 4.94 (q, 7, 1H), 6.06 (s, 4H), 7.37 - 7.67 (m, $\simeq$ 7H), 8.44 (d, 7, 3H), 8.79 (s, 3H) + DMF peaks and 10% of the S-acid

Hydrolysis of Ketal-Acid (60)

The ketal-acid (60 mg, 0.22 m.mole) was dissolved in a mixture of methanol (2 ml) and water (2.5 ml) and concentrated hydrochloric acid (0.6 ml) added. The mixture was stirred (18 hours) under nitrogen, diluted with water and extracted with chloroform (5 x 25 ml). The chloroform layers were dried

($MgSO_4$) and removal of solvent in vacuo gave a gum (40 mg, 80%).

N.M.R. (CD_3OD) : τ = 5.10 (q, 7, 1H), 6.85 - 7.25 (m, $\simeq$ 1H), 7.2 - 8.0 (m, $\simeq$ 6H), 8.38 (d, 7, 3H), 8.92 (s, 3H) + 10% of R-acid peaks at 8.5 τ and 8.85 τ

Epimerisation of R-Keto Acid (58)

Sodium hydride (100 mg, 4.3 m.moles) was added with stirring to (58) (75 mg, 0.33 m.mole) in dimethylformamide and the mixture stirred ($\frac{1}{4}$ hour) under nitrogen with the exclusion of moisture. This was quenched as normal, diluted with water (15 ml) and extracted with chloroform (6 x 10 ml) and ethylacetate (2 x 10 ml). The aqueous layer was vacced down and extracted with ethylacetate (2 x 10 ml).

The combined organic layers were dried ($MgSO_4$) and the solvents removed in vacuo to give a residue (83 mg) containing D.M.F. (13.7 mg) as estimated by N.M.R. The yield was 71 mg (90%).

N.M.R. (d^6Acetone) : τ = 4.85 (q, 7, 1H), 8.46 (d, 7, $\simeq$ 3H), 8.83 (s, 3H) + D.M.F. impurity peaks and 5% R-isomer

Epimerisation of a Mixture of R and S Acids

A 50/50 mixture of R and S acids (250 mg, 1.1 m.mole) was dissolved in dimethylformamide (dry 15 ml) and sodium hydride (200 mg, 2.8 m.moles). The mixture was stirred ($\frac{1}{2}$ hour) under nitrogen with the exclusion of moisture and then worked-up as above to yield a residue (200 mg, 80%) after pumping in vacuo (3 days).

N.M.R. (CH_3OH) : τ = 8.47 (d, 7), 8.85 (s) + 5% R acid.

CHAPTER 4

Relative Configuration of Benzhydrylamine Salt (5a)

The salt (5a) (Cornforth, 60 mg, 0.16 m.mole) was dissolved in 3% sulphuric acid/ethanol (20 ml) and left for 4 days at room temperature. The mixture was diluted with dichloromethane (50 ml) and washed with saturated sodium bicarbonate (2 x 40 ml). The organic layers were dried ($MgSO_4$) and the solvent removed to give a residue (65 mg). This residue was two components by T.L.C. and preparative T.L.C. (0.75 m.m. silica gel, 50:1 CH_2Cl_2 / ethylacetate 3x) gave a single component (27 mg, 80%).

N.M.R. : τ = 4.56 (m, 1H), 5.83 (q, 7, 2H), 7.0 (t, 7, 1H), 7.48 - 8.4 (m, 6H), 8.25 (d, 1, 1H), 8.7 (t, 7, 3H), 8.83 (s, 3H)

I.R. : cm^{-1} = 3050^{w}, 2935^{ms}, 2860^{m}, 2242^{w}, 1740^{s}, 1455^{mw}, 1445^{mw}, 1420^{w}, 1373^{m}, 1350^{mw}, 1298^{mw}, 1255^{m}, 1208^{mw}, 1180^{m}, 1098^{mw}, 1025^{m}, 920^{w}

This was compared with the known ethyl ester (Cornforth) purified by preparative T.L.C. (0.75 m.m. silica gel, 50:1 CH_2Cl_2 /ethylacetate).

N.M.R. : τ = 4.56 (m, 1H), 5.83 (q, 7, 2H), 7.01 (t, 7, 1H), 7.48 - 8.4 (m, 6H), 8.25 (m, 3H), 8.71 (t, 7, 3H), 8.83 (s, 3H)

I.R. : cm^{-1} = 3050^{w}, 2940^{ms}, 2860^{m}, 2241^{w}, 1740^{s}, 1455^{mw}, 1445^{mw}, 1419^{w}, 1372^{m}, 1350^{mw}, 1295^{mw}, 1255^{m}, 1205^{sh}, 1180^{m}, 1098^{mw}, 1024^{m}, 920^{w}

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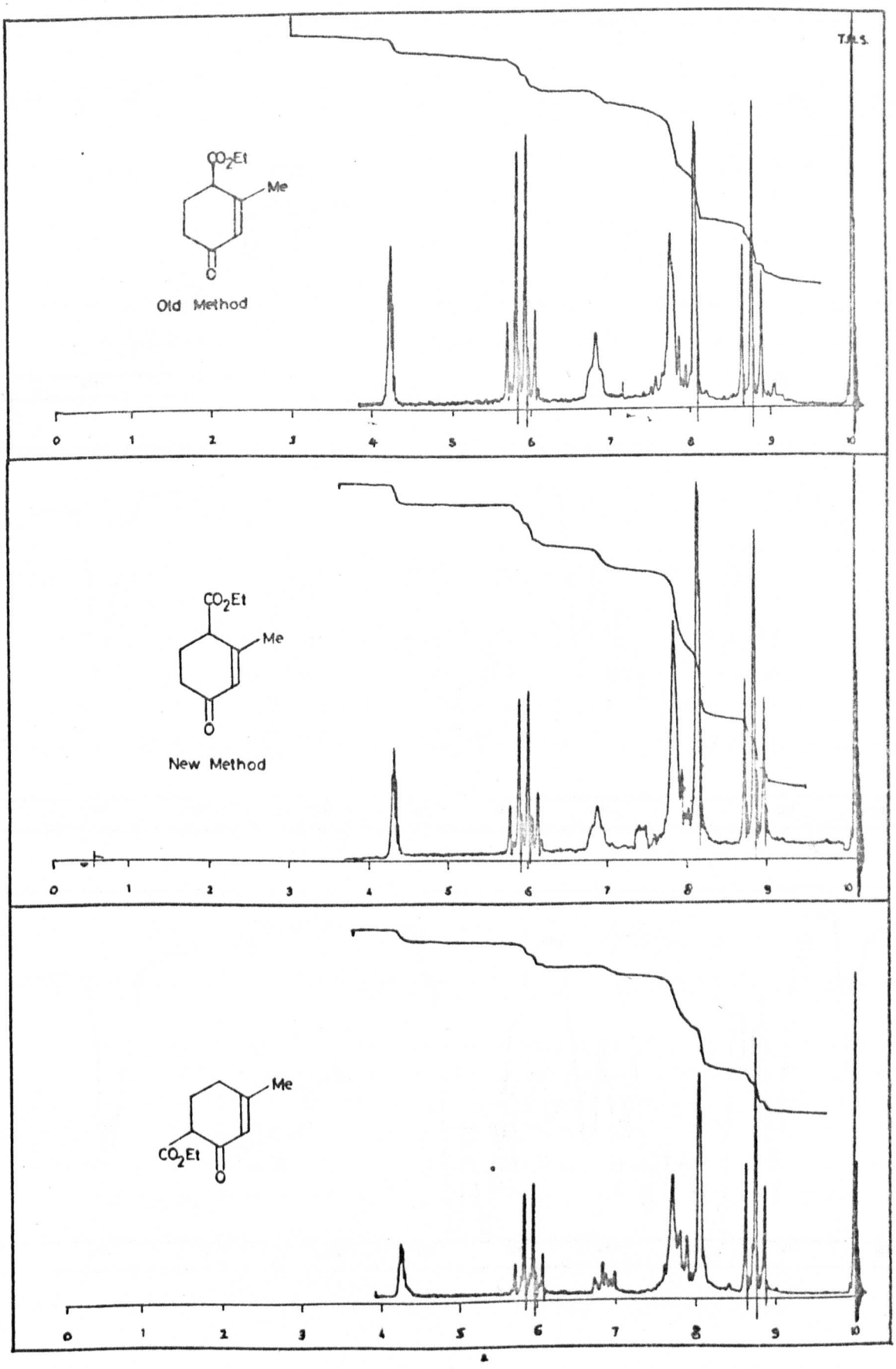
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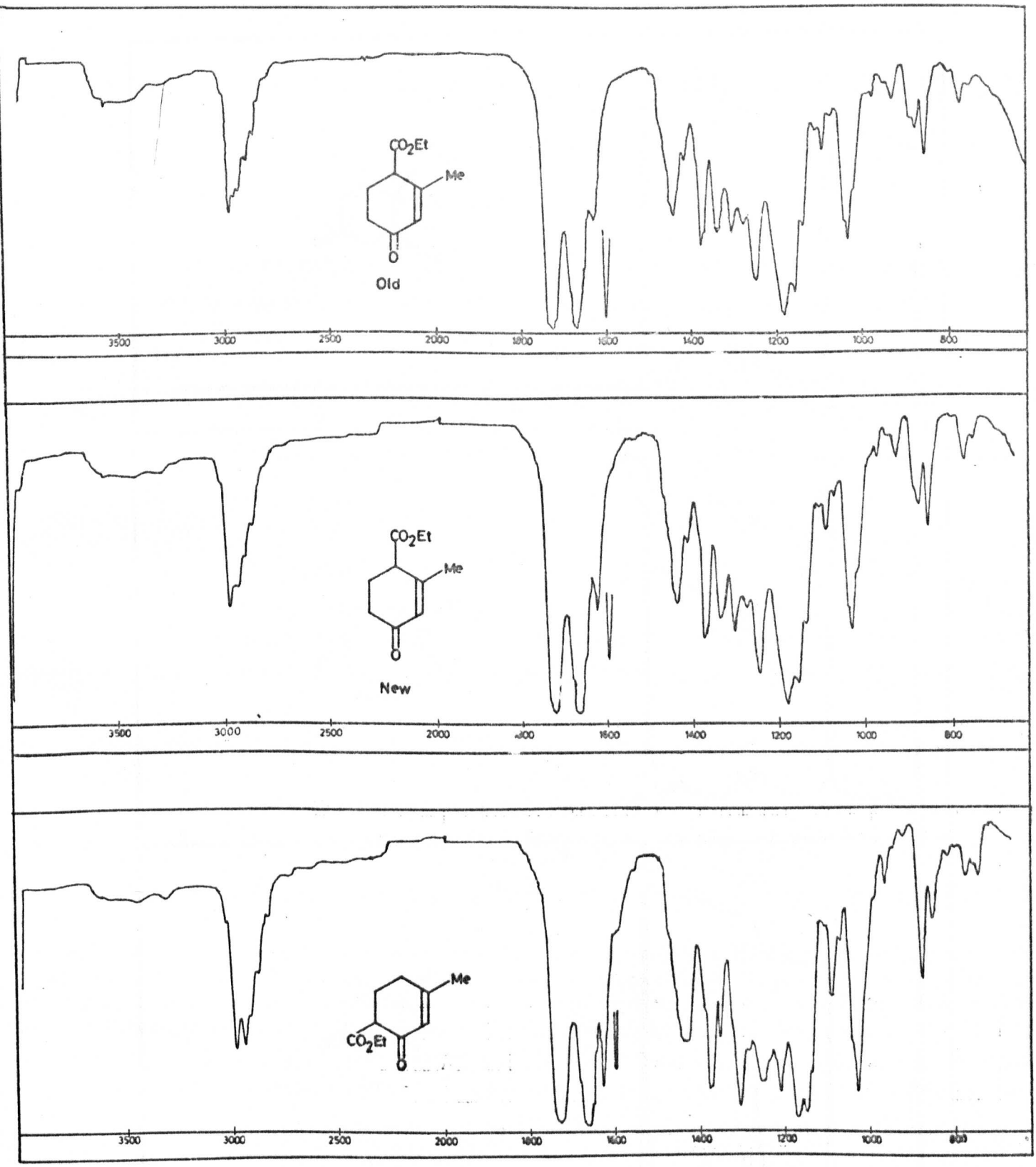
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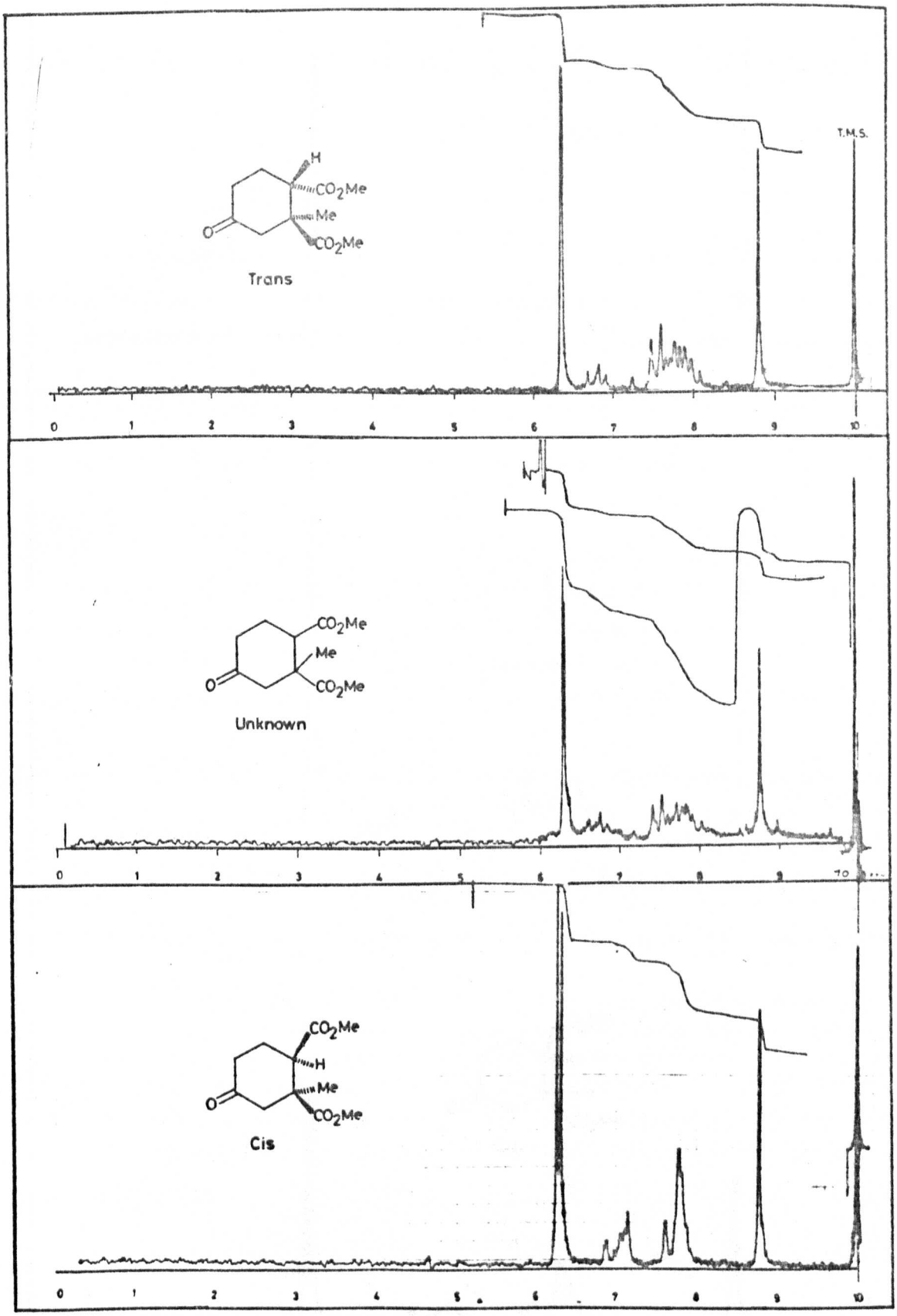
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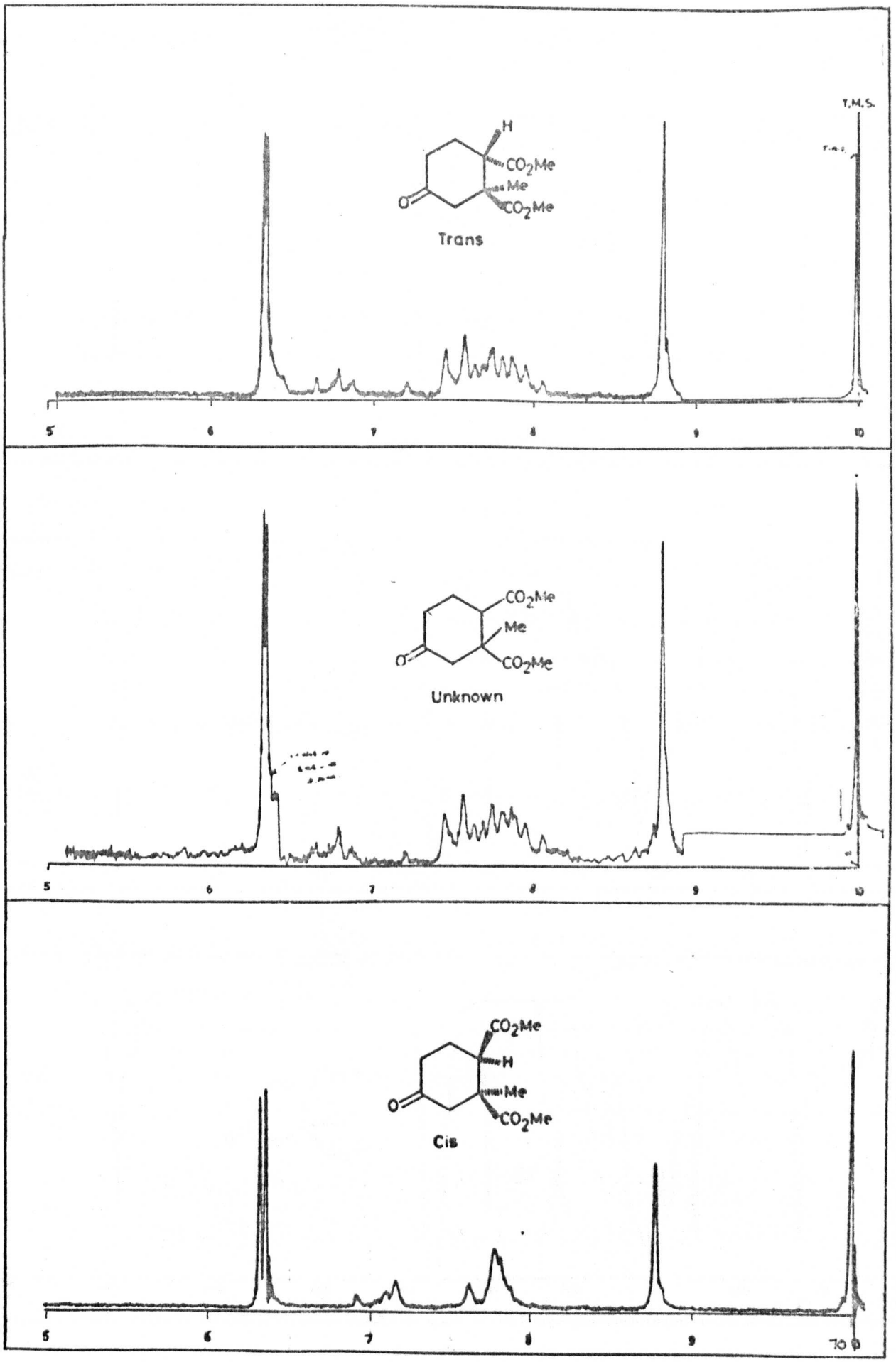
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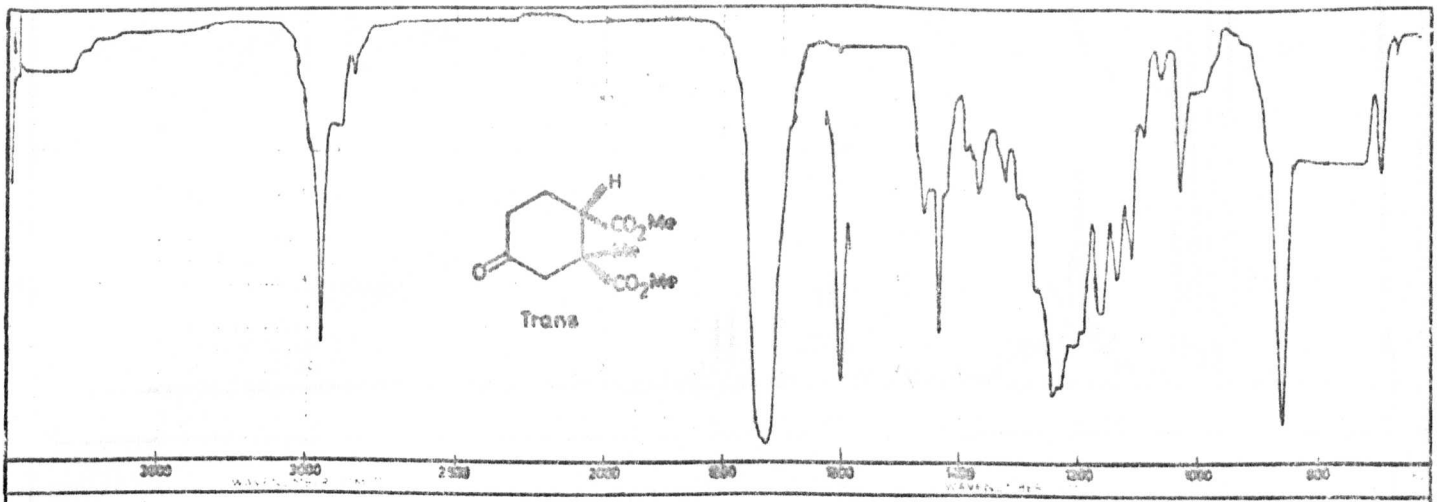
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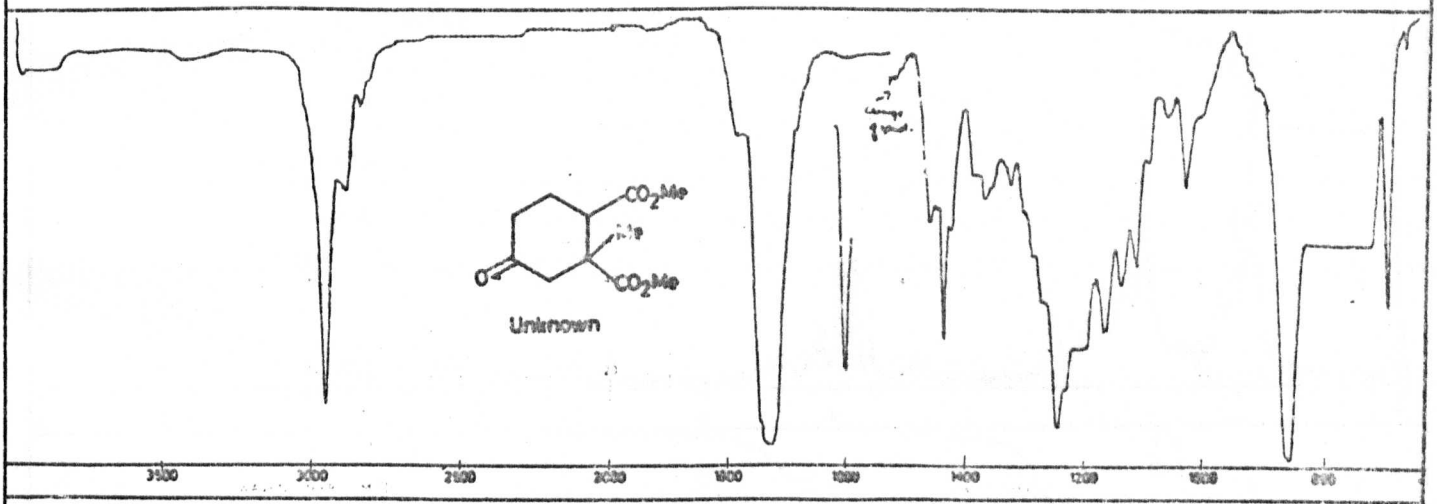
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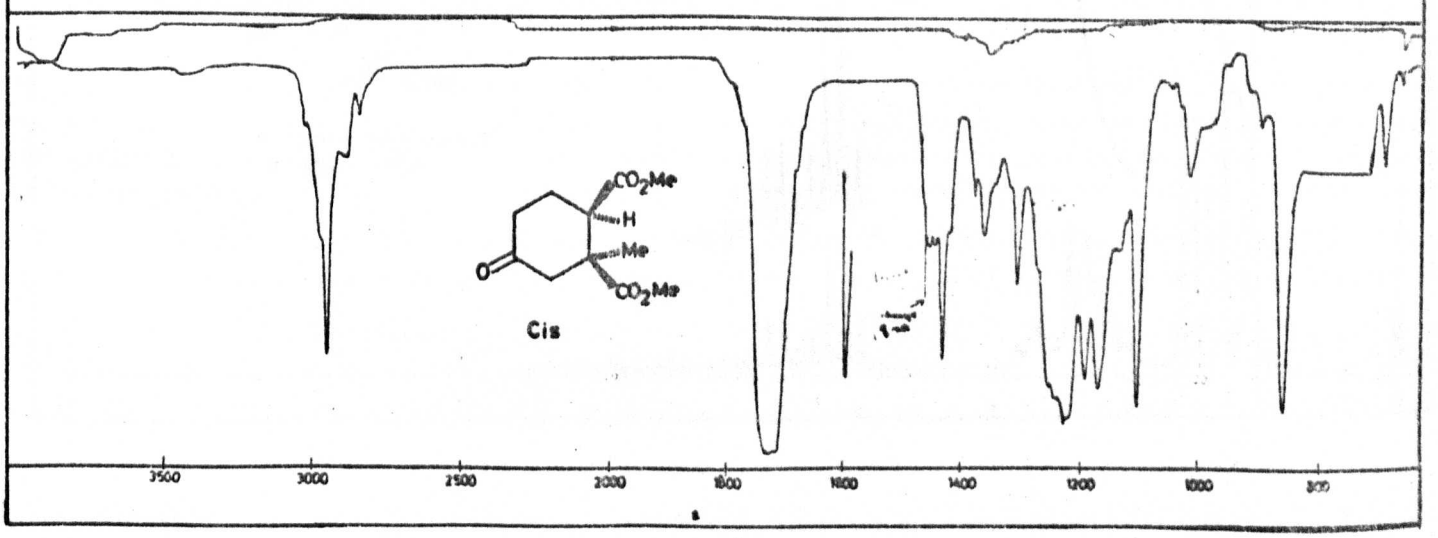
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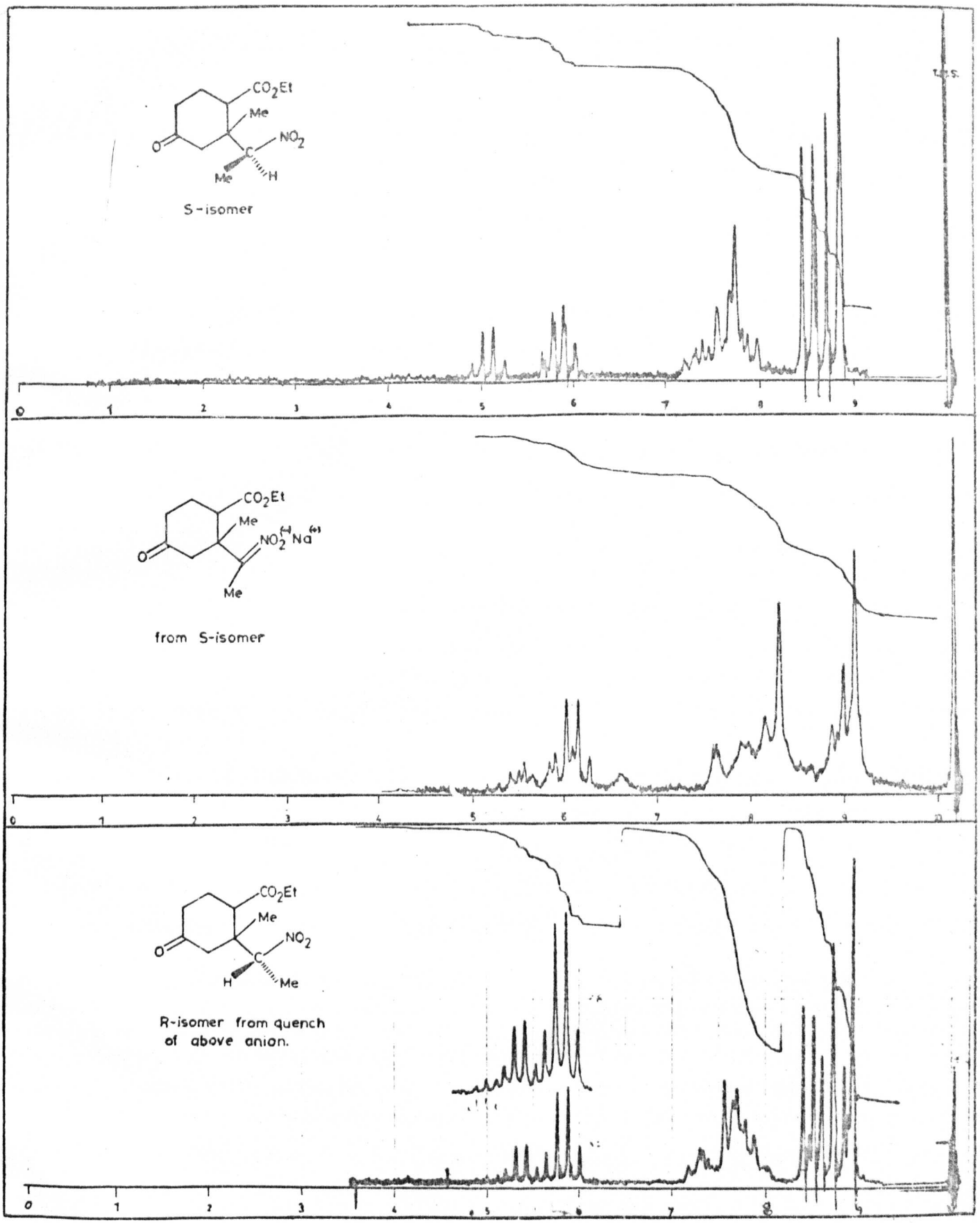
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of above anion.
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