A STUDY IN RING EXPANSION

Thesis presented to the University of Glasgow

for the degree of Ph.D.

by

Adrian Charles Ward Curran

1967

To

Margaret

ACKNOWLEDGEMENTS

I should like to express my gratitude to Dr. G. L. Buchanan, for the encouragement and assistance he has given me during the last three years, and to Professor R. A. Raphael, F.R.S., for the opportunity to carry out this research.

I also wish to thank the staffs of the various departments responsible for recording high-resolution infra-red spectra, micro-analyses, n.m.r. spectra and mass-spectra.

The work described in this thesis was performed during the tenure of a Maintenance Award from the Scientific Research Council (1964 - 67).

SUMMARY

Part I

The acid catalysed ring expansion reaction of 2-(3'-phenyl-3'-oxopropyl)-cyclopentanone to 4-phenylcyclohept-3-one carboxylic acid, has been extended to include substituted aromatic and wholly aliphatic 1,5-diketones. In the case of the latter, where tetrahydroindanones proved to be the thermodynamically favoured product, modified conditions have been developed to afford the alkyl substituted cycloheptene carboxylic acids. The synthetic applicability of the reaction has been studied as a potential route to the alkaloid colchicine and to the guaianolide sesquiterpenes.

Part II

The structure of Mannich bases arising from unsymmetrical ketones has been related to the direction of acid catalysed enolisation. A parallel n.m.r. study of Mannich bases and their quaternary salts revealed useful information regarding the chemical shift of protons in the proximity of the quaternised centre.

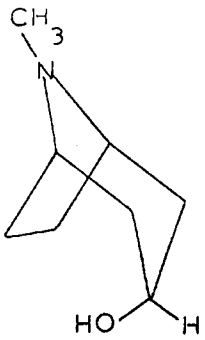
The hitherto disputed existence of a mixture of isomeric Mannich bases arising from unsymmetrical ketones (e.g. isopropy methyl ketone) has been unambiguously proved and

and subsequently related to the isomeric mixture of enols formed under acidic conditions. β,β-Disubstituted Mannich bases have been convincingly shown to be capable of rearrangement under certain conditions (e.g. in the thermal Michael reaction) thus causing them to behave as their isomeric bases. The corresponding quaternary salts are not involved in any rearrangement process.

CONTENTS

PART I

A NOVEL RING EXPANSION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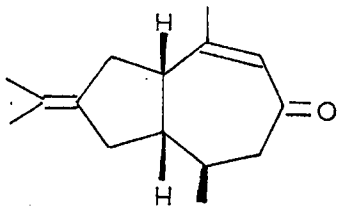
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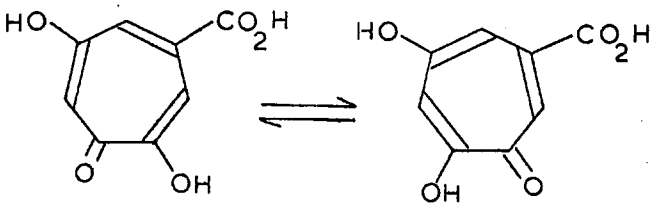
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OH
HO
CO2H
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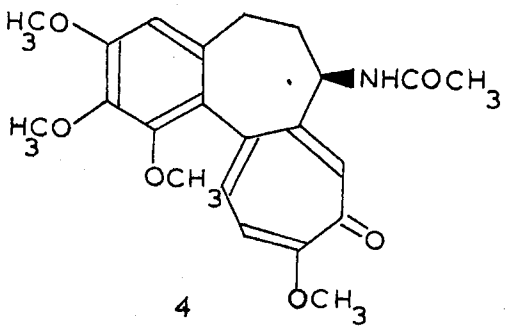
O

3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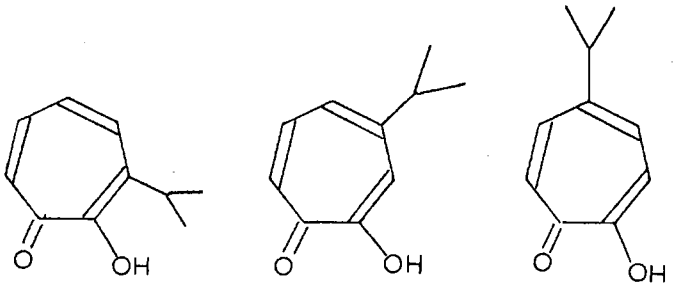
NHCOCH3
O
OCH3

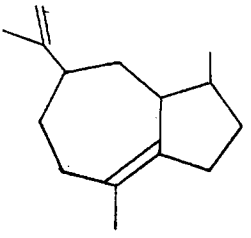
4


O
OH
O
OH
O
OH

5

INTRODUCTION

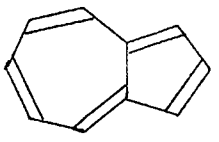
Before 1945, apart from the well authenticated examples of the tropane alkaloids [e.g. tropine (1)], β-vetivone (2) and some naturally occurring azulenes, very few natural products had been shown to incorporate a seven membered ring. In 1945, Dewar[1,2] invoked a tropolonoid ring to rationalise the chemical behaviour of stipitatic acid (3), an acid produced by the mould Penicillium Stipitatum, and to explain the unusual reactions of ring C of the alkaloid colchicine (4) isolated from Colchicum autumnale L. This far reaching postulate was later to be confirmed by synthesis of the tropolone ring by Cook[3] and independently by Nozoe[4] and by the syntheses of stipitatic acid[5] and colchicine[6]. That tropolone derivatives escaped recognition until 1945 must be attributed to their relative scarcity in nature. The few naturally occurring tropolones can be conveniently divided into three groups. The simplest are the isopropyltropolones exemplified by the thujaplicins (5), first isolated from the heartwood of Thujaplicata and identified as three new tropolones by Erdtman[7] in 1948. The second class are the hydroxytropolonecarboxylic acids exemplified by stipitatic acid (3) and the last group is made up of colchicine (4) and a few closely related alkaloids isolated from the various Liliaceae,



12 .

Diacid	Ring Formed	% Yield Calcium Salt	% Yield Thorium Salt
GLUTARIC	4	0	0
ADIPIC	5	45	15
PIMELIC	6	46	70
SUBERIC	7	35	50
AZELAIC	8	5	20
SEBACIC	9	< 1	1·5

Table I



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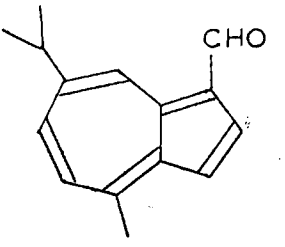

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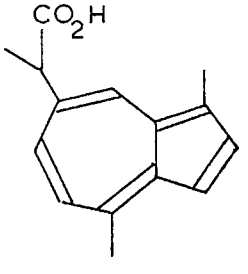

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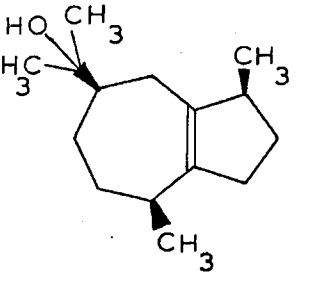

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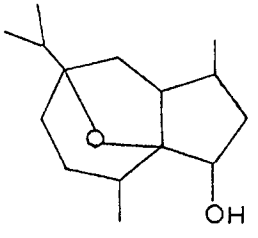

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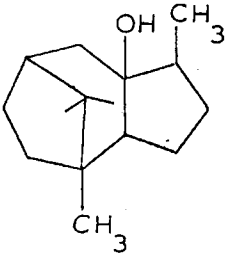

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Piesse in 1864, studying the blue fraction from the oil of wormwood, introduced the name azulene for the compound responsible for the colour. Later, Willstraed[8] made the discovery that an azulene was involved in the blue discolouration appearing on the cut surface of various mushrooms, and in 1936, Plattner[9] showed by synthesis that azulene (6) consisted of a bicyclic system containing a five and a seven membered ring with five double bonds in conjugation. Two examples of naturally occurring azulenes are the red-violet lactaroviolin[10] (7), a guaiazulene from the mushroom Lactarium delicious L and the azulenic acid chamazulene carboxylic acid (8) isolated from Achillea millefolium by Stahl[11]. Guaiol (9), kesyl alcohol (10), patchouli alcohol (11) and α-chigadmarene (12) are a few examples of naturally occurring sesquiterpenes incorporating a cycloheptane ring which on dehydrogenation give substituted azulenes.

The earlier methods of synthesising alicyclic compounds involved a ring closure reaction, the ease of which depended on the strain of the ring formed and the distance between the reacting centres. Distillation of the rare earth salts of dicarboxylic acids introduced by Ruzicka[13] was modified in 1928 to give moderate yields of cycloheptanone derivatives (see Table I). The Dieckmann reaction, an

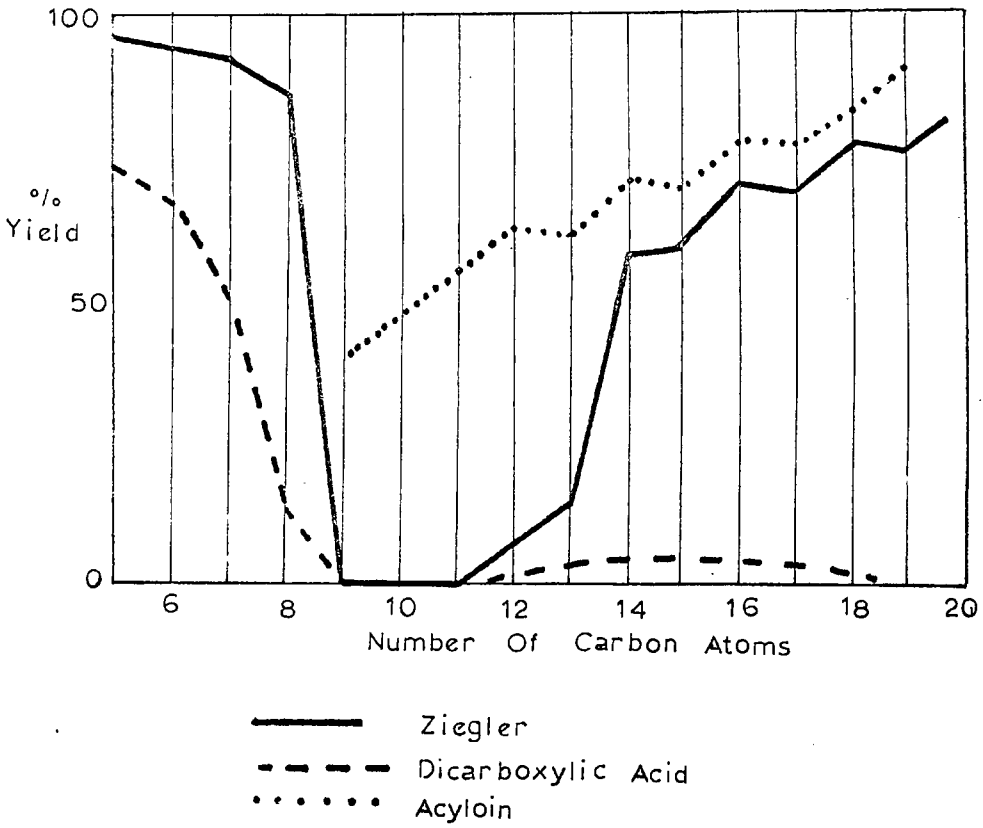
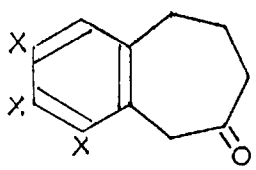


Fig. I



$X = OCH_3$

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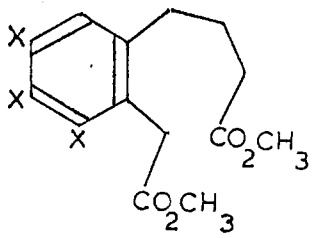

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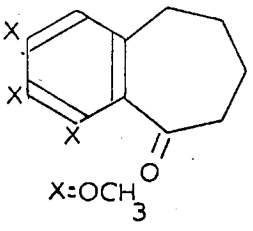

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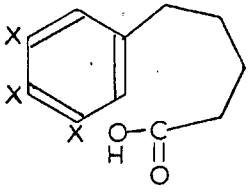

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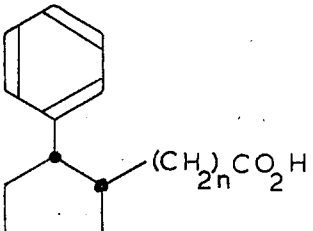

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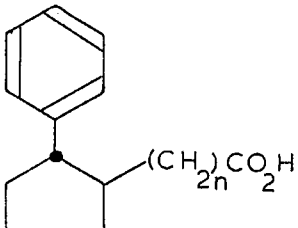
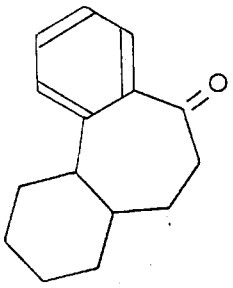
(b) n = 2



18 (a) n = 1
(b) n = 2

intramolecular condensation, gives seven membered rings in low yield, whereas the Thorpe-Ziegler[14] reaction involving an intramolecular condensation of dinitriles under high dilution, affords cycloheptane rings in acceptable yields. The introduction of the acyloin synthesis by Prelog[15] in 1947 provided a good route to medium sized rings. Figure I[16] shows the dependence of yield on ring size for the three most general procedures for the preparation of many membered ring compounds involving a ring closure step.

During the period 1950 - 1960, much attention was focussed on the synthesis of the alkaloid colchicine, and as a result, a diverse range of new synthetic routes to cycloheptane and tropolone rings was developed. Rappaport[17], in 1951, achieved a synthesis of trimethoxy-β-benzosuberone (13), a fused cyclic ketone, by the intramolecular condensation of the phenyl substituted dicarboxylic acid ester (14). Two years before this Caunt and Lowenthal[19] in 1961, obtained trimethoxy-α-benzosuberone (15) by an intramolecular Friedel-Crafts acylation of δ-(3,4,5-trimethoxyphenyl) valeric acid(16). Employing similar conditions, Gutsche[20] compared the yields of cyclisation achieved for 2-phenylcyclohexane acetic acids (17a, 18a) and for 2-phenylcyclohexane propionic acids (17b, 18b) thus substantiating the well known fact that six membered



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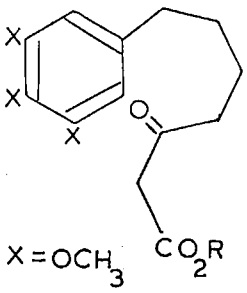

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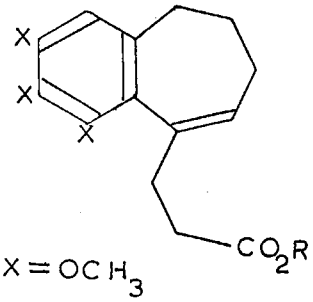

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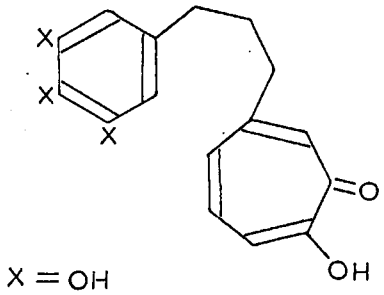

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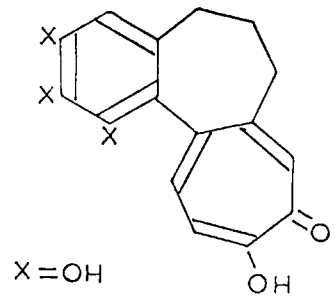

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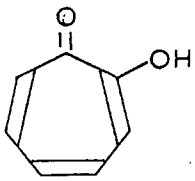

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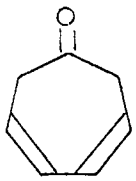
rings form with greater ease than their seven membered counterparts. Gutsche found that the yield of the tricyclic ketone (19), incorporating a seven membered ring, could be substantially improved by cyclisation of the acid chloride under standard Friedel-Crafts conditions.

Yet another intramolecular cyclisation in this series was achieved by Martel[21] in the early stages of his colchicine synthesis when he successfully converted ethyl ω-(3,4,5-trimethoxyphenyl)-γ-oxooctanoate (20) to the bicyclic ester (21) under the conditions of paratoluene sulphonic acid. A synthesis of a cycloheptane ring, of interest because of its novelty rather than its practical application was that devised by Scott[22] in 1965 and based on a biogenetic theory. It involved an oxidative free radical phenol-tropolone coupling of the β-(3-arylpropyl) tropolone (22) to desmethyldesacetamidocolchicine (23).

The ring enlargement of carbocyclic ketones by means of diazomethane was first discovered by Mosettig[23] but the potential of this reaction was not realised until 1950 when Doering[24] achieved a remarkable synthesis of tropolone (24) by irradiation of a solution of diazomethane in benzene and subsequent oxidation of the resultant cycloheptatriene with aqueous potassium permanganate. Cycloheptadienones have



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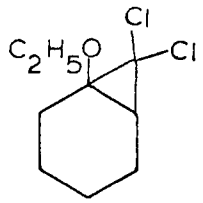

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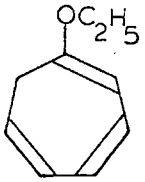

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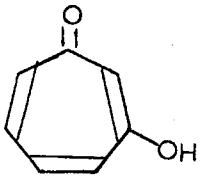

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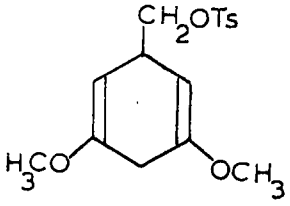

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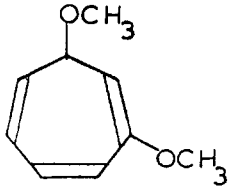

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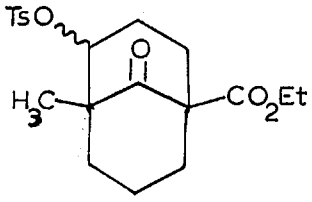

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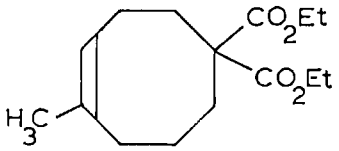
proved to be valuable intermediates in the synthesis of tropones and tropolones and to this end, a simple method of obtaining 3,5-cycloheptadienone (25), involving a ring expansion, was devised by Craig[25] in 1958 and later developed by Dodson[26] in 1962. The reaction of 1-ethoxycyclohexene with dichlorocarbene gave 1-ethoxy-7,7-dichloronorcarane (26) which rearranged in hot quinoline to afford 1-ethoxy-1,3,5-cycloheptatriene (27) from which the required 3,5-cycloheptadienone was obtained by hydrolysis. Birch[27] used a similar procedure for the conversion of 2,5-dihydroanisole to β-tropolone (28). At about the same time as Craig's cycloheptadienone synthesis, Nelson[28] introduced a third method of ring expansion employing the solvolysis of 1,4-dihydrobenzyl alcohol tosylates with formation of cycloheptatriene rings. This idea was developed by Chapman[29] in 1961 for the synthesis of β-tropolone (28). Solvolysis of the tosylate of 3,5-dimethoxy-1,4-dihydrobenzyl alcohol (29) in pyridine gave 1,3-dimethoxycycloheptatriene (30) which on oxidation with bromine afforded β-tropolone (28) in high yield.

Interest in this department, in the synthesis of cycloheptane rings arose from the discovery[31] that bridge fission of a bicyclo[3,3,1]nonane afforded an eight membered carbocycle, The mixture of epimeric tosylates (31), under appropriate basic conditions, afforded the cyclooctene



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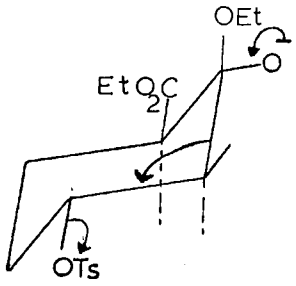

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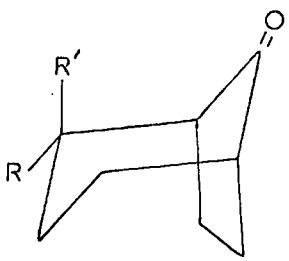
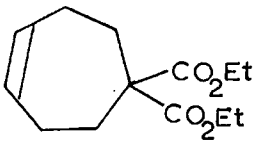


34 (a) R = H, R' = OTs
(b) R = OTs, R' = H



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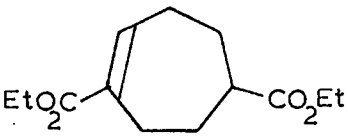

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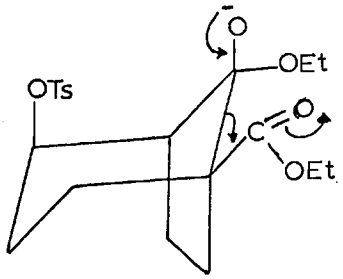

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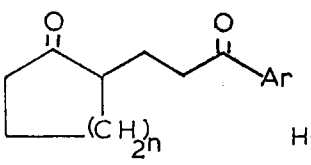
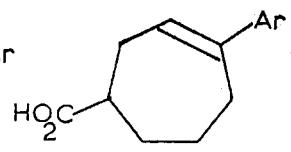


38 (a) n = 2
(b) n = 1



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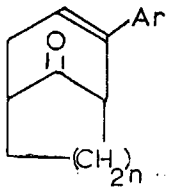
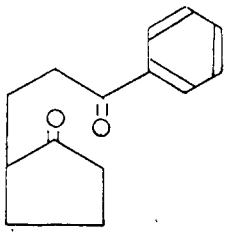


39 (a) n = 2
(b) n = 1

diester (32) together with unreacted axial tosylate; the equatorial tosylate having reacted by a concerted β-elimination process (33). Application of this ring expansion technique to the analogous bicyclo[3,2,1]octane system, afforded the required seven membered carbocycle[32]. In this case the epimeric tosylates could be separated and each isomer subjected to basic conditions. The equatorial tosylate (34b) afforded the gem diester (35) by a concerted β-elimination process, whereas the axial tosylate (34a) afforded the unsaturated diester (36) by a retro-Claisen ester reaction (37) followed by a β-elimination of the tosylate function.

Recent work by Buchanan[33] in this department has been initiated by Cope's[34] discovery that the 1,5-diketone (38a) cyclised under acid conditions to give the 2-phenylbicyclo-[3,3,1]non-2-en-9-one (39a). Application of this reaction by Buchanan[33] to the corresponding cyclopentanone derivative (38b) afforded not the expected bicyclo[3,2,1]octenone (39b) but rather a cycloheptene carboxylic acid (40) thus giving, in one operation, a synthesis of a seven membered carbocycle by a ring expansion of a cyclopentanone.

It is the object of this thesis to examine the scope, mechanism and synthetic applicability of this novel ring expansion of 1,5-diketones (38b) to cycloheptene carboxylic acids (40).



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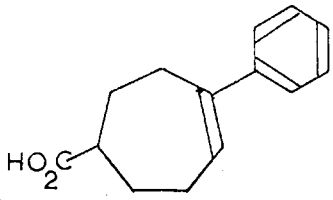

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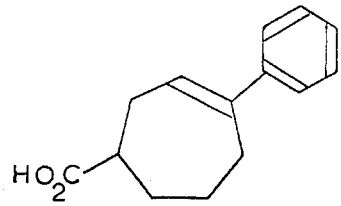

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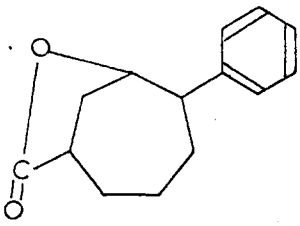

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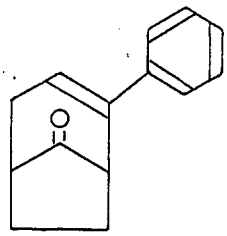

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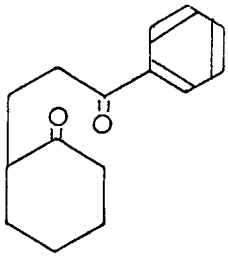

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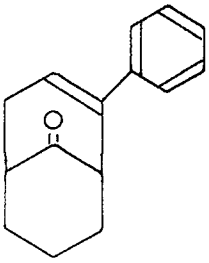

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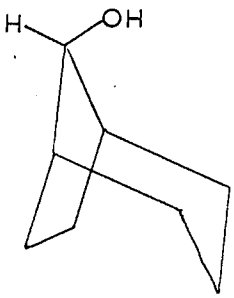

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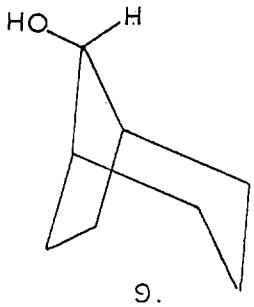
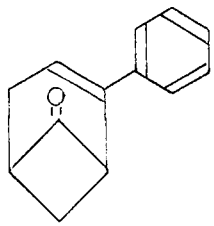


9.

PART 1

DISCUSSION

Work in this laboratory on the synthesis of cycloheptene carboxylic acids was initiated by the discovery that acid treatment of 2-(3'-phenyl-3'-oxopropyl)cyclopentanone (1) resulted in the formation of two isomeric cycloheptene carboxylic acids (2) and (3) and a γ-lactone (4).[30,35] Further investigation[30] indicated that the reaction proceeded via the intermediate 2-phenylbicyclo-(3,2,1)-oct-2-en-8-one (5), isolable only under special conditions. The course of this reaction was thus strikingly different from Cope's[34] conversion of the analogous diketone 2-(3'-phenyl-3'-oxopropyl)-cyclohexanone (6) to 2-phenylbicyclo-(3,3,1)-non-2-en-9-one (7) under similar acidic conditions. This apparent anomaly can be readily explained in terms of the inherent strain in bicyclo(3,2,1)-octenones. Strain is absent in the related bicyclo-(3,3,1)-nonenones and bicycl-(4,3,1)-decenones, thus accounting for the relative stability to acid. This strain theory is borne out by the high carbonyl frequency[45] (1758 $cm.^{-1}$) of bicyclo-(3,2,1)-octenones. For the same reason, Cope[13] and independently Foote[36] experienced difficulty in converting the tetrahedral carbon at C_8 in the alcohols (8) and (9) into a trigonal carbon atom by oxidation.



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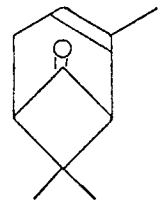

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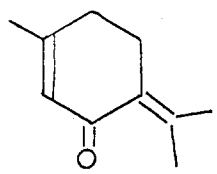

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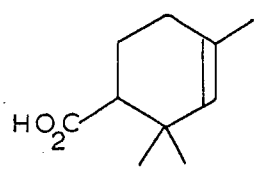

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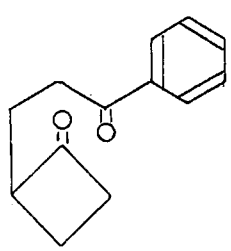

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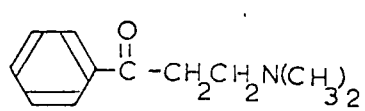
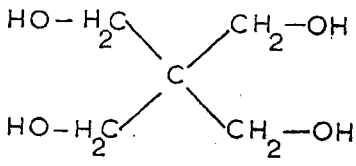


15.

Onthis premise, the corresponding bicyclo-(3,1,1)-heptenones (10) should be so strained as to inhibit formation, or once formed should be so unstable as to undergo facile fragmentation by bridge fission. Infact, chrysanthenone (11) is a stable naturally occurring bicyclo-(3,1,1)-heptenone and fragments in acid, base or on heating[37] to give three different fragmentation species (Schemes I - III). The acid catalysed fragmentation product from chrysanthenone was reported to be piperitenone (12) and not 2,2,4-trimethylcyclohex-4-ene carboxylic acid (13) as would have been predicted from the analogous fragmentation of bicyclo-(3,2,1)-octenones. It is possible that chrysanthenone undergoes an alternative fragmentation (Scheme I) because of the effect of the gem dimethyl group. Also, this effect could account for the unexpected stability of chrysanthenone (11). To prove this, 2-(3'-phenyl-3'-oxopropyl)-cyclobutanone (14) was prepared for ring expansion studies from cyclobutanone and β-dimethylaminopropiophenone (15).

The preparation of cyclobutanone proved troublesome despite the reported synthesis of cyclobutanone from diazomethane and ketene[38], the only isolable product was found to be acetic anhydride arising from hydration of ketene. However, a high yield of cyclobutanone was



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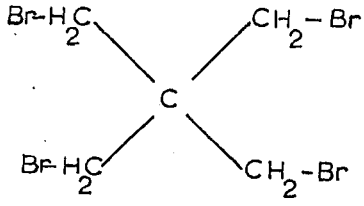

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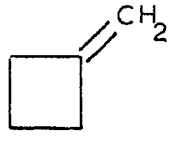

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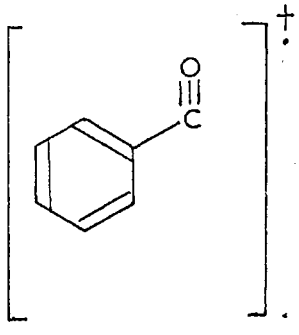

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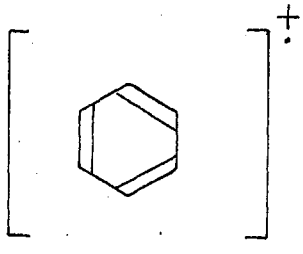
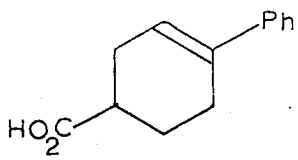


20.

obtained by using a modification of the methods reported by Shand[39] and Conia[40]. Pentaerythritol (16) was converted to pentaerythrityltetrabromide by treating the benzene sulphonate with sodium bromide. The tetrabromide was subsequently debrominated with zinc dust to give a high yield of methylene cyclobutane (Scheme IV). Ozonolysis of this hydrocarbon, with thermal decomposition of the ozonide, gave cyclobutanone as a colourless volatile liquid, showing the characteristically high carbonyl stretching frequency in the infra-red at 1780 $cm.^{-1}$. The required diketone 2-(3'-phenyl-3'-oxopropyl)-cyclobutanone (14) was prepared from the thermal Michael condensation of β-dimethylaminopropiophenone and a 3 molar excess of cyclobutanone, and isolated as a colourless oil analysing for $C_{13}H_{14}O_2$. The infra-red spectrum showed carbonyl absorption at 1783 $cm.^{-1}$ (cyclobutanone) and 1693 $cm.^{-1}$ (aryl ketone). The mass spectrum showed the parent ion at 202 m/e with the base peak at 105 m/e corresponding to the stable ion (19) which showed a loss of 28 m/e to give the second most abundant ion at 77 m/e i.e. (20).

Treatment of the diketone (14) with hydrochloric acid in glacial acetic acid gave a low yield (~ 10%) of anacidic material isolated as a white solid analysing for



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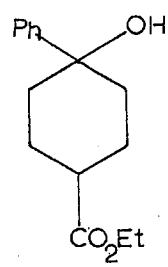

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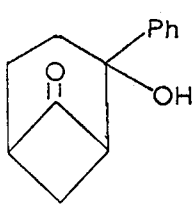

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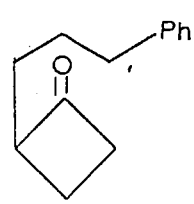
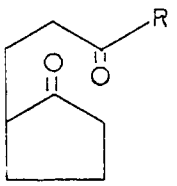


14.

$C_{13}H_{14}O_2$. The same acid was obtained in a more acceptable yield (≈40%) by using the more forcing conditions of p-toluene sulphonic acid in ethylene glycol. The mass spectrum gave the molecular ion at 202 m/e showing the loss of 45 m/e fragment to give the base peak at 157 m/e i.e. characteristic of carboxylic acids. The ultraviolet spectrum showed characteristic styrene bands at 248 mμ and 218 mμ maxima and the vinyl proton resonated at 3.9 τ as a sharp triplet in the n.m.r. spectrum. From the spectral evidence, the acidic material was identified as 4-phenylcyclohex-3-ene carboxylic acid (21). The structure of this acidic material was further established by an alternative synthesis of the acid (21) from p-hydroxybenzoic acid as follows. Esterification and hydrogenation gave 4-carbethoxycyclohexanol which was oxidised and treated with phenyl magnesium bromide to afford the alcohol (22). Dehydration and hydrolysis gave 4-phenylcyclohex-3-ene carboxylic acid (21) as a white solid, identical in all respects (mixed m.p. and spectral data) with the acidic material isolated from the ring expansion of the diketone (14).

Thus the formation of the acid (21) from the diketone (14), albeit in low yield, signifies the existence of the bicyclo-(3,1,1)-heptenones (10) which undergoes ready bridge fission. The low yield of acid probably means that the dehydration of the bicyclic ketol (23) to the bicyclic enone (10) is not favoured and hence isolation of the bicyclic enone (10) would be expected to prove difficult. In fact all attempts to isolate 2-phenyl-bicyclo-(3,1,1)-hept-2-en-7-one (10) by treating the diketone (14) with p-toluene sulphonic acid in benzene, toluene, or xylene, under anhydrous conditions, proved unsuccessful.

The ring expansion reaction of 1,5-diketones (e.g.24), under acidic conditions, can be interpreted in terms of four mechanistic schemes (V - VIII - R = H); all viable in that they satisfactorily explain the simultaneous formation of both isomeric acids together with the corresponding γ-lactone. A protonation step, dependent on the electron density in the double bond of the bicyclic intermediates, and hence on the nature of the substituent R, is common to three of these mechanistic schemes (VI - VIII). The fourth scheme (V) involves the formation of a carbonium ion from a bicyclic ketol, a step again dependent on



24.

$RCOCH_2CH_2N(CH_3)_2$

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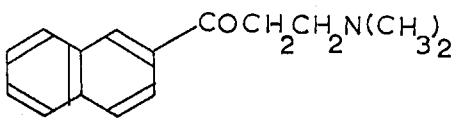

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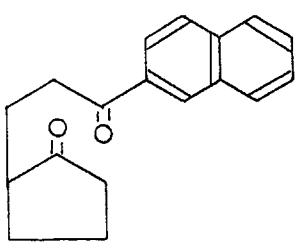

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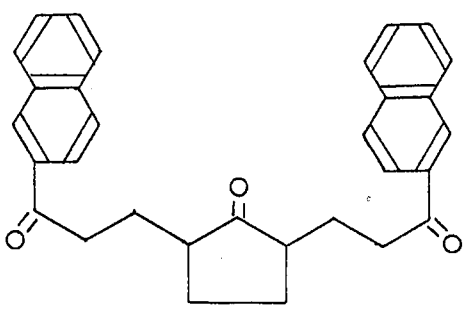


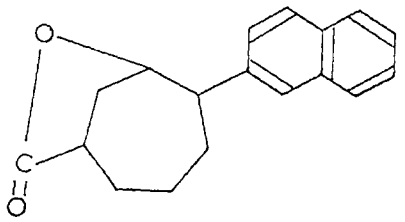
28.

the nature of R. Hence to establish that such proposed steps do in fact intervene in the ring expansion reaction, it should be sufficient to study the yield of ring expansion products (acid + lactone), for a variety of substituents R, to give a crude measure of the ease of protonation or carbonium ion formation. The ring expansion sequence from 1,5-diketone to cycloheptene carboxylic acid has been postulated as proceeding through a bicyclic intermediate[30] and hence it will be our practice to relate the results obtained to the starting diketone without isolating the relatively inaccessible and unstable intermediate. To obtain the maximum amount of information relating to the mechanism and scope of the ring expansion reactions, it will be necessary to investigate two classes of 1,5-diketones of the type (24), where R is (a) aromatic and (b) aliphatic. Of all the available routes to 1,5-diketones (24), the most satisfactory method was found to be the thermal Michael[41] condensation of the appropriate Mannich base (25) with cyclopentanone.

2-(3'-β-Naphthyl-3'-oxopropyl)-cyclopentanone (27) was chosen as the parent example for the aromatic class (a) since it incorporates neither electron withdrawing nor electron releasing substituents. Methyl-β-naphthyl

ketone was prepared from naphthalene by a standard Friedel Craft's acylation reaction, and separated from the α-isomer by fractional recrystallisation. The corresponding Mannich base[42] (26) was treated with a three molar excess of cyclopentanone at reflux temperature to give the required diketone (27) together with an impurity assumed to be the di-addition product[30] (28). Distillation and recrystallisation gave the diketone (27) as colourless needles analysing for $C_{18}H_{18}O_2$, and showing the expected carbonyl absorption bands in the infra-red at 1648 $cm.^{-1}$ (naphthylketone) and 1739 $cm.^{-1}$ (cyclopentanone). The u.v. spectrum showed characteristic naphthalene absorption bands at 248, 283 and 291 mμ maxima. N.M.R. studies showed the methylene protons at C_2' to resonate at 6.8 τ as a well defined triplet. This splitting pattern of the C_2' methylene protons in the n.m.r., and the doublet carbonyl in the infra-red, was used throughout this study as a diagnostic test for 1,5-diketone formation.

Treatment of this diketone (27) with concentrated hydrochloric acid in glacial acetic acid (standard fragmetnation conditions) gave a neutral material, shown by g.l.c. (1% Polymer Z at 200°) to be mainly unreacted diketone; the other neutral component (~ 5%) was assumed



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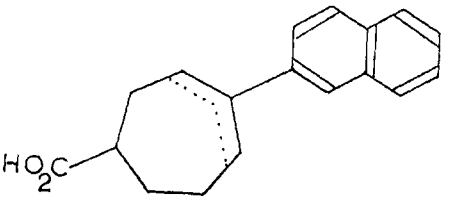

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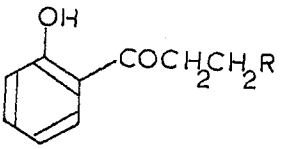
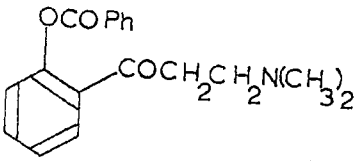


31. (a) $R = N(CH_3)_2 \cdot HCl$

(b) $R = N(CH_3)_2$



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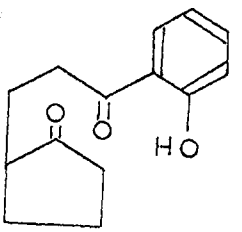
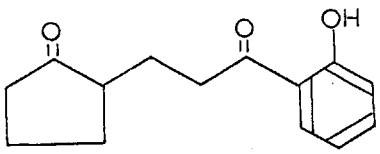


33.

to be the lactone (29) on the basis of its infra-red spectrum (1780 $cm.^{-1}$). The acidic product (80%) was isolated as a white solid analysing for $C_{18}H_{18}O_2$ and identified as the mixture of 4-β-naphthylcyclohept-3 and 4-ene carboxylic acids (30). The n.m.r. showed the vinylic proton as a complex region at 3.8 τ. Had the ring expansion given a single acid, the vinylic proton would have appeared as a clean triplet. The formation of both Δ^3 and Δ^4 isomeric acids (30) was corroborated by g.l.c. examination of the corresponding methyl esters which convincingly showed a 1:1 mixture. The high yield of cycloheptene acid (~80%) is clearly consistent with the proposed mechanism since the aromatic residue would promote protonisation of the double bond to give a resonance stabilised carbonium ion.

This class of 1,5-diketones was extended to incorporate an electron releasing substituent [e.g. 2-(3'-o-hydroxyphenyl-3'-oxopropyl)-cyclopentanone (33)] in anticipation of an even higher yield of ring expansion products under similar fragmentation conditions. Because of the amphoteric nature of β-dimethylamino-o-hydroxypropiophenone (31b), this Mannich base could not be liberated from its hydrochloride. In an attempt to overcome this

difficulty, the free hydroxyl in o-hydroxyacetophenone was protected by acetylation. However, under the mildly acidic Mannich reaction conditions, the protective acetyl group was hydrolysed to give only β-dimethylamino-o-hydroxy-propiophenone hydrochloride. It was thus essential to select a protective group capable of surviving the Mannich reaction conditions, and to this end o-benzoyloxyacetophenone was successfully converted to β-dimethylamino-o-benzoyloxy-propiophenone (32). Treatment of this Mannich base with cyclopentanone gave a high yield (~90%) of a phenolic di-ketone analysing for $C_{14}H_{16}O_3$ i.e. 2-(3'-o-hydroxyphenyl-3'-oxopropyl)-cyclopentanone (33), arising from hydrolysis of the benzoate by the dimethylamine evolved during the thermal Michael condensation. The infra-red showed the aryl carbonyl frequency to have been lowered from 1695 $cm.^{-1}$, in o-benzoyloxyacetophenone, to 1638 $cm.^{-1}$ in the phenolic diketone. Dilution studies in the infra-red showed this to be a direct consequence of intramolecular hydrogen bonding of the free hydroxyl with the carbonyl at $C_{3'}$. This hydrogen bonding has been fully discussed by Gordy[43] with reference to o-hydroxyacetophenone.



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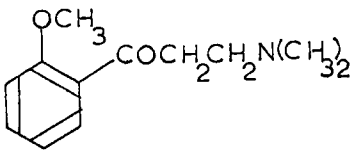

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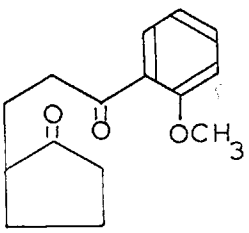
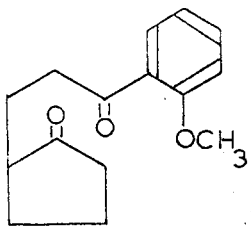


35.

When the diketone (33) was subjected to standard fragmentation conditions, there was a quantitative recovery of unreacted starting material. Even the more forcing conditions of p-toluene sulphonic acid in ethylene glycol failed to effect any reaction. This unexpected observation raises the question - does the ring expansion reaction proceed by an alternative pathway prohibited for the diketone (33), thus invalidating the proposed mechanistic schemes, or is the initial aldolisation step, proposed in the existing mechanisms, inhibited by the strong hydrogen bonding ? To answer this question, the analogous diketone 2-(o-methoxyphenyl-3'-oxopropyl)-cyclopentanone (35) was prepared for ring expansion studies.

o-Methoxyacetophenone, prepared from o-hydroxyacetophenone by methylation with dimethyl sulphate, was converted into the corresponding Mannich base (34) and identified as its picrate. The methoxyl protons appeared in the n.m.r. as a sharp singlet at 6.15 τ, and the six N-methyl protons as a singlet at 7.00 τ. Treatment of the free base with cyclopentanone, under standard thermal Michael conditions gave the required diketone (35) as a colourless oil analysing for $C_{15}H_{18}O_3$. The infra-red showed the character-



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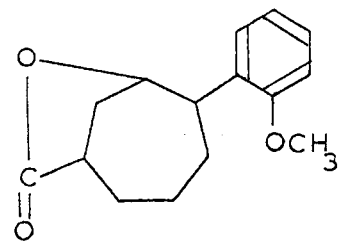

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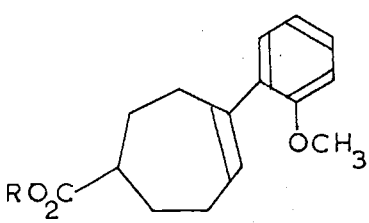
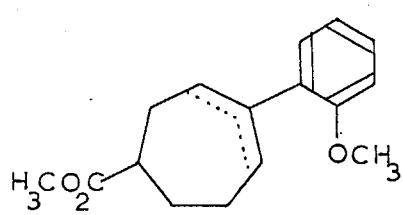


37. R = H

38. R = CH_3

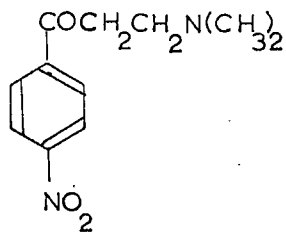


39.

istic carbonyl doublet at 1738 cm.$^{-1}$ (cyclopentanone) and 1695 cm.$^{-1}$ (aryl ketone). The n.m.r. showed the methoxyl protons as a singlet at 6.12 τ and the methylene protons at C_2, as a sharp triplet at 6.9 τ. Thus with the structure firmly established, the diketone (35) was treated with dilute acid (standard fragmentation conditions) to give an acidic product (60%) and a neutral fraction (25%), shown by g.l.c. to contain a negligible amount of unreacted diketone. The neutral material material analysed for $C_{15}H_{18}O_3$ and was shown by infra-red (1778 cm.$^{-1}$) to be 3-hydroxy-4-(o-methoxyphenyl)-cycloheptane carboxylic acid lactone (36). The acidic material refused to solidify and was subsequently converted into its methyl ester which, after distillation, analysed for $C_{16}H_{20}O_3$ i.e. 1-carbomethoxy-4-o-methoxyphenol-cyclohept-4-ene (38). The n.m.r. showed the single vinyl proton as a sharp triplet at 4.07 τ, suggesting the presence of only one double band isomer. More convincingly, g.l.c. analysis on 1% F 60 and 1% P.E.G.A. demonstrated homogeneity. It is probable that the Δ^3 isomer exists solely as the γ-lactone (36) and the n.m.r. and g.l.c. results relate only to the Δ^4 isomer (38).

Although the γ-lactone is readily removable by acid-base extraction, its formation could be regarded as dis-

advantageous in a synthetic route to a seven membered carbocycle. To overcome this problem of lactone formation, and to demonstrate that the Δ^3 isomer exists solely as lactone, the diketone (35) was treated with concentrated sulphuric acid in methanol. Under these modified fragmentation conditions, a high yield (~93%) of ring expansion product was isolated and identified by g.l.c. analysis as a 1:1 mixture of the isomeric esters (39). The n.m.r. of the mixture showed a complex splitting pattern for the vinylic proton. Thus, when lactone formation is prevented, the corresponding Δ^3 ester is isolated along with the Δ^4 isomer. The high yield of ring expansion products, from the concentrated hydrochloric acid reaction (~85%), and from the concentrated sulphuric acid reaction (~93%), is in agreement with the proposed mechanistic schemes and demonstrates, moreover, that the non-reactivity of 2-(3'-o-hydroxyphenyl-3'-oxopropyl)-cyclopentanone (33) was related to the hydrogen bonding inhibiting the initial aldolisation step. It is pertinent to note at this stage that the mechanistic scheme for the concentrated sulphuric acid-methanol fragmentation reaction, can be regarded as proceeding via a similar path to the one proposed for the hydrochloric acid - glacial acetic acid reaction (Scheme V - VIII, R = CH_3).



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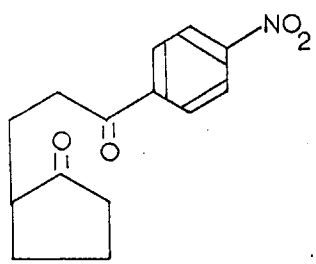

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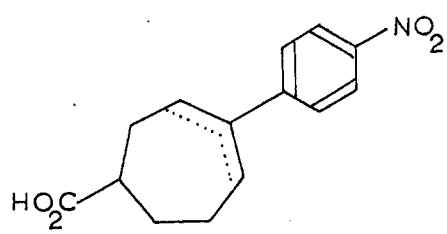
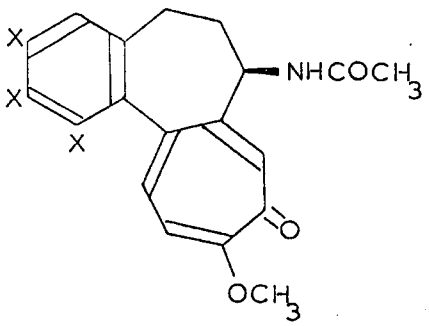


42.

To complete the mechanistic proof for the ring expansion reaction, a 1,5-diketone with an electron withdrawing substituent [e.g. 2-(3'-p-nitrophenyl-3'-oxopropyl)-cyclopentanone (41)] was studied under standard fragmentation conditions. Here the electron withdrawing effect of the nitro substituent should inhibit protonation and destabilise the carbonium ion and hence a low yield of ring expansion products would be anticipated. At first sight it appeared that this diketone (41) could not be prepared by the thermal Michael procedure since the Mannich base β-dimethylamino-p-nitropropiophenone (40) has been reported on three occasions[44,45,46], as being so reactive that liberation from the hydrochloride gave only polymeric p-nitrophenyl vinyl ketone. Also, the alternative route via the condensation of 2-dimethylaminomethylcyclopentanone and p-nitroacetophenone gave no identifiable products.

However, by working at sub-zero temperatures and under mildly basic conditions, the free base (40) was successfully isolated from the hydrochloride as a pale yellow solid m.p. 36-8°. The infra-red showed three characteristic N-methyl bands at 2810 - 2840 $cm.^{-1}$, and nitro bands at 1534 $cm.^{-1}$ and 1343 $cm.^{-1}$. The n.m.r. showed the six

N-methyl protons as a singlet at 7.7 τ and the methylene protons at C_2 and C_3 as a pair of triplets at 6.85 τ and 7.15 τ respectively. This new compound was further characterised as the picrate which analysed for $C_{17}H_{17}N_5O_{10}$. Condensation of the free base (40) and cyclopentanone gave an acceptable yield of the required diketone (41) as a white solid analysing for $C_{14}H_{15}NO_4$. The infra-red showed the aryl ketone at 1697 $cm.^{-1}$ and the cyclopentanone carbonyl at 1738 $cm.^{-1}$ with characteristic nitro bands at 1534 $cm.^{-1}$ (asym.) and 1343 $cm.^{-1}$ (sym.). The methylene protons at $C_{2'}$ resonated as a sharp triplet in the n.m.r. Under standard fragmentation conditions an acid was isolated as a white solid in 20% yield and analysed for $C_{14}H_{15}NO_4$ i.e. 4-p-nitrophenylcyclohept-3 and 4-ene carboxylic acids (42). The neutral fraction was shown by infra-red and mixed m.p. to be unreacted diketone. Under the more forcing conditions of p-toluene sulphonic acid in ethylene glycol, the yield of acid (42) was raised to 40%. The absence of lactone was regarded as being in accordance with the proposed mechanisms since the electron withdrawing substituent would inhibit isomerisation of the Δ^4 to the Δ^3 acid.



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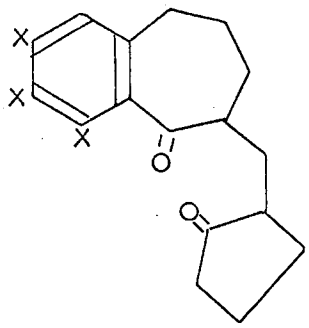

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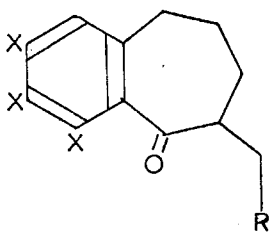
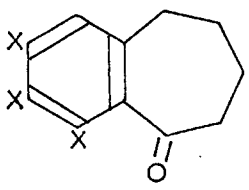


45. R = $N(CH_3)_2$

46. R = $N(CH_3)_2 \cdot HCl$



47.

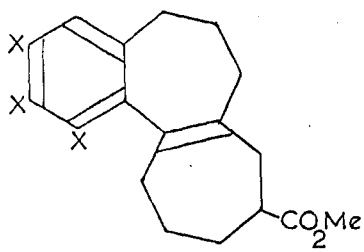
X = OCH_3

The final aromatic case to be investigated demonstrates the synthetic applicability of the ring expansion reaction. In the five synthetic routes to colchicine (43), discussed in the introduction, the yield determining step was the construction of the seven membered rings B or C. From the encouraging results outlined above, the application of this reaction to a suitably constructed 1,5-diketone (e.g. 44) should afford a cycloheptene acid with the colchicine ring skeleton. Accordingly 4-(2''-cyclopentanonyl-methyl)-3',4',5'-trimethoxy-1,2-benzocycloheptene-3-one (44) was prepared from the dimethylamino Mannich base of trimethoxy-α-benzosuberone (45) and cyclopentanone. The n.m.r. spectrum showed the nine methoxyl protons as a sharp singlet at 6.1 τ and the aromatic proton as a singlet at 3.5 τ. Under standard fragmentation conditions the diketone (44) gave a carboxylic acid with no vinyl protons and only two methoxyl groups- the n.m.r. showed a 6 x H singlet at 6.1 τ. The acid gave a positive test for a phenol (ferric chloride). It is known that in substituted aromatic systems containing three adjacent methoxyl groups the central methoxyl is readily hydrolysed by acid due to the steric congestion caused by the neighbouring methoxyls.[47] On these

Table I

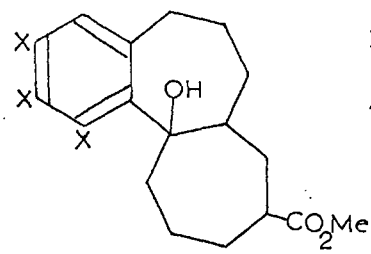
Uitraviolet Spectra

Compound	λ_{max}^{EtOH} (log ε)	λ_{min}^{EtOH} (log ε)
Unsaturated Ester (1)	255mμ (4·15)	243mμ (3·91)
Saturated Ester (2)	270mμ (3·5)	249mμ (3·2)
Saturated Ester (3)	273mμ (3·4)	251mμ (3·1)
Conjugated Derivatives (70) eg. (4)	254 – 258mμ (4·1)	241 – 245mμ (3·95)
Non-conjugated Deriv. (69) eg (5)	274 – 280mμ (2·95 – 3·18)	252 – 262mμ (2·45 – 2·9)
Oxycolchicine (48.) (6)	281mμ (2·51)	264 mμ (2·43)



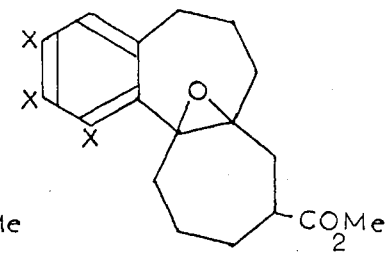
X = OMe

(1)

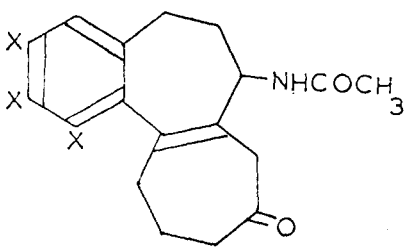


X = OMe

(2)



(3)



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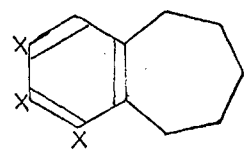

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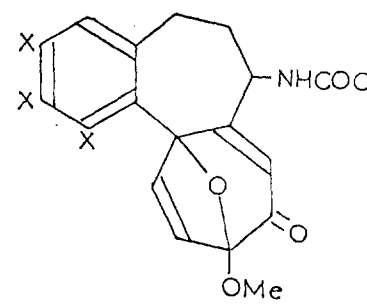
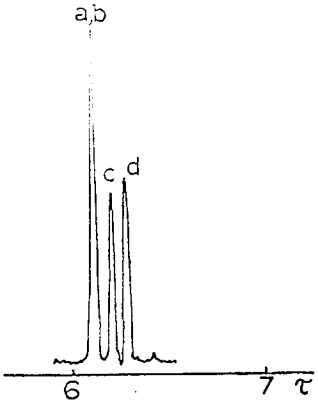
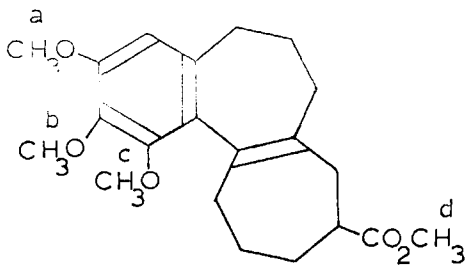


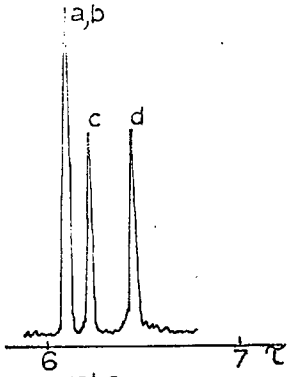
(6)

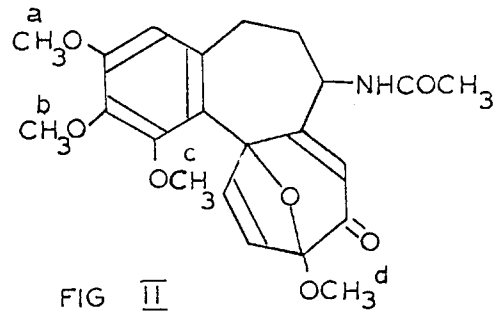




50.

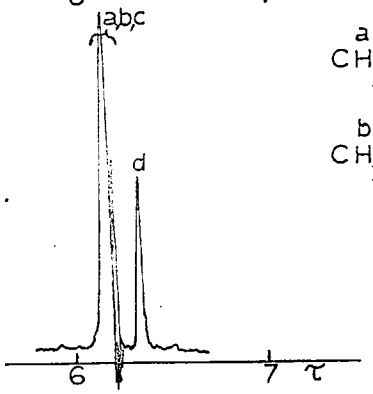
FIG I

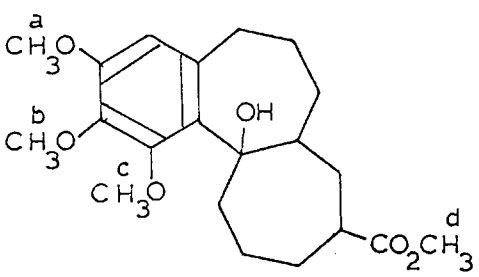




53.

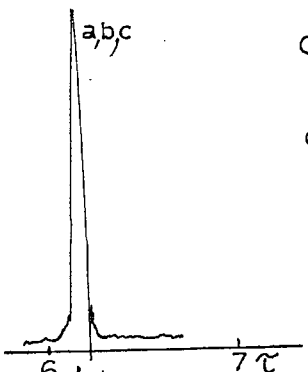
FIG II

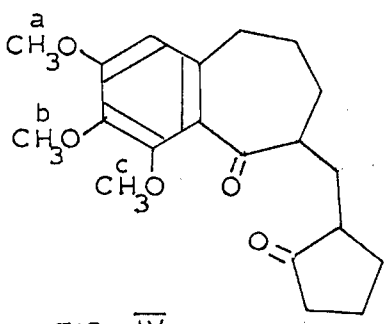




51.

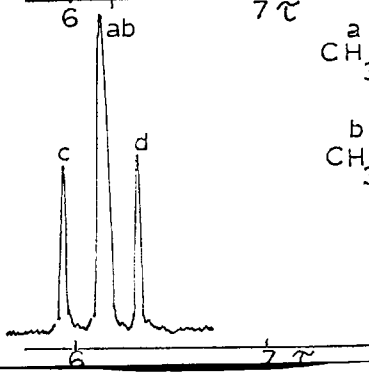
FIG III

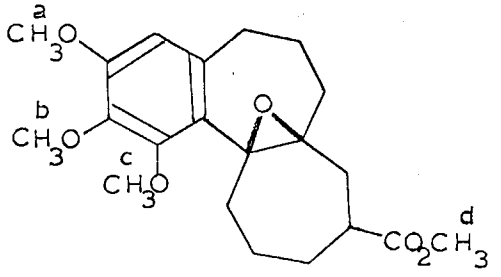




44.

FIG IV





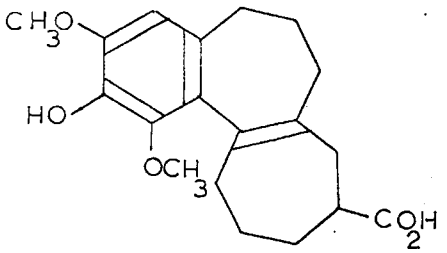
52.

FIG V

grounds it might appear that the C_4' methoxyl has been hydrolysed to give the phenolic acid (48). However, later work provides evidence for the hydrolysis of the C_3' methoxyl. Methylation of this phenolic acid, with alkaline dimethylsulphate gave a 1:1 mixture of esters which were separated by chromatography into polar and less polar fractions.

The non-polar component was isolated as a white solid analysing for $C_{21}H_{28}O_5$; the molecular weight was determined by mass spectrometry as 360. The u.v. spectrum showed characteristic[48] trimethoxy styrene absorption bands at $\lambda_{max.}$ 255 mμ and $\lambda_{min.}$ 243 mμ (Table I) and the n.m.r. showed no vinylic protons indicating a tetra substituted styrene double bond. The aromatic proton resonated at 3.45 τ as a sharp singlet, and of the nine methoxyl protons, three appeared at 6.26 τ as a singlet and six at 6.1 τ as a singlet (Fig. I). The infra-red showed ester absorption bands at 1730 $cm.^{-1}$ and 1240 $cm.^{-1}$. From this spectral data, the non-polar material derived from the diketone (44) was identified as the ester (50).

The polar ester was isolated as a pale yellow viscous oil for which satisfactory analysis figures were unobtainable. However, mass spectrometry gave the



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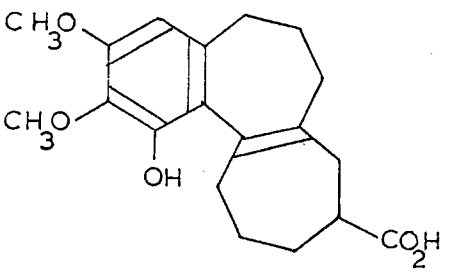

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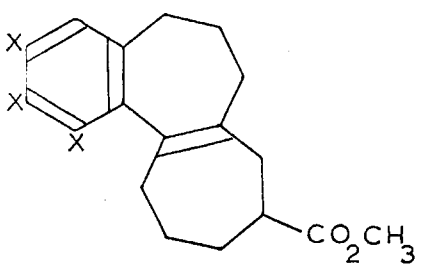

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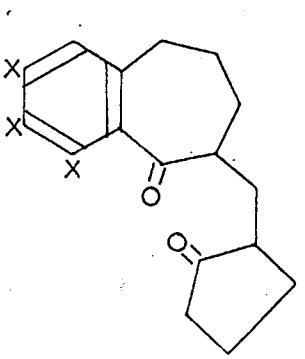
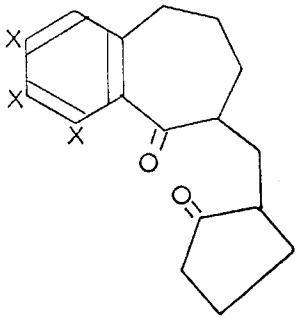


44.

X = OCH_3

molecular ion as 378 m/e which showed a facile loss of 18 m/e fragment to give the 360 m/e ion. The u.v. spectrum showed characteristic[48] trimethoxybenzene bands at $\lambda_{max.}$ 270 mμ and $\lambda_{min.}$ 249 mμ (Table I) i.e. no trimethoxy styrene chromophore. The n.m.r. showed the nine methoxyl protons as two superimposed singlets at 6.1 τ and one aromatic proton as a singlet at 3.62 τ (Fig. III). The methyl ester protons resonated at 6.35 τ as a singlet and two benzylic protons at 7.5 τ as a multiplet. The infra-red showed characteristic ester absorption at 1735 $cm.^{-1}$ and 1240 $cm.^{-1}$ and methoxyl absorption at 1020 $cm.^{-1}$. From this spectral data, the polar material arising from diketone (44) was tentatively identified as the ester (51) i.e. identical to ester (50) except for a hydrated double bond. However, the infra-red showed no hydroxyl absorption bands; it is possible that a hydrogen bond exists between the π electrons of the aromatic ring and the tertiary hydroxyl in the benzylic position. Such bonding would perhaps be the explanation for the aromatic proton resonating at a higher field in ester (51), (3.62 τ) than in ester (50), (3.4 τ). The structure of the polar material was firmly established as (51) by dehydration to



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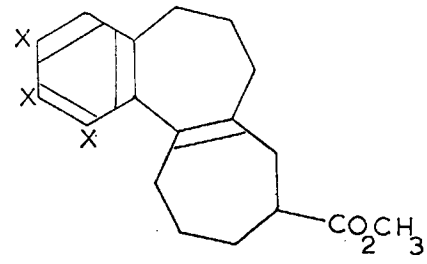

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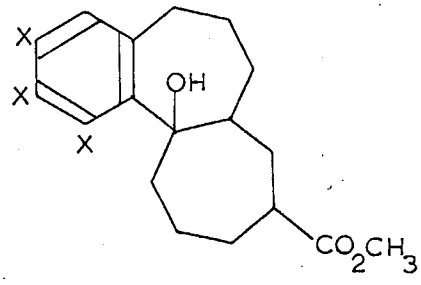

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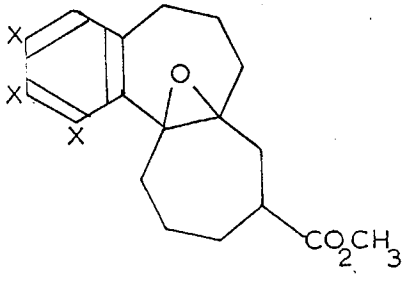

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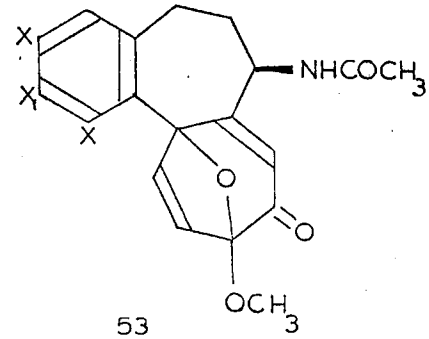
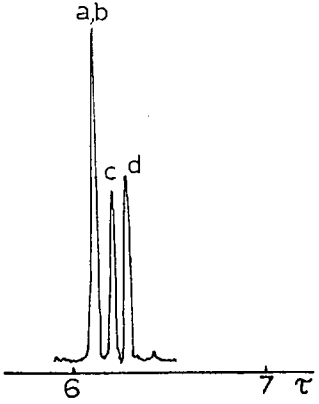


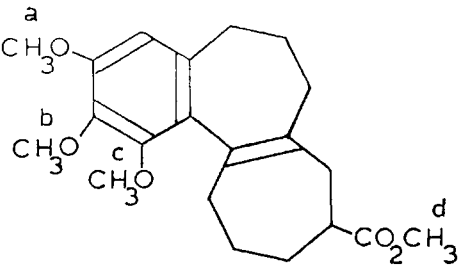
53

X = OCH_3

the unsaturated ester (50). This same unsaturated ester (50) was obtained from the diketone (44) by using the alternative conditions of concentrated sulphuric acid in methanol, thus preventing the hydrolysis of the methoxyl group, which was experienced by using the conventional ring expansion conditions.

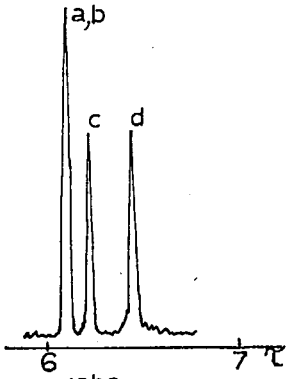
Fig.III and IV show the nine methoxyl protons in the hydrated ester (51) and also the nine methoxyl protons in the diketone (44) as singlets at 6.2 τ. However, in oxycolchicine[48] (53), (Fig. II) and also in the unsaturated ester (50), (Fig. I) six methoxyl protons resonate at 6.1 τ as a singlet and three methoxyl protons at 6.2 τ as a singlet. By comparing these n.m.r. spectra it seems probable that the difference in chemical shifts is due to the double bond exerting a shielding effect on the C_3' methoxyl protons thus causing them to resonate at higher fields than the C_4' and C_5' methoxyl protons. Examination of the chemical shifts of the methoxyl protons in the saturated ester should confirm this. However all attempts to hydrogenate the hindered styrene double bond in the ester (50) proved unsuccessful. The ester (50) was epoxidised as an alternative method of removing the double bond. The epoxide was isolated as a

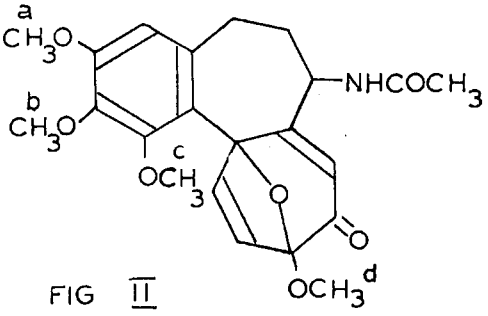




50.

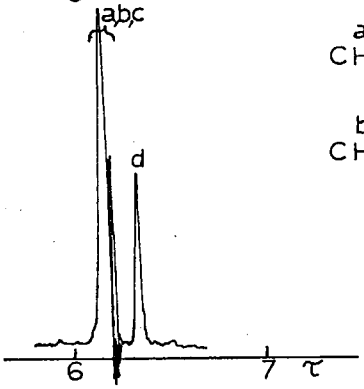
FIG I

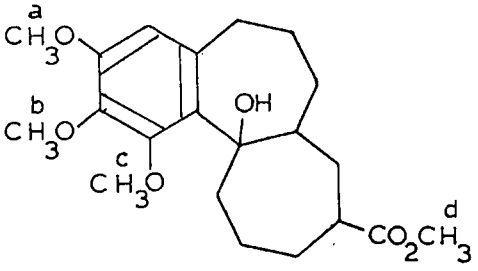




53.

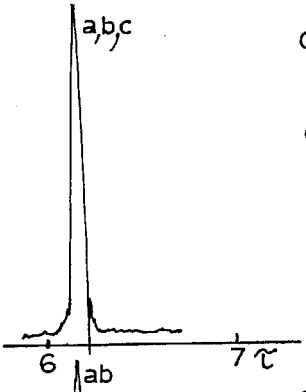
FIG II





51.

FIG III



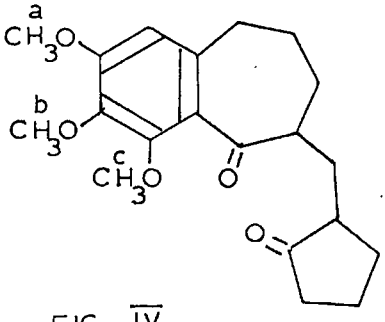


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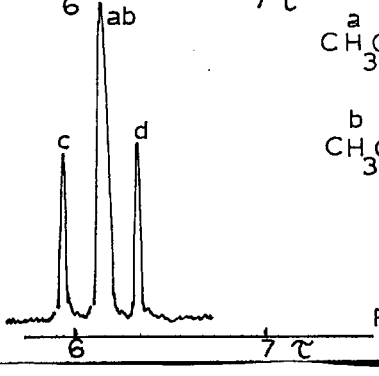
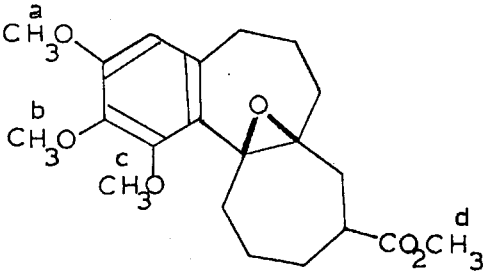
FIG IV

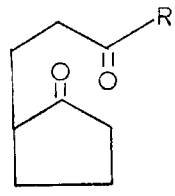




52.

FIG V

colourless oil shown by GC-MS (L.K.B.) to be an isomeric mixture of epoxides (both showing molecular ions at 376 m/e and having similar fragmentation patterns). Fractional recrystallisation gave one of the isomeric epoxides as a white solid analysing for $C_{21}H_{28}O_6$. The u.v. spectrum showed only trimethoxybenzene absorption bands at $\lambda_{max.}$ 273 mμ and $\lambda_{min.}$ 251 mμ (Table I). The n.m.r. showed the methoxyl protons as a 6 x H singlet at 6.1 τ and a 3 x H singlet at 5.95 τ (Fig. V). Removal of the shielding effect of the double bond should have caused the C_3' methoxyl protons to resonate at the same field as the C_4' and C_5' methoxyl protons as observed in the hydrated ester (51) and the diketone (44). Presumably the epoxide exerts a deshielding effect on the C_3' methoxyl protons causing them to resonate at a lower field. By examining Fig. I - V it is evident that the C_3' methoxyl protons are affected by the nature of ring B and hence it is now possible to ascertain which of the methoxyl groups was removed during the ring expansion of the diketone (44). The phenolic acid was assumed to incorporate a styrene double bond since methylation gave an ester containing the trimethoxy styrene chromophore. The n.m.r. of the phenolic acid showed 6 methoxyl protons



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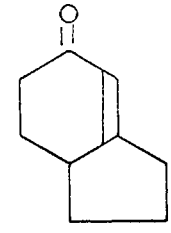

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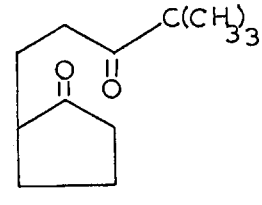

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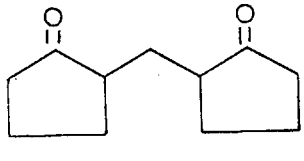

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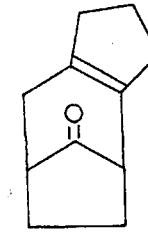
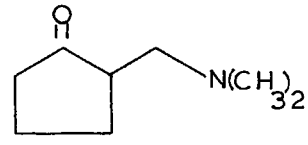


57.

resonating as <u>one</u> singlet at 6.1 τ whereas methylation gave an ester showing <u>two</u> singlets at 6.1 τ and 6.2 τ; the latter being assigned to the C_3' methoxyl protons. Thus the C_3' methoxyl group is removed by acid hydrolysis. Work is now in progress to tropolonise ring C of the ester (50) as the final stage in the synthesis of colchicine.

With the mechanism of the ring expansion reaction established, it remained only to investigate the scope of the reaction by studying class (b) of 1,5-diketones i.e. wholly aliphatic [e.g. (24), R = CH_3]. Here the fragmentation reaction is frustrated by the possibility of an alternative aldol condensation at C_4', in the initial stage, to give the hydroindanone (54). In order to study the yield of ring expansion products for the aliphatic series, it was thus necessary to select a diketone unable to condense at C_4' e.g. 2-(3'-t-butyl-3'-oxopropyl)-cyclopentanone (55). However, this diketone has been shown[30] to be too sterically hindered to particpate in an aldol reaction at C_5.

Bis-cyclopentanonyl methane (56), having a completely symmetrical structure, can only aldolise to give a bicyclic system (57) and hence this diketone will be used as the representative example of the aliphatic series for ring



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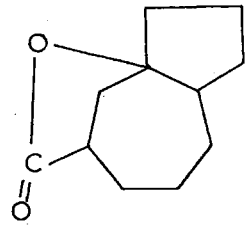

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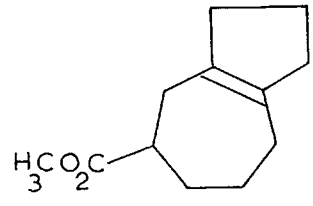
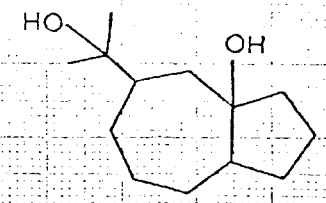


60.

expansion studies. Dauben[49] has speculated that a completely aliphatic bicyclo-(3,2,1)-octenone is capable of fragmentation in the fashion described above for the aromatic series and if this is the case, the carbonium ion intermediate should be stabilised to a lesser extent than in the aromatic series and hence a lower yield of ring expansion products is to be anticipated. To test this theory, bis-cyclopentanonyl methane[50,51,52] (56) was prepared from 2-dimethylaminomethylcyclopentanone (58) and subjected to standard fragmentation conditions. The only ring expansion product was the lactone (59) isolated in 58% yield and identified by its i.r. spectrum, (1780 $cm.^{-1}$) and n.m.r. which showed no absorption below 8.3 τ. By applying the alternative conditions of concentrated sulphuric acid-methanol, an 80% yield of the methyl ester (60) was isolated as a colourless oil analysing for $C_{12}H_{18}O_2$. The n.m.r. showed no vinylic protons and g.l.c. showed homogeneity i.e. the double bond is located in the tetra substituted position, with no isomerism.

Both of these ring expansion products, lactone (59) and ester (60), have been assumed, from experience and mechanistic speculation, to incorporate a cycloheptene ring in a bicyclo-(5,3,0)-decane system. Before applying the ring

FIG. VI



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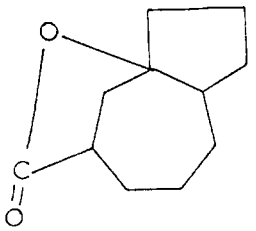

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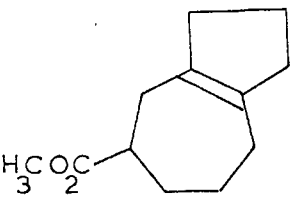

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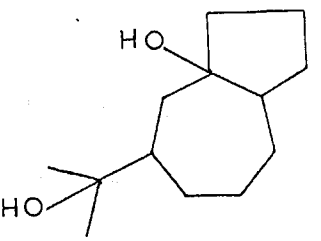

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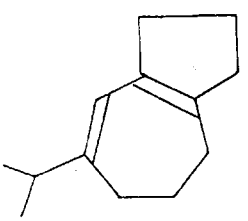

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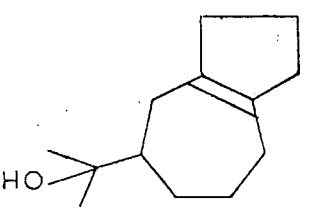


63.

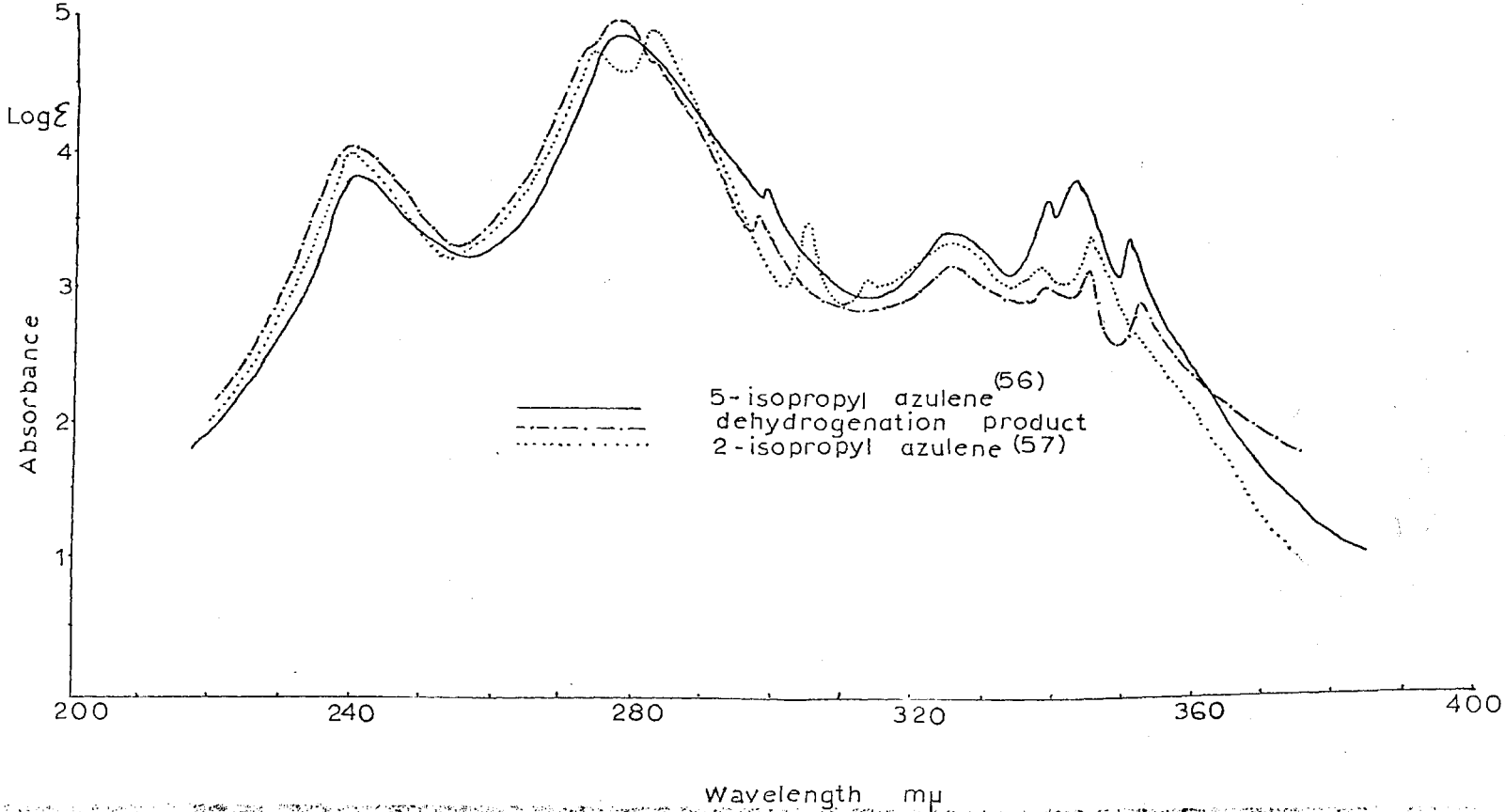
expansion reaction to a synthetic route to guaianolide sesquiterpenes, it was considered necessary to have concrete rather than speculative, proof for the structures.

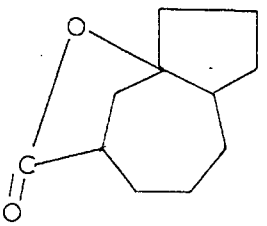
Treatment of the lactone (59) with an excess of methyl magnesium iodide in ether, gave a high yield of the diol (61) which was isolated as a white solid analysing for $C_{13}H_{24}O_2$. The infra-red spectrum showed hydroxyl bands at 3456 $cm.^{-1}$ and 3302 $cm.^{-1}$ which decreased in intensity on dilution i.e. intermolecular hydrogen bonding. The n.m.r. integrated for two hydroxyl protons which resonated as a singlet at 8.1 τ (D_2O exchange). The six methyl protons resonated at 8.8 τ as a <u>singlet</u> i.e. one hydroxyl group situated on the α position of the isopropyl group, and the remaining hydroxyl group at C_{10} having been derived from the C_{10} oxygen of the lactone. The mass spectrum showed no parent ion but gave the M-18 ion at 194 m/e which lost the 18 m/e fragment to give the base peak at 176 m/e with a metastable at 160 m/e (calc. 159.9 m/e). Scheme IX shows a proposed fragmentation process based on the abundant ions given in Fig. VI . Acid catalysed dehydration of the diol gave a diene in which the positions of the double bonds were eastablished by u.v. and n.m.r. spectroscopy. The u.v.

spectrum showed a homoanular diene with an absorption band at $\lambda_{max.}$ 263 mμ [calc. for (62) as 263 mμ] and the n.m.r. showed one vinyl proton at 4.5 τ as a sharp singlet. The six methyl protons appeared as a doublet at 9.02 τ (J = 6 c/s.) and the methine proton as a subsplit quartet at 6.55 τ (J = 6 c/s.). From this spectral data, the diene was identified as 5-isopropylbicyclo-(5,30)-decaliene-4,9 (62). The same diene was obtained from 5-carbomethoxy-bicyclo-(5,3,0)-decene-9 (60) as follows. Treatment of this ester with methyl magnesium iodide gave the tertiary alcohol (63) isolated as a white solid analysing for $C_{13}H_{22}O$. The infra-red showed a non-bonded hydroxyl at 3615 $cm.^{-1}$ which was observed to resonate in the n.m.r. at 8.5 τ as a singlet (D_2O exchange). The position of the hydroxyl was established from the splitting pattern of the isopropyl methyl protons which resonated as a sharp singlet at 8.8 τ i.e. hydroxyl on the α-position of the C_5 isopropyl group. Dehydration of this alcohol gave a diene which was shown by g.l.c. analysis on 1% OV 17 at 75° and 25% cyano B at 75° to be identical to the diene (62).

Dehydrogenation of this diene (62) with sulphur[53,54] at 280° gave an unidentifiable product shown by mass spectrometry to incorporate a molecule of sulphur. An alternative[55]

Fig. VII


Log ε
5
4
3
2
1
Absorbance
200
240
280
320
360
400
Wavelength mμ
5-isopropyl azulene (56)
dehydrogenation product
2-isopropyl azulene (57)



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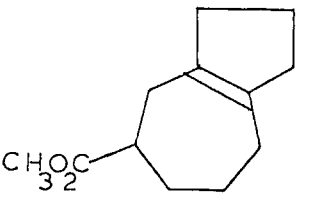

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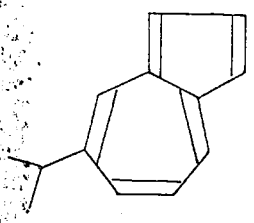

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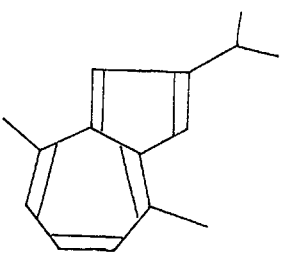

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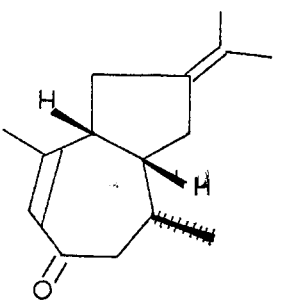

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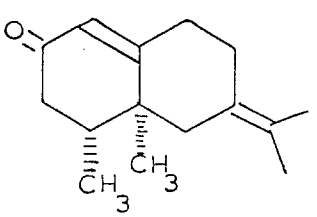
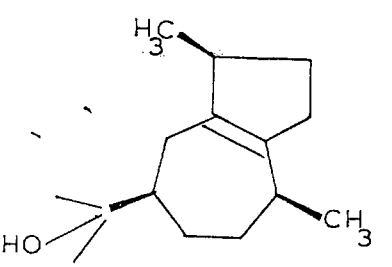


67.

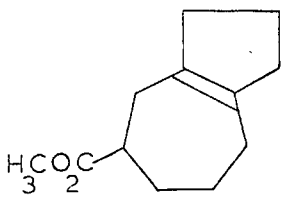


68.

method for dehydrogenation using selenium at 300° gave a dark brown oil which was chromatographed on silica to give a deep blue liquid, too volatile for analysis. The ultraviolet spectrum showed maxima at 293 mμ and 276 mμ, and compared favourably with the u.v. spectrum of an authentic sample of 5-isopropyl azulene (64)[56,57] (Fig. VII). The u.v. spectrum was taken as adequate evidence for the orientation of the synthetic azulene, since every isopropyl azulene isomer has its own characteristic u.v. spectrum[56,57](Fig. VII).

Recent work by De Mayo[58] and independently by Marshall[59], has cast doubt on the conclusions that can be drawn from high temperature dehydrogenation experiments. Pfau and Plattner[60] sucessfully dehydrogenated α-vetivone to vetivazulene (65) and hence assigned the bicyclo-(5,3,0)-decane structure (66) to α-vetivone. However, De Mayo and Marshall have now shown unambiguously that the terpene has an eremophiloide structure (67) and that vetivazulene was formed via a rearrangement. Hence an alternative degradative scheme is required to prove the structures of the ester (60) and the lactone (59).

Ruzicka[61] and Plattner[62] successfully degraded Guaiol (68) to 1-oxo-2,5-dimethyl-8-isopropenyl-$\Delta^{9,10}$-octalin



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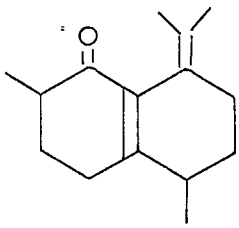

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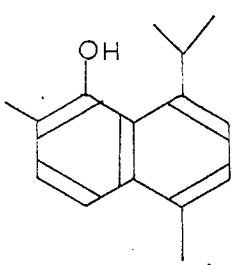

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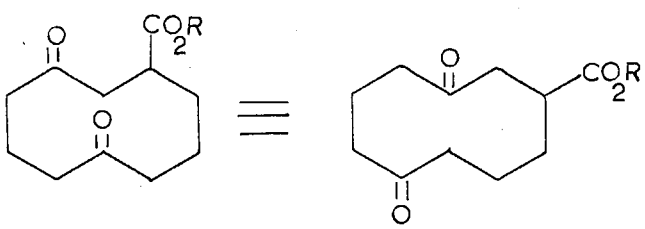
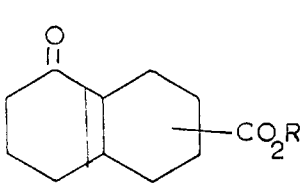


(a) (b)

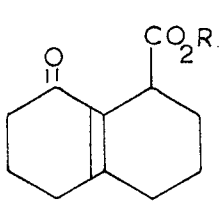
71. R = CH_3

72. R = H



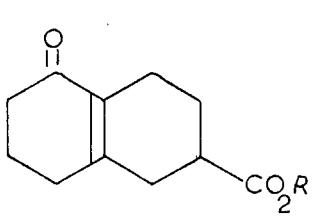
73. R = CH_3

74. R = H



75. R = CH_3

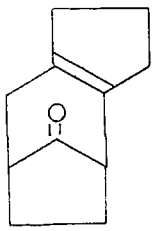
76. R = H



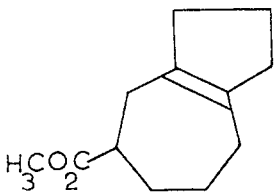
77. R = CH_3

78. R = H

(69) by ozonolysis followed by a transannular aldol identifying this product by dehydrogenation to 1-hydroxycadalene (70). Similarly, ozonolysis of the ester (60) gave a colourless oil, shown by g.l.c. to be homogeneous, and characterised as its 2,4 dnp derivative which was isolated as deep-red needles analysing for $C_{18}H_{20}N_4O_6$. The infra-red of the ozonolysis product showed an α,β-unsaturated carbonyl at 1675 $cm.^{-1}$, substantiated by the enone absoprtion in the u.v. at 244 mμ. Thus it may be concluded that the initial ozonolysis product (71) had cyclised to give a carbomethoxylated $\Delta^{9,10}$-octalin (73). Such a ring closure-dehydration step can proceed in two possible directions (71a or b) but g.l.c. analysis showed the presence of only one product and hence one direction must be favoured from steric considerations and (or) from the stability of the final enone. The direction represented by (71a) would proceed via a sterically hindered transition state resulting in the formation of the octalin (75) with the carbomethoxyl group in the overcrowded C_8 position. On the other hand, the alternative cyclisation (71b) would proceed via a strain free transition state to give a thermodynamically stable enone (77). Hence on steric grounds this latter direction of cyclisation would be preferred. However, this proposal is not in accordance with



57.



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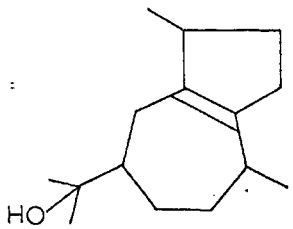

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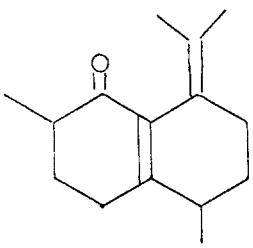
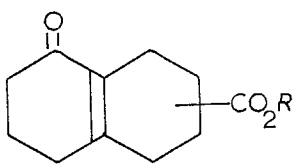
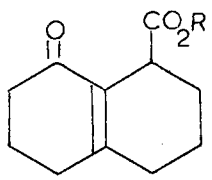


69.



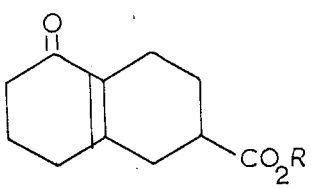
73. R = CH_3

74. R = H



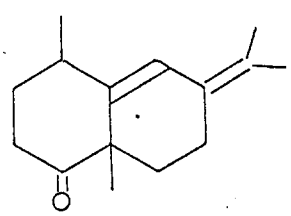
75. R = CH_3

76. R = H



77. R = CH_3

78. R = H



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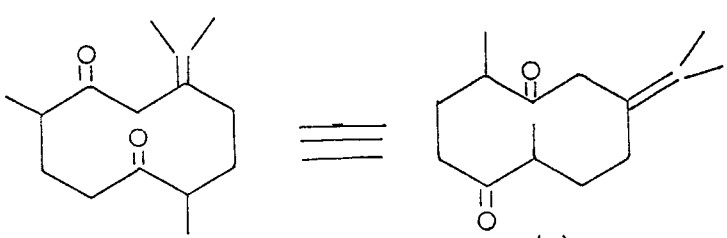
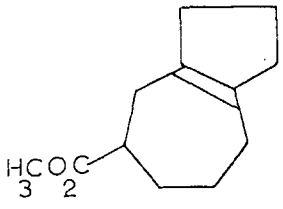


(a) (b)

79.

Ruzicka's observation[61] that ozonolysis of guaiol (68) gave the octalin (69) i.e. the least favoured isomer on steric grounds. Consideration of his intermediate diketone (79) indicates that of the two possible directions for ring closure, the one resulting in the thermodynamically favoured enone (69) i.e. direction (79a) would be preferable, despite the overcrowding at C_8, to the altenative $\Delta^{5,10}$ unconjugated enone (80).

To establish which isomer had in fact resulted from our degradation of ester (60) the ozonolysis product (73) was hydrolysed to the corresponding acid (74) which was isolated as a white solid analysing for $C_{11}H_{14}O_7$. The infrared showed the α,β-unsaturated carbonyl at 1675 $cm.^{-1}$ i.e. unchanged by hydrolysis. Thus the ozonolysis product can now be assigned the structure (77) since hydrolysis of the isomeric ester (75) would have given an acid (76) which would hydrogen bond with the carbonyl thus lowering its frequency from 1675 $cm.^{-1}$ to ~1650 $cm.^{-1}$. Moreover, the same keto acid (78), was obtained when the double bond in 2,3-cyclopentenobicyclo-(3,2,1)-oct-2-en-8-one (57) was cleaved by ozonolysis. The ozonolysis product was isolated as a



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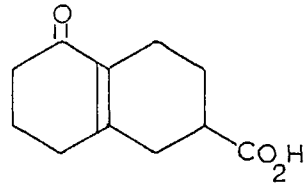

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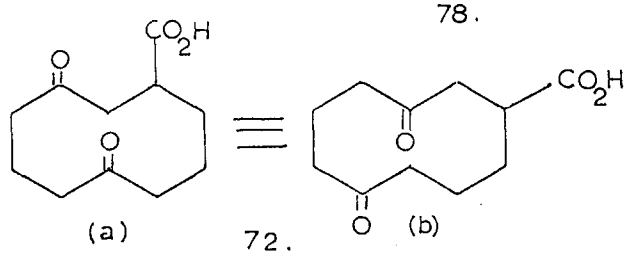

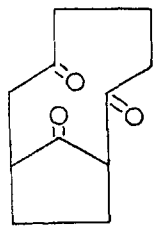

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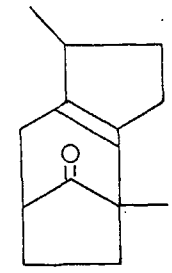

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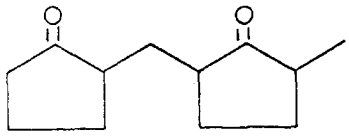
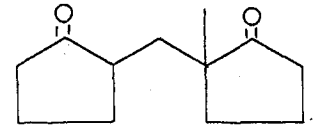
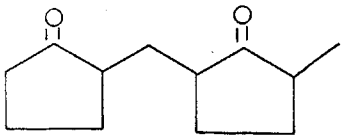


83.



84.

white solid analysing for $C_{11}H_{14}O_3$ and shown by mixed m.p. and g.l.c. of the methyl ester to be identical to 1-oxo-$\Delta^{9,10}$-octalin-6-carboxylic acid (78) derived from ester (60). The initially formed 1,3-diketone (81) was presumably opened in acid to give the cyclodecane-1,5-diketone (72) which ring closed as described above to give the $\Delta^{9,10}$-octalin (78) (Scheme X). Thus the proposed bicyclo-(5,3,0)-decane structures for the ring expansion products of biscyclopentanonyl methane has been proved and the reaction can now be confidently used in a proposed synthesis of guaiol. It can be seen that ring expansion of the bicyclic ketone (82) would give a cycloheptene methyl ester with the two methyl groups having the correct orientation of guaiol . Thus 2-methyl-5-(2'-cyclopentanonyl methyl)-cyclopentanone (83) was prepared from 2-methylcyclopentanone and 2-dimethylaminomethylcyclopentanone. The diketone showed the methyl protons as two overlapping doublets at 8.95 τ (J = 6 c/s.) and the infra-red showed the absorption at 1738 $cm.^{-1}$. Thus the thermal Michael condensation had proceeded in the predicted[67] direction i.e. at the least substituted C_5 atom to give the diketone (83). It is relevant to note that had the isomer (84) been required, it could have been



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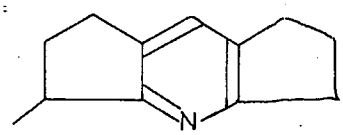

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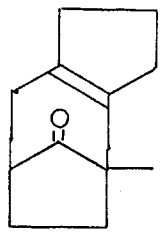

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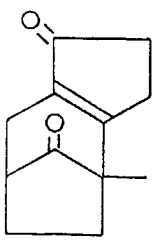
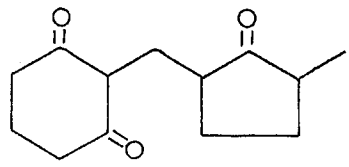
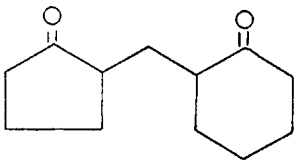


86 a.

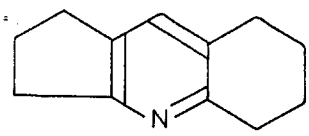


87.

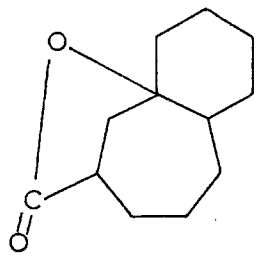
readily obtained using the method of Ross[68] i.e. by condensing 2-methylenecyclopentanone and 2-methylcyclopentanone under alkaline conditions, The presence of the two overlapping doublets in the n.m.r. of (83) arises from the existence of both C_2 epimers. This was convincingly shown by conversion to 2,3-(2'-methylcyclopentene)-6,7-dihydro-5H-pyrindine (85) which altered the methyl signal to a sharp doublet at 8.7 τ (J = 6 c/s). Treatment of this diketone (83) with p-toluene sulphonic acid in benzene, with removal of the water formed, gave a camphoraceous smelling liquid analysing for $C_{12}H_{16}O$. The infra-red showed an absorption band at 1758 $cm.^{-1}$ i.e. characteristic of the strained cyclopentanone carbonyl at C_8 in a bicyclo-(3,2,1)-octen-8-one. The n.m.r. showed the methyl protons as a sharp singlet at 8.95 τ with no suggestion of a doublet i.e. the aldolisation step had occurred only in the required direction to give the bicyclic enone (86). It was planned to introduce the C_3 methyl by a selective[63,64,65] allylic oxidation. However, this position proved so unreactive that all attempts to oxidise it with SeO_2 failed. As an alternative route to this desired bicyclic diketone (86a), the model triketone (87) was prepared as described in Part II, p. 141, for ring closure studies. However, all



88.



89.



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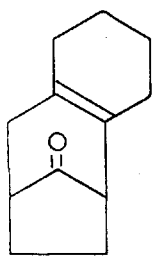

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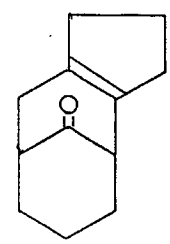
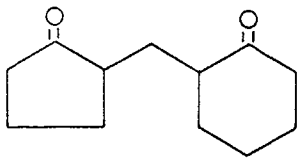


92.

attempts to induce aldolisation were unsuccessful. Doubtless this is due to the fact that cyclohexan-1,3-dione exists predominantly as the enol. Thus the synthesis of guaiol, based on these hitherto promising lines was abandoned.

To investigate the possibility, and the extent, of the alternative aldolisation process in an unsymmetrical aliphatic 1,5-diketone, 2-(2'-cyclopentanonylmethyl)-cyclohexanone (88) was prepared from cyclohexanone and 2-dimethylaminomethylcyclopentanone. The infra-red showed doublet carbonyl absorption at 1720 $cm.^{-1}$ (cyclohexanone) and 1740 $cm.^{-1}$ (cyclopentanone). Ring closure at C_5, would produce a bicyclo-(3,2,1)-octenone (91) capable of fragmentation to the γ-lactone (90) whereas the alternative aldolisation at C_6 would give a bicyclo-(3,3,1)-non enone (92) stable to further attack by acid. Thus, measurement of the yields of (90) and (92) should give a rough indication of the more favoured aldolisation path. Treatment of the diketone (88) with concentrated hydrochloric acid in glacial acetic acid gave a neutral product but no acidic material. The neutral fraction, after removal of unreacted diketone, was shown by g.l.c. to contain three compounds. Chromatography gave the least polar material as a mixture of two closely



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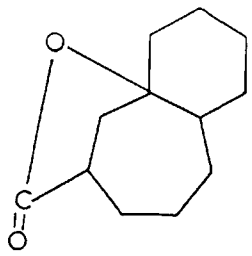

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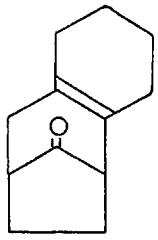

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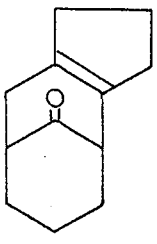

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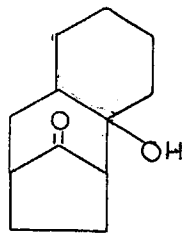
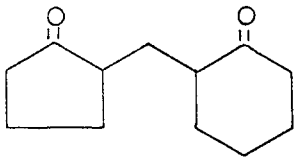


93.

related compounds (similar R_t on 10% P.E.G.A. at 175° and identical R_f in 25% ethyl acetate-petrol). Further elution gave the most polar compound as a colourless oil analysing for $C_{12}H_{18}O_2$ and identified as 11-hydroxy-bicyclo(5,4,0)-undecane-6-carboxylic acid lactone (90) by its infra-red (1778 $cm.^{-1}$) and n.m.r. which showed no absorption below 8.3 τ. From experience and mechanistic speculation, the mixture of compounds in the non-polar fraction was assumed to be the bicyclo-(3,3,1)-non enone (92) (1727 $cm.^{-1}$) and the bicyclo-(3,2,1)-octenone (91) (1755 $cm.^{-1}$). By utilising their differing stabilities to acid, the latter was converted to the lactone (90). The bicyclo-(3,3,1)-non enone (92) was thus separated from the lactone by chromatography and isolated as a colourless oil analysing for $C_{12}H_{16}O$. A quantitative g.l.c. analysis of the neutrals arising from the diketone (88) showed peaks corresponding to returned diketone (28%), lactone (48%), bicyclo-(3,2,1)-octenone (14%) and bicyclo-(3,3,1)-non enone (10%). Thus the aldol condensation at C_5' is more favoured than that at C_6. It is most likely that the fragmentation of the bicyclic ketol (93) proceeds faster than the formation of the bicyclo-(3,3,1)-non enone (92) (Scheme XI).



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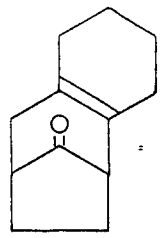

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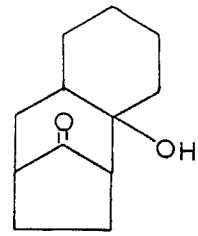
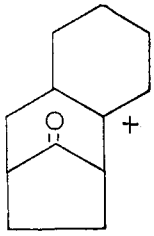


93.



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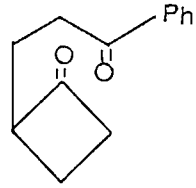

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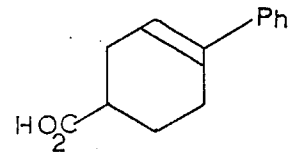

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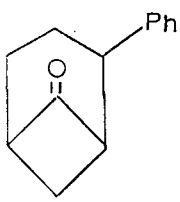

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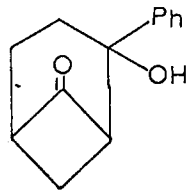

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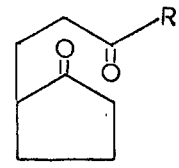
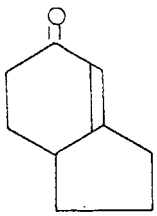


24.

It has been shown that the ring expansion reaction proceeds by either a protonation step (Schemes VI-VIII) or by the formation of a carbonium ion (Scheme V), In the ring expansion of the diketone (88), a high recovery of the supposed intermediate bicyclo-(3,2,1)-octenone (91) makes it unlikely that this compound can act as an intermediate since its isolation indicates relative stability to acid. On the other hand the ketol (93) could both fragment via the carbonium ion (94), and dehydrate to the bicyclic ketone (91). Thus the ketol-carbonium ion -lactone mechanism appears to operate in this particular example. An additional piece of evidence in favour of the carbonium ion mechanism is the ability of 2-(3'-phenyl-3'-oxopropyl)-cyclobutanone (14) to give 4-phenylcyclohex-3-ene carboxylic acid (21) whereas the proposed intermediate bicyclo-(3,1,1)-heptenone (10) could not be isolated and could thus be regarded as too strained to exist as an intermediate. On the other hand, the ketol (23) would be more stable, and hence could readily fragment to the acid via the carbonium ion.

The remaining class of wholly aliphatic 1,5-diketones, to be investigated under the standard fragmentation conditions, are those (e.g.24, R=CH_3) which can theoretically



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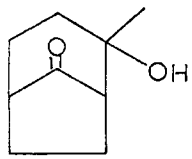

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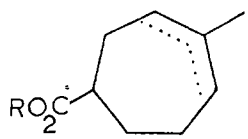
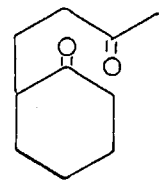
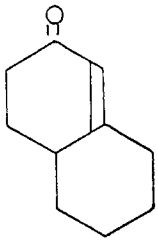


96. R = CH_3
97 R = H



98.



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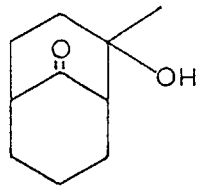

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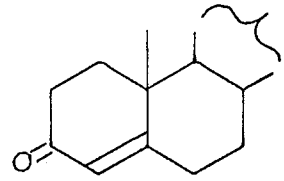

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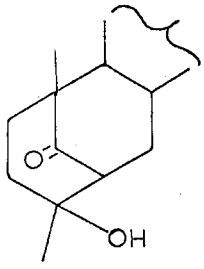

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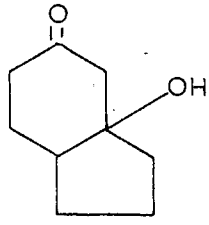

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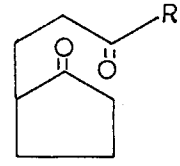


104. R = CH_3

105. R = $CH_2CH(CH_3)_2$

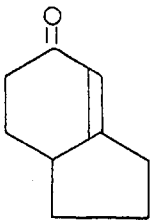
$RCOCH_2CH_2N(CH_3)_2$

106. R = CH_3

107. R = $CH_2CH(CH_3)_2$

cyclise to give either tetrahydroindanone (54) or a bicyclic ketol (95); the latter fragmenting further to give a cycloheptene carboxylic acid (97). The preferred aldolisation path for such a system can be predicted by a comparison with the analogous cyclohexanone system (98) studied by Johnson.[66] He observed that acid catalysed cyclisation of the diketone (98) gave the thermodynamically favoured enone (99) and proposed that the reaction proceeded via the kinetically favoured bicyclic ketol (100). In support of this proposal, Johnson obtained the conjugated enone (101) by base catalysed dehydration of the bicyclic ketol (102); thus demonstrating the existence of an equilibrium between both aldolisation products (Scheme XII). It appears feasible that a similar equilibrium between the ketol (103) and the bicyclic ketol (95) might arise from cyclisation of the 1,5-diketone (24, R=CH_3) and that dehydration would give the thermodynamically more stable enone (54).

To test this idea, 2-(3'-oxobutyl)-cyclopentanone (104) and 2-(5'-methyl-3'-oxohexyl)-cyclopentanone (105) were prepared from the appropriate Mannich bases (106) and (107) and cyclopentanone. Under standard fragmentation conditions, both diketones afforded negligible amounts of acid.



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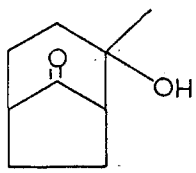

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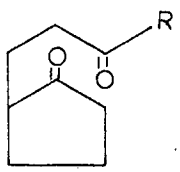
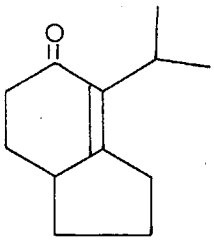


104. $R = CH_3$

105 $R = CH_2CH(CH_3)_2$



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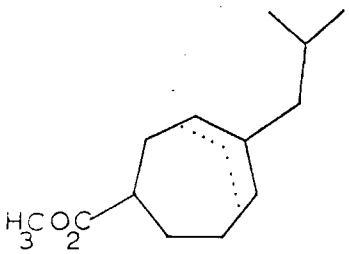

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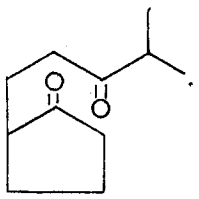
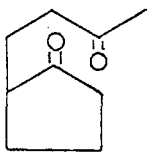
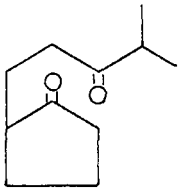
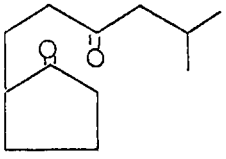
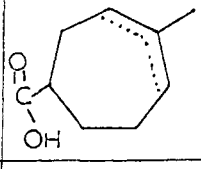
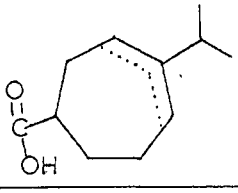
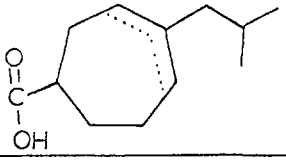
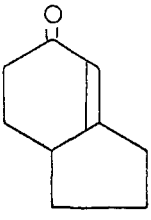
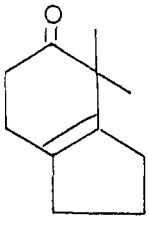
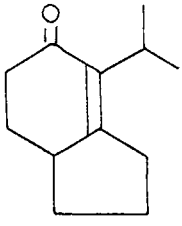


110.

The major component from the diketone (104) was isolated as a colourless oil in 60% yield. The presence of an enone system was effectively demonstrated in the u.v. spectrum by a band at 240 mμ and in the i.r. spectrum by absorption at 1680 $cm.^{-1}$. This enone was identified as 5-oxo-$\Delta^{4,9}$-tetrahydroindene (54) by comparing its 2,4-dnp with an authentic sample.[78] Similarly, the neutral product derived from the diketone (105) showed enone absorption in the u.v. at 247 mμ and in the i.r. at 1678 $cm.^{-1}$. The 2,4-dnp derivative was obtained as red needles analysing for $C_{18}H_{22}N_4O_4$. On this evidence the enone was identified as 4-isopropyl-5-oxo-$\Delta^{4,9}$-tetrahydroindene (108).

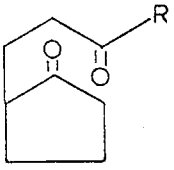
Thus it can be assumed that in the case of these two diketones (104) and (105), the conditions used for fragmentation are precisely those favouring the formation of the thermodynamically stable conjugated enone. Hence it should be possible to alter the course of the reaction, to give a cycloheptene acid, by either selecting a diketone unable to cyclise to a conjugated enone or by employing conditions more likely to favour a rapid formation and fragmentation of the bicyclic ketol (95). To investigate the first of these two possibilities, the diketone (110) was prepared

Diketone			
Acid			
%Yield(a)	3	25	2
%Yield(b)	66	68	80
Hydrindone			
%Yield(a)	65	60	75
%Yield(b)	0	0	5

(a) : Standard Conditions

(b) : Forcing Conditions

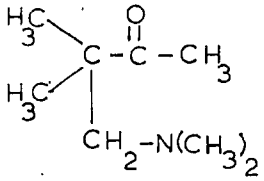
Table II



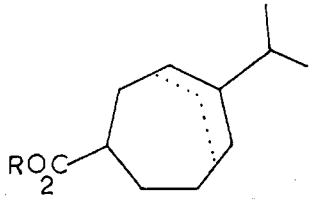
104. $R = CH_3$

105. $R = CH_2CH(CH_3)_2$

110. $R = CH(CH_3)_2$

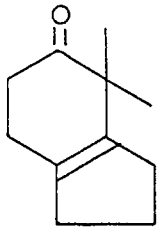


111.



112. $R = CH_3$

113. $R = H$



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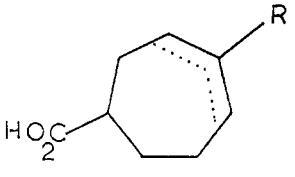

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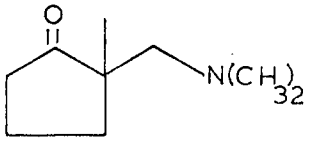


116.

from the Mannich base (111) and cyclopentanone (Part II, p.139). Standard fragmentation conditions gave an acidic product (~ 25%) and a neutral product (~ 60%). The acid was treated with diazomethane and the resultant esters analysed for $C_{12}H_{20}O_2$ and identified as 1-carbomethoxy-4-isopropylcyclohept-3 and 4-ene (112) which was shown by g.l.c. to be a 1:1 mixture of isomers. The n.m.r. of the ester (112) showed one vinylic proton as a multiplet at 4.07 τ and six methyl protons as a doublet at 8.9 τ. The neutral product showed end absorption only in the u.v. spectrum and a non conjugated ketone at 1718 $cm.^{-1}$ in the i.r. spectrum. The n.m.r. showed six methyl protons as a singlet at 8.8 τ. The mass spectrum gave the molecular weight as 166. On this evidence, the neutral material was identified as 4,4-dimethyl-5-oxo-$\Delta^{8,9}$-tetrahydroindene (114). The diketone (110) was unable to cyclise to give a conjugated enone and hence the yield of cycloheptene acid was improved from ~ 2% for diketones (104) and (105) to ~ 25% for diketone (110).

To examine the effect of experimental conditions on the course of aldolisation, the three diketones (104), (105) and (110) were subjected to the more forcing conditions of p-toluene sulphonic acid in ethylene glycol. Table II

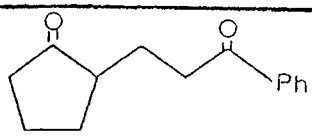
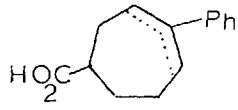
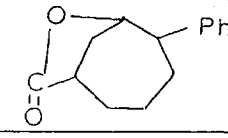
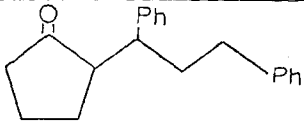
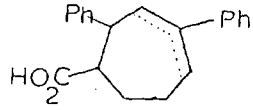
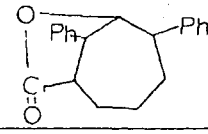
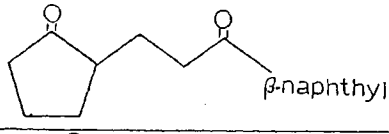
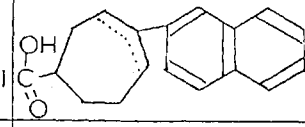
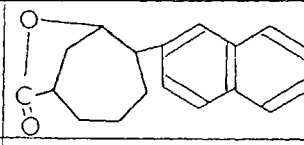
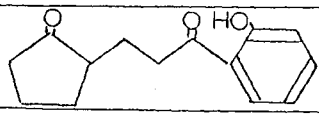
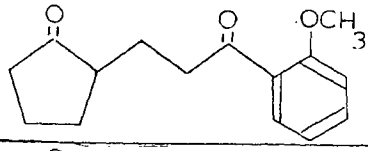
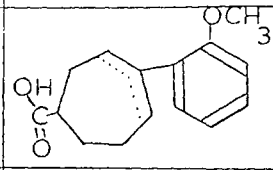
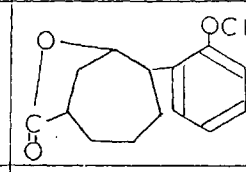
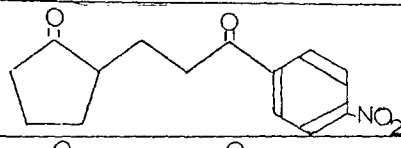
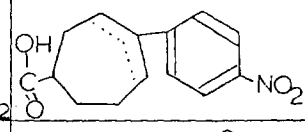
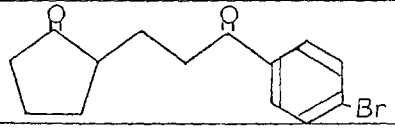
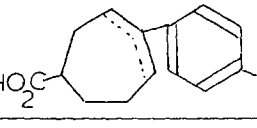
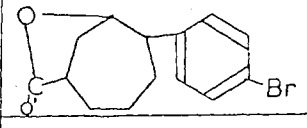
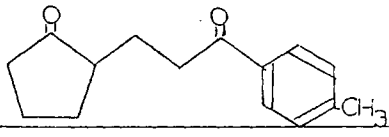
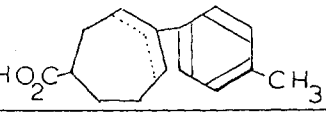
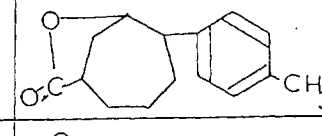
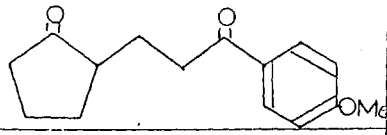
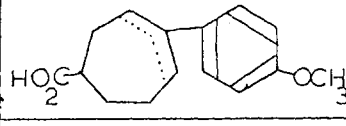
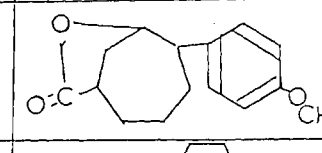
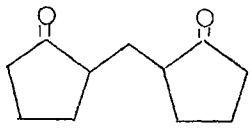
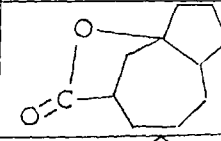
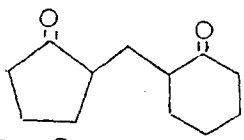
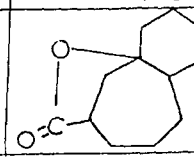
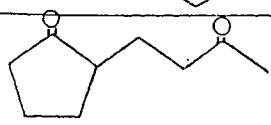
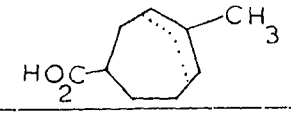
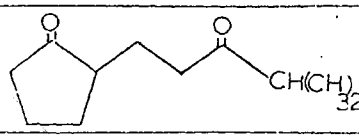
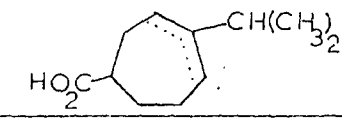
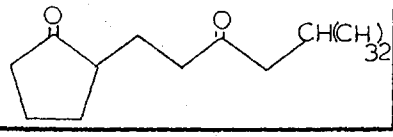
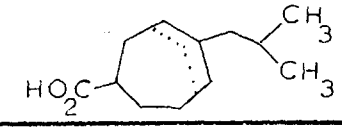
1,5 - Diketone	Carboxylic Acid	Yield %	Lactone	Yield %
		75		10
		85		2
		80		10
	—	0	—	0
		60		24
		20	—	0
		70		20
		80		10
		80		4
	—	0		40
	—	0		37
		3	—	0
		25	—	0
		2	—	0

Table III

shows that in each case there was a high yield of cycloheptene carboxylic acid with only trace amounts of the corresponding tetrahydroindene. These results can be interpreted as evidence for the equilibrium process illustrated in Scheme XIII. Under the relatively mild conditions of hydrochloric acid - glacial acetic acid, the ketol (a) can be regarded as dehydrating to the thermodynamically stable enone (54), thus causing the equilibrium to be mainly in this direction. However under the more forcing conditions, the kinetically favoured bicyclic ketol (b) appears to fragment to the cycloheptene acid (115) more rapidly than isomerisation to the ketol (a).

Table III demonstrates the scope of the ring expansion reaction which, as can be seen, offers a route to substituted cycloheptene compounds in high yield from simple precursors.

EXPERIMENTAL

General

Melting points were recorded on a Kofler microscope hot stage and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were recorded on a Unicam SP.200 and SP.200G spectrophotometers. Solution spectra were determined on a Unicam SP.100 double beam spectrophotometer, equipped with an SP.130 sodium chloride prism grating double beam monochromator operated under vacuum conditions. Ultra-violet absorption spectra were determined on a Unicam SP.800 spectrophotometer in ethanolic solution.

Nuclear Magnetic Resonance spectra were recorded on a Perkin Elmer R.S.10 (60 megacycle) in deuterated chloroform with tetramethylsilane as internal reference.

Gas-liquid Chromatography (g.l.c.) was carried out on Pye Argon and Perkin Elmer F.11 Gas Chromatographs. Chromatoplates, both for analytical and preparative use, were made by the method of Stahl using Kieselgel G (Merk). Column Chromatography was carried out using B.D.H. silica referred to as 'fine silica'.

High resolution mass spectra were recorded on the A.E.I. MS 9 mass spectrometer.

EXPERIMENTAL

Methylene cyclobutane (18)

This compound was prepared from pentaerythrityltetrabromide[82] (17) according to the method of Shand[39] and isolated as a colourless liquid in 80% yield, b.p. 40 - 2°/760 mm.

Cyclobutanone

This ketone was prepared by ozonolysis of methylene cyclobutane (18) according to the method of Conia[40] in 70% yield, and isolated as a colourless liquid, b.p. 98 - 9°/760 mm.

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1783 cm.$^{-1}$.

2-(3'-Phenyl-3'-oxopropyl)cyclobutanone (14)

(a) Cyclobutanone (1.605 gm., 0.023 m.) and β-dimethylaminopropiophenone (15) (1.239 gm., 0.007 m.) were heated at reflux temperature, with stirring, for 90 minutes. The cooled reaction mixture was neutralised with glacial acetic acid and diluted with ether. The ethereal solution was brine washed, dried and evaporated to give a pale yellow

oil (1.2 gm.). Chromatography on fine silica gave the required diketone (14) as a colourless oil (720 mgs., 60%), b.p. 125-30/0.03 mm. Found: C, 77.3; H, 7.01, $C_{13}H_{14}O_2$ requires C, 77.2; H, 6.98%.

Mass spectrometry gave the molecular weight as 202.

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1783 $cm.^{-1}$ (cyclobutanone),
1693 $cm.^{-1}$ (aryl ketone).

N.M.R. spectrum: 2.3 τ (5 x H, complex),
6.8 τ (5 x H, multiplet) and
7.9 τ (4 x H, multiplet).

(b) Cyclobutanone (1.3 gm., 0.015 m.) was added to a solution of β-dimethylaminopropiophenone (2.9 gm., 0.015 m.) dissolved in petrol (120°) (6 ml.). The mixture was refluxed with stirring for 3 hours and the cooled residue acidified with glacial acetic acid and diluted with ether. The ethereal solution was brine washed, dried, and evaporated to give the required diketone (14) as a colourless oil, b.p. 120-8°/0.02 mm. (0.8 gm., 40%).

Acid treatment of 2(3'-phenyl-3'-oxopropyl)cyclobutanone (14)

(a) Hydrochloric acid - glacial acetic acid

The diketone (14) (500 mgs., 0.007 m.) was dissolved in glacial acetic acid (2.5 ml.) and concentrated hydrochloric acid (1 ml.). The mixture was refluxed for 24 hours and the solvent removed. The residue was dissolved in ether and the ethereal solution washed with dilute sodium hydroxide, brine, dried and evaporated to give the neutral fraction as a pale yellow oil (300 mgs.). This neutral material was shown by t.l.c. and i.r. to be returned diketone (14). The alkaline washings were acidified, ether extracted and the combined ethereal extracts brine washed, dried and evaporated to give the acidic fraction as a pale yellow solid (43 mgs., 8%). Recrystallisation from petrol gave colourless needles, m.p. 156-7°. The acidic material was identified as 4-phenylcyclohex-3-ene carboxylic acid (21) by the following physical data. Found: C, 77.75; H, 7.08, $C_{13}H_{14}O_2$ requires C, 77.20; H, 6.98%.

The mass spectrum gave the molecular weight as 202.

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1706 cm.$^{-1}$ (acid).

U.V. spectrum: $\lambda_{max.}^{EtOH}$ 210 mμ, ε 10,000, 218 mμ, ε 9,000 and 248 mμ, ε 11,000. i.e.

characteristic of a styrene chromophore.

N.M.R. spectrum: 3.9 τ (1 x H, triplet) i.e. vinylic proton.

(b) Para toluene sulphonic acid - ethylene glycol

The diketone (14) (300 mgs., 0.001 m.) and p-toluene sulphonic acid (300 mgs.) were dissolved in ethylene glycol (500 mgs.) and the mixture refluxed for 2 hours. The cooled residue was treated with a solution of sodium hydroxide (500 mgs.) in water (12 ml.) and the mixture refluxed for 2 hours. The cooled residue was extracted with ether and the combined ethereal extracts, brine washed, dried and evaporated to give returned diketone (30 mgs.) identified by t.l.c. and i.r. The alkaline solution was acidified and extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to give 4-phenylcyclohex-3-ene carboxylic acid (21) as a white solid (210 mgs., 70%), identified as (21) by mixed m.p. (157°).

Attempted isolation of 2-phenylbicyclo-(3.1.1)-hept-2-en-7-one (10)

p-Toluene sulphonic acid (1 gm.) and dry toluene (15 ml.) were refluxed in a 'Dean and Stark' water separator for 2 hours. The diketone (14) (700 mgs.) in dry toluene (5 ml.) was added to the cooled solution, and the mixture refluxed for 4 hours. The cooled residue was neutralised by standing over anhydrous potassium carbonate for 6 hours. The toluene was evaporated to give a colourless oil (600 mgs.) identified as returned diketone by its infra-red and by t.l.c. comparison.

The reaction was repeated at a higher reflux temperature (xylene) and for an increased period of time (12 hours). Work up as above gave only returned diketone (t.l.c. pure).

Ethyl-p-hydroxybenzoate

This compound was obtained from p-hydroxybenzoic acid in 80% yield and isolated as a white solid. m.p. 112-4° $\nu_{C=O}^{CCl_4}$ 1690 cm.$^{-1}$ (Aryl ester).

4-Carbethoxycyclohexanol

Hydrogenation of ethyl-p-hydroxybenzoate, in the presence of raney nickel catalyst, according to the method of Ungnade[72] gave the required alcohol as a colourless oil b.p. 170-5°/15 mm. in 60% yield.

N.M.R. spectrum: 5.9 τ (2 x H quartet),
8.3 τ (3 x H, triplet) i.e. characteristic ethyl ester resonance.
7.6 τ (1 x H, singlet) i.e. hydroxyl proton determined by D_2O exchange.

4-Carbethoxycyclohexanone

A standard solution of chromium trioxide in sulphuric acid (Jones' reagent) was added dropwise to a stirred solution of 4-carbethoxycyclohexanol (5.7 gm.) in acetone (200 ml.) at 0°C until a permanent brown colour persisted. The mixture was diluted with water (300 ml.) and extracted with ether (3 x 50 ml.). The combined ethereal extracts were brine washed, dried ($MgSO_4$), and the solvent removed. Distillation gave 4-carbethoxycyclohexanone as a colourless

oil (3.5 gm., 66%) b.p. 158°/20 mm.[73]

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1726 cm.$^{-1}$ (cyclohexanone) and 1737 cm.$^{-1}$ (ester).

The 2,4-dinitrophenylhydrazone was obtained as orange rods m.p. 115-6° (petrol). Found: C, 51.29; H, 5.00; N, 15.88. $C_{15}H_{18}N_4O_6$ requires C, 51.43; H, 5.18; N, 15.99%.

4-Phenylcyclohex-3-ene carboxylic acid(21)

Phenyl magnesium bromide, prepared from bromobenzene (2.0 gm., 0.012 m.) and magnesium (300 mgs., 0.014 m.) in dry ether (5 ml.), was added dropwise, with stirring, to an ice-cold solution of 4-carbethoxycyclohexanone (1.13 gm., 0.007 m.) in ether (5 ml.). The reaction mixture was stirred at 0° for 15 min. and at room temperature for a further 3 hours and was then poured on to aqueous ammonium chloride in ice and extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to give 1-phenyl-4-carbethoxycyclohexanol-1 (22) (1.74 gm.) $\nu_{C=O}^{CCl_4}$ 1735 cm.$^{-1}$ (ester).

The crude alcohol (1.5 gm.) was dissolved in 20% sulphuric acid (10 ml.) and the mixture heated at reflux temperature for 3 hours. The cooled residue was extracted

with ether and the ethereal extracts washed with dilute sodium hydroxide and discarded. The alkaline solution was acidified and ether extracted. The combined ethereal extracts were brine washed, dried and evaporated to give 4-phenylcyclohex-3-ene carboxylic acid as a white solid (1.46 gm., 80%) m.p. 157-8° (colourless needles from petrol). The infra-red and n.m.r. spectra were identical to those of the acid obtained from the ring expansion reaction. Final identification by mixed m.p. (158°).

Methyl-β-naphthyl ketone

This compound was prepared from naphthalene and acetyl chloride as described by Vogel,[71] and isolated as a white solid m.p. 50-3° (acetic acid) $\nu^{CCl_4}_{C=O}$ 1690 cm.$^{-1}$.

β-Dimethylaminoethyl-β-naphthyl ketone hydrochloride

This Mannich base hydrochloride was prepared according to the method of Blicke[42] and isolated as a white solid m.p. 153-6° (ethanol). The free base (26) was isolated in the normal manner by treatment of the hydrochloride with alkali and used without further purification $\nu^{CCl_4}_{N-CH_2}$ 2810 cm.$^{-1}$, 2780 cm.$^{-1}$.

2-(3'-β-Naphthyl-3'-oxopropyl)cyclopentanone (27)

β-Dimethylaminoethyl-β-naphthyl ketone (26) (7.43 gm., 0.03 m.) was refluxed with cyclopentanone (8.32 gm., 0.09 m.), with stirring, for 30 minutes, and the cooled reaction mixture acidified with glacial acetic acid and diluted with ether. The ethereal solution was brine washed, dried and evaporated to afford a yellow oil (6.2 gm.). Distillation removed the remaining cyclopentanone and gave the required diketone (27) as a colourless oil solidifying on standing (3.5 gm., 50%) b.p. 190-200°/0.02 mm ; m.p. 75-6° (petrol). R_t = 33.5 min. on 1% Polymer Z at 200°. Found: C, 80.93; H, 6.84, $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81%.

Mass spectrum : P = 266 m/e.

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1739 cm.$^{-1}$, 1684 cm.$^{-1}$.

U.V. spectrum : $\lambda_{max.}^{EtOH}$ 291 mμ, ε 10,000; 283 mμ, ε 11,000; 248 mμ, ε 50,000.

N.M.R.spectrum: 2.2 τ (2 x H, multiplet), 6.8 τ (2 x H, triplet, 6 c.p.s.).

Acid treatment of diketone (27)

The diketone (27) (1.65 gm., 0.006 m.) was dissolved in a mixture of glacial acetic acid (7.5 ml.) and concentrated hydrochloric acid (3 ml.) and refluxed for 24 hours.

The solvent was removed at the water pump and the residue flooded with water and extracted with ether (3 x 5 ml.). The combined ethereal extracts were washed with 4$\bar{N}$ sodium hydroxide, brine, dried and evaporated to give a yellow oil (250 mgs.) shown by g.l.c. to be returned diketone (90%) and lactone (29) (10%). The latter being identified by its i.r. at 1780 cm.$^{-1}$.

The alkaline washings were acidified with concentrated hydrochloric acid and ether extracted. The combined ethereal extracts were brine washed, dried and evaporated to give 4-β-naphthylcyclohept-3-ene carboxylic acid (30) as a white solid (1.2 gm., 80%) m.p. 100-2° (benzene-petrol). Found: C, 81.56; H, 6.88. $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81%

$\nu_{C=O}^{CCl_4}$ 1700 cm.$^{-1}$ N.M.R. : 3.8 τ (1 x H, multiplet)

The acid was esterified with diazomethane for g.l.c. analysis. R_t = 14.5 min., 16.0 min. (1:1) on 1% Polymer Z at 200°.

β-Dimethylamino-o-hydroxypropiophenonehydrochloride (31a)

This compound was prepared from o-hydroxyacetophenone, dimethylaminehydrochloride and paraformaldehyde according to

the method of Padfield[74] m.p. 199°

νN-CH_2 (Nujol) 2700 cm.$^{-1}$ (3 bands)

νC=O (Nujol) 1650 cm.$^{-1}$

The hydrochloride was dissolved in water and made basic with sodium bicarbonate. The aqueous solution was extracted with ether and the ethereal extracts brine washed, dried and evaporated to give only a trace amount of the required Mannich base. i.e. the base was either very soluble in water or in the sodium bicarbonate.

β-Dimethylamino-o-acetoxypropiophenonehydrochloride

o-Acetoxyacetophenone (4.2 gm., 0.023 m.) was dissolved in ethanol (5 ml.) and treated with dimethylamine-hydrochloride (7.5 gm., 0.032 m.) and paraformaldehyde (900 mgs., 0.01 m.) at reflux temperature for 2 hours. The cooled residue was poured into acetone (20 ml.) and a white solid (3.4 gm.) isolated. m.p. 199-200° $\nu_{C=O}^{(Nujol)}$ 1640 cm.$^{-1}$ and blank at 1748 cm.$^{-1}$ (acetoxy carbonyl). Identified by mixed m.p. as β-dimethylamino-o-hydroxypropiophenonehydrochloride (mixed m.p. 199-199.5°).

o-Benzoyloxyacetophenone

o-Hydroxyacetophenone (5 gm.) was dissolved in 5% sodium hydroxide (100 ml.) and cooled to 0°. Redistilled benzoyl chloride (10 ml.) was added dropwise and the mixture shaken for 30 minutes and left overnight at room temperature. The required benzoate (6.1 gm., 70%) was filtered, washed with water and recrystallised from ethanol m.p. 82-4°.[75,76]

$\nu_{C=O}$ (Nujol) 1728 cm.$^{-1}$ (benzoate), 1690 cm.$^{-1}$ (acetophenone)

β-Dimethylamino-o-benzoyloxypropiophenone (32)

o-Benzoyloxyacetophenone (7.5 gm., 0.03 m.), paraformaldehyde (4.05 gm., 0.04 m.) and dimethylaminehydrochloride (3.6 gm., 0.045 m.) were dissolved in isoamyl alcohol (18 ml.) and the mixture refluxed for 3 hours, cooled, dissolved in water and extracted with ether. The ethereal extracts were discarded and the aqueous solution basified with 4$\overline{N}$ sodium hydroxide and ether extracted. The combined ethereal extracts were brine washed, dried and evaporated to afford the required Mannich base (32) as a colourless oil (4.5 gm., 55%) used without further purification.

$\nu^{film}_{N-CH_2}$ 2700-2820 cm.$^{-1}$ (3 bands) $\nu^{film}_{C=O}$ 1728, 1680 cm.$^{-1}$.

2-(3'-o-Hydroxy[illegible]enyl-3'-oxopropyl)cyclopentanone (33)

Method (i)

β-Dimet[illegible]amino-o-benzoyoxypropiophenone (32) (4.2 gm., 0.014 m.) was d[illegible]solved in cyclopentanone (3.53 gm., 0.04 m.) and the mixtur[illegible]irred under reflux for 2 hours. The cooled residue [illegible]s neutralised with glacial acetic acid and diluted with e[illegible]r. The ethereal solution was washed with dilute sodium [illegible]roxide (4 x 5 ml.) and discarded. The alkaline washi[illegible]s were acidified with concentrated hydrochloric acid and ether extracted. The combined ethereal extracts were b[illegible]ine washed, dried and evaporated. The excess cyclopentanone was removed leaving the required diketone (33) as a white solid (3.2 gm., 95%) recrystallised from petrol as colourless needles m.p. 105-6° R_t = 22.0 min. on 1% P.E.G.A. [illegible] 175°. Found: C, 72.64; H, 6.65, $C_{14}H_{16}O_2$ requires C, 72.40; H, 6.94%.

Infra-red: [illegible]4 1740 cm.$^{-1}$ (cyclopentanone),

[illegible]38 cm.$^{-1}$ (hydrogen bonded acetophenone carbonyl).[43]

The extinction coefficient of the hydroxyl band showed no change on dilution.

U.V.: $\lambda_{max.}^{EtOH}$ 213 mμ, ε 11,000; 255 mμ, ε 9,000; 299 mμ, ε 2,700 (with bathochromic shift to 360 mμ on addition of alkali).

Method (ii)

2-Dimethylaminomethylcyclopentanone (10 gm., 0.07 m.) and o-hydroxyacetophenone (28 gm., 0.21 m.) were heated at reflux temperature for 90 minutes. Standard work up procedure gave a mixture of the required diketone (33) and o-hydroxyacetophenone. The excess ketone was removed by distillation (b.p. 98-100°/14 mm.) leaving 2-(3'-o-hydroxyphenyl-3'-oxopropyl)cyclopentanone (33) as a white solid (8 gm., 50%) (mixed m.p. 104°) R_t = 22.0 min. on 1% P.E.G.A. at 175°.

Acid treatment of 2-(3'-o-hydroxyphenyl-3'-oxopropyl)cyclopentanone (33)

(a) Hydrochloric acid - glacial acetic acid

The diketone (33) (500 mgs.) was dissolved in a mixture of glacial acetic acid (2.5 ml.) and concentrated hydrochloric acid (1 ml.) and heated under reflux for 24 hours. The solvent was evaporated and the residue flooded

with water and extracted with ether. The combined ethereal extracts were washed with sodium bicarbonate (4 X), brine, dried ($Mg.SO_4$) and evaporated to a white solid (400 mgs.) m.p. 105-6° shown to be returned starting material by mixed m.p. (105°) and g.l.c. analysis: R_t = 22.0 min. on 1% P.E.G.A. at 175°.

The alkaline washings afforded no acidic product. Extension of reaction time to 3 days gave only returned starting material (33).

(b) Para-toluene sulphonic acid - ethylene glycol

The diketone (33) (600 mgs.) was dissolved in ethylene glycol (1 gm.) and treated with p-toluene sulphonic acid (0.5gm) under reflux for 2 hrs. The cooled residue was treated with a solution of potassium hydroxide (1 gm.) in water (5 ml.) and refluxed for 2 hours. The cooled mixture was ether extracted and the combined ethereal extracts brine washed, dried and evaporated to afford no neutral product. The alkaline solution was acidified and ether extracted (5 x 5 ml.). The combined ethereal extracts were washed with aqueous sodium bicarbonate, brine, dried and evaporated to give a white solid (350 mgs.) which was shown by g.l.c. and mixed m.p. to be returned diketone.

The sodium bicarbonate washings were acidified and ether extracted and the combined ethereal extracts brine washed, dried and evaporated to afford trace amounts of acidic material (6 mgs.).

o-Methoxy acetophenone

This compound was prepared from o-hydroxyacetophenone by methylation with dimethyl sulphate[83] and isolated in 80% yield as a colourless oil b.p. 116-20°/10 mm. $\nu_{C=O}^{CCl_4}$ 1680 cm.$^{-1}$.

β-Dimethylamino-o-methoxypropiophenone (34)

o-Methoxyacetophenone (4.7 gm., 0.015 m.), dimethylamine hydrochloride (3.3 gm., 0.02 m.) and paraformaldehyde (1.2 gm., 0.007 m.) were dissolved in ethanol (15 ml.), acidified with concentrated hydrochloric acid (10 drops), and the mixture heated at reflux temperature for 2 hours. The cooled residue was diluted with water, extracted with ether and the ethereal solution discarded. The aqueous solution was basified with 4$\overline{N}$ sodium hydroxide and ether extracted. The combined ethereal extracts were brine washed, dried and evaporated to give the required Mannich

base (34) as a pale yellow oil (4.5 gm., 75%) and used without further purification.

$\nu_{N-CH_2}^{CCl_4}$ 2800 cm.$^{-1}$ (doublet), $\nu_{C=O}^{CCl_4}$ 1685 cm.$^{-1}$

The picrate was recrystallised from ethanol as yellow needles m.p. 138-9°. Found: C, 49.54; H, 4.62; N, 12.84. $C_{18}H_{20}N_4O_9$ requires C, 49.37; H, 4.80; N, 13.09%.

N.M.R.: 2.7 τ (4 x H singlet), 6.15 τ (3 x H singlet), 7.00 τ (6 x H singlet) $\nu_{C=O}^{KCl}$ 1678 cm.$^{-1}$.

2-(3'-o-Methoxyphenyl-3'-oxopropyl)cyclopentanone (35)

The Mannich base (34) (4.3 gm., 0.02 m.) and cyclopentanone (5.04 gm., 0.06 m.) were heated at reflux temperature, with stirring, for 1 hour. Standard work up procedure gave a pale yellow oil (6 gm). Distillation afforded the required diketone (35) as a colourless oil (4 gm., 80%) b.p. 150-5/0.15 mm. R_t = 21 min. on 1% P.E.G.A. at 175°. Found: C, 72.5; H, 7.10. $C_{15}H_{10}O_2$ requires C, 73.15; H, 7.37%.

I.R.: $\nu_{C=O}^{CCl_4}$ 1738 cm.$^{-1}$ (cyclopentanone), 1695 cm.$^{-1}$ (acetophenone).

N.M.R. : 6.1 τ (3 x H singlet), 6.9 τ (2 x H triplet, J = 6 c.p.s.).

Acid treatment of 2(3'-o-methoxyphenyl-3'-oxopropyl)cyclopentanone (35)

(a) Hydrochloric acid - glacial acetic acid

The diketone (35) (5gm.) was treated with concentrated hydrochloric acid (10 ml.) and glacial acetic acid (25 ml.) in the usual manner. Standard work up gave a neutral fraction (1.2 gm.) and an acidic fraction (3.5 gm.). The acidic material was esterified with ethereal diazomethane, and distillation gave 1-carbomethoxy-4-o-methoxyphenylcyclohept-4-ene (38) as a colourless oil (3.3 gm., 60%) b.p. 145-8°/0.25 mm. R_t = 6.0 min. on 1% P.E.G.A. at 175° and 10.75 min. on 1% F 60. at 150°. Found: C, 73.02; H, 7.63, $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.63%.

I.R.: $\nu_{C=O}^{CCl_4}$ 1735 cm.$^{-1}$.

N.M.R.: 4.07 τ (1 x H, triplet, J = 6 c.p.s.)
6.16 τ (3 x H, singlet) and 6.25 τ (3 x H, singlet).

The neutral material was recrystallised from petrol as colourless needles (1.1 gm., 24%) m.p. 123-4°. R_t = 28.5

min. on 1% P.E.G.A. at 175°. Found: C, 73.07; H, 7.33. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.37%.

I.R.: 1778 cm.$^{-1}$ (lactone).

N.M.R.: 6.15 τ (3 x H, singlet)

i.e. 3-hydroxy-4-o-methoxyphenylcycloheptane carboxylic acid lactone (36).

(b) Sulphuric acid - methanol

The diketone (35) (2 gm.) was dissolved in methanol (40 ml.) and acidified with concentrated sulphuric acid (4 ml.). The mixture was heated at reflux temperature for 2 days and most of the solvent removed by evaporation. The cooled residue was flooded with water and extracted into ether. The combined ethereal extracts were brine washed, dried and evaporated to give a pale yellow oil (2.0 gm.). Distillation gave pure 1-carbomethoxy-4-o-methoxyphenyl-cyclohept-3(4)-ene (39) 1.95 gm., 93%) as a colourless oil b.p. 140-5°/0.3 mm. and identified as (39) by g.l.c. analysis. R_t = 6.0 min., 5.5 min. on 1% P.E.G.A. at 175°; 10.75 min., 10.55 min., (shoulder) on 1% F 60. at 150°.

I.R.: $\nu_{C=O}^{CCl_4}$ 1736 cm.$^{-1}$

N.M.R.: 4.1 τ (1 x H, multiplet), 6.16 τ (3 x H, singlet) and 6.25 τ (3 x H, singlet).

β-Dimethylamino-p-nitropropiophenone hydrochloride

This compound was prepared according to the method of Ginsberg[44] and isolated as a white solid in 80% yield m.p. 186-8° (ethanol).

I.R. ν_{N-CH_2} (Nujol) 2750 cm.$^{-1}$, 2800 cm.$^{-1}$, 2840 cm.$^{-1}$.

β-Dimethylamino-p-nitropropiophenone (40)

β-Dimethylamino-p-nitropropiophenone hydrochloride (3 gm.) was dissolved in water (10 ml.) and cooled to 0°. Ether (5 ml.) was added and the mixture made basic with solid potassium carbonate added portionwise with swirling. The ethereal layer was separated and the aqueous solution extracted with ice-cold ether (2 x 10 ml.). The combined ethereal extracts were washed with ice-cold brine (5 x), dried and evaporated under reduced pressure at room temperature to afford the required Mannich base as a pale yellow solid (1.6 gm., 60%) m.p. 36-8° (petrol).

I.R.: ν_{N-CH_2} (Nujol) 2810 cm.$^{-1}$, 2840 cm.$^{-1}$.

N.M.R.: 1.8 τ (4 x H, doublet), 7.15 τ (2 x H, triplet) 6.85 τ (2 x H, triplet) and 7.7 τ (6 x H singlet).

The picrate was obtained as yellow needles from T.H.F. -

petrol m.p. 160-1°. Found: C, 45.19; H, 3.89. $C_{17}H_{17}N_5O_{10}$ requires C, 45.24; H, 3.80%.

2-(3'-p-Nitrophenyl-3'-oxopropyl)cyclopentanone (41)

(a) β-Dimethylamino-p-nitropropiophenone (40) (10 gm., 0.05 m.) was dissolved in cyclopentanone (15 gm., 0.15 m.) and the mixture refluxed, with stirring, for 1½ hours. Standard work up procedure gave the required diketone (41) as a white solid 7.2 gm., 65%). m.p. 75-7° (petrol). Found: C, 64.36; H, 5.79; N, 5.36. $C_{14}H_{15}NO_4$ requires C, 64.07; H, 5.58; N, 5.20%.

I.R.: $\nu_{C=O}^{CCl_4}$ 1697 cm.$^{-1}$ (acetophenone), 1738 cm.$^{-1}$ (cyclopentanone), 1534 cm.$^{-1}$ (nitro) and 1343 cm.$^{-1}$ (nitro)

N.M.R.: 1.7 τ (4 x H, multiplet), 6.8 τ (2 x H, triplet).

(b) β-Dimethylaminomethylcyclopentanone (5 gm., 0.032 m.) and p-nitroacetophenone (4.28 gm., 0.032 m.) were dissolved in petroleum ether (10 ml., 100°) and the mixture heated under reflux for 1½ hours. The usual work up procedure yielded a brown gum (6.8 gm.) which was absorbed on to silica and eluted with benzene-chloroform. No identifiable products could be isolated.

Acid treatment of 2-(3'-p-nitrophenyl-3'-oxopropyl)cyclopentanone (41)

(a) Hydrochloric acid - glacial acetic acid

The diketone (41) (500 mgs.) was dissolved in glacial acetic acid (3 ml.) and concentrated hydrochloric acid (1 ml.) and the mixture refluxed for 24 hours. Standard work up procedure gave a neutral fraction (300 mgs.) and an acidic fraction (130 mgs. 20%).

The neutral material proved to be returned diketone (41) (mixed m.p. 75-7° and i.r. $\nu_{C=O}^{CCl_4}$ 1695 cm.$^{-1}$, 1738 cm.$^{-1}$. The acidic material was recrystallised from benzene-petrol as colourless needles m.p. 116-8°. Found: C, 64.62; H, 5.94; N, 5.20. $C_{14}H_{15}NO_4$ requires C, 64.36; H,5.79; N, 5.36%.

$\nu_{C=O}^{CCl_4}$ 1700 cm.$^{-1}$ (carboxylic acid), 1534 and 1343 cm.$^{-1}$ (nitro)

i,e. 4-p-nitrophenylcyclohept-3(4)-ene carboxylic acid (42).

(b) p-Toluene sulphonic acid - ethylene glycol

The diketone (41) (500 mgs.) was dissolved in ethylene glycol (5 ml.) and treated with p-toluene sulphonic acid (500 mgs.). The mixture was heated under reflux for 2 hours, cooled, treated with a solution of potassium hydroxide (1 gm.) in water (10 ml.) and heated under reflux for 2 hours.

Standard work up procedure gave a neutral fraction (120 mgs.) (shown to be returned diketone (41) by mixed m.p. 75°) and an acid fraction (210 mgs., 40%) which was shown to be 4-p-nitrophenylcyclohept-3(4)-ene carboxylic acid (42) by mixed m.p. 116-7°.

4-Dimethylaminomethyl-3',4',5'-trimethoxy-1,2-benzocyclohepten-3-one hydrochloride (46)

This compound (46) was prepared from α-trimethoxybenzosuberone[19] (47), dimethylamine hydrochloride and paraformaldehyde according to the method of McCrae[77] and isolated as colourless needles m.p. 160-2° (ethyl acetate-petrol).

ν_{N-CH_2} (Nujol) 2500-2800 cm.$^{-1}$ (3 bands) and
$\nu_{C=O}$ (Nujol) 1690 cm.$^{-1}$ (aryl ketone).

The free base was isolated in the usual manner, by treatment with sodium hydroxide, and used without further purification.

4-(2'-Cyclopentanonylmethyl)-3',4',5'-trimethoxy-1,2-benzocycloheptene-3-one (44)

This 1,5-diketone was obtained from the Mannich base (45) and cyclopentanone in the usual manner, as described by McCrae[77]. It was isolated as a colourless oil

b.p. 200-5°/0.3 mm. The infra-red showed absorption at 1740 cm.$^{-1}$ (cyclopentanone) and 1685 cm.$^{-1}$ (aryl ketone) and 1020 cm.$^{-1}$ (methoxyl). The N.M.R. showed: 3.5 τ (1 x H, singlet), 6.1 τ (9 x H, singlet).

Treatment of diketone (44) with acid

(a) Hydrochloric acid - glacial acetic acid

The diketone (44) (5 gm.) was dissolved in glacial acetic acid (50 ml.) and treated with concentrated hydrochloric acid and heated under reflux for 24 hours. Standard work up procedure gave a neutral fraction [identified as diketone (44)] and an acidic fraction (4 gm.) isolated as a brown viscous oil. The infra-red showed acid hydroxyl absorption at 3540-2800 cm.$^{-1}$. The acid gave a +ve ferric chloride test i.e. hydrolysis of a methoxyl had occurred to afford a phenolic carboxylic acid (49). The n.m.r. showed the remaining six methoxyl protons as a singlet at 6.2 τ.

Methylation of phenolic acid (49)

The crude acid (49) (3.3 gm., 0.01 m.) was dissolved in aqueous sodium hydroxide (0.5 gm. in 5 ml.) and cooled to 10°. Purified dimethyl sulphate (3.4 gm., 0.022 m.) was added portionwise with stirring and the

mixture refluxed for 2 hours. The alkaline solution was cooled and ether extracted, and the combined ethereal extracts brine washed, dried and evaporated to yield a pale yellow oil (3 gm.) shown by t.l.c. and g.l.c. to consist of two components, R_t = 17.0 min. and 9.0 min. (1.5:1) on 1% SE 30 at 200°. The mixture was separated by chromatography into a non-polar component (900 mgs.) and a polar component (1.1 gm.).

(i) Non-polar

This component was isolated as a white solid m.p. 86-7° (colourless needles from petrol). R_t = 9.0 min. on 1% SE 30 at 200°. Found: C, 70.08; H, 7.95, $C_{21}H_{28}O_5$ requires C, 69.98; H, 7.83%.

Mass spectrometry gave the molecular weight as 360.

N.M.R.: 3.45 τ (1 x H, singlet), 6.1 τ (6 x H, singlet), 6.2 τ (3 x H, singlet), 6.26 τ (3 x H, singlet), 7.5 τ (8 x H, multiplet) and 8.1 τ (7 x H, multiplet).

U.V.: $\lambda_{max.}^{EtOH}$ 255 mμ, ε 7,700 and $\lambda_{min.}^{EtOH}$ 243 mμ.

I.R.: $\nu_{max.}^{CCl_4}$ 1730 $cm.^{-1}$ (ester), 1600 $cm.^{-1}$ (aromatic), 1240 $cm.^{-1}$ (ester), 1020 $cm.^{-1}$ (methoxyl).

From the preceding evidence the compound was shown to be desoxydesmethoxydesacetamido-8,9,10,11,12-hexahydrocolchicine-9-carboxylic acid methyl ester (50).

(ii) Polar

This component was isolated as a viscous oil b.p. 180-5°/0.1 mm. R_t = 17.00 min. on 1% SE 30 at 200°. Mass spectrometry gave the molecular ion as 378 m/e showing a facile loss of 18 m/e fragment to give the 360 m/e ion. Ultra-violet spectroscopy showed absorption at $\lambda_{max.}^{EtOH}$ 270 mμ ε 3,000 and $\lambda_{min.}^{EtOH}$ 249 mμ, (i.e. no trimethoxystyrene absorption bands).

N.M.R. showed 3.6 τ (1 x H, singlet), 6.17 τ (9 x H, singlet), 6.35 τ (3 x H, singlet), 7.5 τ (2 x H, multiplet) and 8.0 - 8.5 τ (14 x H, broad multiplet).

I.R.: $\nu_{max}^{CCl_4}$ 1735 cm.$^{-1}$ (ester), 1600 cm.$^{-1}$ (aromatic), 1240 cm.$^{-1}$ (ester) and 1020 cm.$^{-1}$ (methoxyl).

The above spectral data suggested the polar ring expansion product to be the ester (51).

Dehydration of ester (51)

The ester (51) (500 mgs.) was dissolved in methanol (20 ml.) and acidified with concentrated sulphuric acid

(1 ml.). The mixture was heated at reflux temperature for 2 hours and the cooled residue flooded with water and ether extracted. The combined ethereal extracts were brine washed, dried and evaporated to afford a colourless oil (450 mgs.).

G.l.c. analysis on 1% SE 30 indicated a 20% conversion to the ester (50)

(a) ester (51) : R_t = 24.50 min.

(b) dehydration product : R_t = 24.50 min., 13.00 min. (5:1).

(c) ester (50) : R_t = 13.00 min.

The minor component from the dehydration of ester (51) was isolated by prep. t.l.c. as a white solid, m.p. 85-7° (mixed m.p. with (50) : 86-7°). R_t = 13.00 min. Ultra violet spectrum: $\lambda_{max.}$ 258 mμ, ε 1400 and $\lambda_{min.}$ 241 mμ, (i.e. trimethoxystyrene).

Treatment of diketone (44) with acid

(b) Concentrated sulphuric acid - methanol

The diketone (44) (1 gm.) was dissolved in methanol (20 ml.), treated with concentrated sulphuric acid (2 ml.) and the mixture refluxed for 24 hours. The methanol was evaporated and the cooled residue flooded with water and

extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to give a yellow oil which solidified on standing, m.p. 86-7°(colourless needles from petrol). This ring expansion product was identified as the ester (50) by mixed m.p.(86-7°) and g.l.c. comparison (R_t = 9.0 min. on 1% SE 30 at 200°) with the authentic sample obtained from (a).

Epoxidation of ester (50)

The ester (50) (60 mg., 0.0002 m.) was dissolved in dry chloroform (5 ml.) and treated with a solution of m-chloroperbenzoic acid (150 mgs., 0.001 m.) in chloroform (10 ml.). The mixture was stirred for 36 hours at room temperature in the absence of light. The excess peracid was removed by washing with sodium bisulphite and sodium sodium bicarbonate. The chloroform solution was brine washed, dried and evaporated to afford a pale yellow oil (55 mgs.). G.l.c. examination indicated the presence of two components: R_t = 11.25 min., 14.00 min. (2:1) on 1% SE 30 at 200°. Examination by G.C.-M.S. showed the two components to be isomeric (molecular weight: 376). The crude mixture solidified on standing and recrystallisation from ethanol gave the major isomer as colourless needles,

m.p. 126-7°. R_t= 11.25 min. on 1% SE 30 at 200°. Found C, 66.60; H, 7.10; $C_{2-}H_{28}O_6$ requires C, 67.00; H, 7.50%

The trimethoxystyrene chromophore bands were absent in the u.v. (only an unconjugated trimethoxybenzene band at $\lambda_{max.}^{EtOH}$ 273 mμ, ε 3,000 and $\lambda_{min.}^{EtOH}$ 248 mμ. The infra-red showed ester absorption bands at 1730 $cm.^{-1}$ and 1240 $cm.^{-1}$.

N.M.R.: 3.45 τ (1 x H, singlet), 5.95 τ (3 x H, singlet), 6.1 τ (6 x H, singlet), 6.2 τ (3 x H, singlet), 7.3 τ (2 x H, multiplet), 7.8 - 8.2 τ (13 x H, broad unresolved multiplet).

The above spectral evidence is consistent with the required β-epoxy ester (52).

Attempted hydrogenation of ester (50)

The ester (50) (100 mgs.) was dissolved in glacial acetic acid and the solution hydrogenated over Adam's catalyst for 4 hours with stirring. The catalyst was filtered off and the solvent removed under reduced pressure to give a colourless oil (90 mgs.) which solidified on standing, m.p. 86-7°. Ultra-violet spectrum: $\lambda_{max.}^{EtOH}$ 258 mμ, ε 14,000 and $\lambda_{min.}^{EtOH}$ 241 mμ, i.e. returned ester (50).

2-(3'-Oxobutyl)-cyclopentanone (104)

This compound was prepared from dimethylaminobutan-3-one (106) and cyclopentanone according to the method

described by Gill.[41] It was isolated in 60% yield as a colourless oil, b.p. 140-5/14 mm. $\nu_{C=O}^{CCl_4}$ 1738 cm.$^{-1}$ (cyclopentanone) and 1720 cm.$^{-1}$ (chain ketone).

Acid treatment of 2-(3'-oxobutyl)cyclopentanone (104)

(a) Hydrochloric acid - glacial acetic acid

The diketone (104) (2 gm.) was dissolved in glacial acetic acid (30 ml.) and concentrated hydrochloric acid (3 ml.) and the mixture refluxed for 10 hours. Standard work up procedure gave a neutral component (900 mgs., 55%) and an acidic fraction (100 mgs., 3%).

The neutral material was purified by distillation, b.p. 100-5°/14 mm. and identified as 5-oxo-$\Delta^{4,9}$-tetra hydroindene (54).

I.R.: $\nu_{C=O}^{CCl_4}$ 1680 cm.$^{-1}$ (αβ unsaturated cyclohexanone).

U.V.: $\lambda_{max.}^{EtOH}$ 240 mμ, ε 10,000 [calc. for (54) as 243 mμ].

The 2,4-dinitrophenylhydrazone was obtained as deep red needles from dioxan-ethanol, m.p. 198-9° (lit.[78] 197.5-9°).

The acidic component was esterified with ethereal diazomethane. Distillation gave pure 4-carbomethoxy-cyclohept-3(4)-ene (96) as a colourless oil, b.p. 60°/0.8 mm. R_t = 6 min. and 7.2 min. (1:1) on 5% Q.F.1. at

100°. Found: C, 70.99; H, 9.42. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%.

I.R.: $\nu_{C=O}^{CCl_4}$ 1739 cm.$^{-1}$ (ester)

N.M.R.: 6.2 τ (3 x H, singlet), 4.1 τ (1 x H multiplet).

(b) p-Toluene sulphonic acid - ethylene glycol

The diketone (104) (3 gm.) was treated with p-toluene sulphonic acid (3 gm.) in ethylene glycol (5 gm.) at reflux temperature for 3 hours. The cooled residue was treated with potassium hydroxide (5 gm.) in water (120 ml.) and the mixture heated at reflux temperature for 2 hours. Standard work up procedure gave a small amount of returned diketone (104) together with an acidic material (1.9 gm., 66%) isolated as a pale yellow oil. Esterification with diazomethane and distillation gave 4-carbomethoxycyclohept-3(4)-one (96) as a colourless oil and identified by its i.r. ($\nu_{C=O}^{CCl_4}$ 1739 cm.$^{-1}$) and g.l.c. [R_t = 6 min., 7.2 min. on 5% Q.F.1. at 100° (1:1)].

2-(4'-Methyl-3'-oxopentyl)cyclopentanone (110)

This 1,5-diketone was prepared under modified thermal Michael conditions as described in Part II, p.139.

Treatment of diketone (110) with acid

(a) A mixture of the diketone(110) (2.6 gm.), concentrated hydrochloric acid (6 ml.) and glacial acetic acid (20 ml.) was heated at reflux temperature for 18 hours. Standard work up procedure gave the neutral product as a yellow oil (1.7 gm.) and an acidic product as a pale yellow oil (450 mgs., 25%). The neutral material was purified by chromatography on fine silica. Elution with 4% ethyl acetate-petrol gave a colourless oil (1.5 gm., 52%) purified by distillation b.p. 130-5°/14 mm. and identified as 4,4-dimethyl-5-oxo $\Delta^{8,9}$-tetrahydroindene (114) by the following physical data. R_t = 9.0 min. on 10% A.P.L. at 130°.

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1718 cm.$^{-1}$ (unconjugated cyclohexanone).

U.V. spectrum: end absorption only i.e. no enone absorption at 240 mμ.

N.M.R.spectrum: 8.8 τ (6 x H, singlet), no vinylic proton

Mass spectrum: parent ion at 164 m/e [required for $C_{11}H_{16}O$ i.e. (114) : 164].

The 2,4-dinitrophenyl hydrazone was obtained as yellow plates (ethanol) m.p. 142-4°. Found: C, 59.61; H, 5.36; N, 16.62. $C_{17}H_{20}N_4O_4$ requires C, 59.29; H, 5.78; N, 16.27%.

The acidic material was esterified with ethereal diazomethane and the resultant ester isolated as a colourless oil b.p. 60-2°/0.1 mm. R_t 11.5 min. and 13.4 min. on 5% Q.F.I. at 100° (1:1). Found C, 72.63; H, 10.11. $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%.

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1740 cm.$^{-1}$ (ester)

N.M.R.spectrum: 4.07 τ (1 x H, multiplet), 6.16 τ (3 x H singlet) and 8.9 τ (6 x H, doublet, J = 6 c.p.s.).

The above physical data is consistent with 4-isopropyl-1-carbomethoxycyclohept-3(4)-ene (112).

(b) p-Toluene sulphonic acid - ethylene glycol

The diketone (110) (3 gm.) was dissolved in ethylene glycol (5 gm.) and the mixture treated with p-toluene sulphonic acid (3 gm.) under the usual conditions. Standard work up procedure gave an acidic product (2.2 gm., 65%) with a negligible amount of neutral material. The acid was distilled b.p. 98°/0.1 mm. and esterified with ethereal diazomethane. The resultant ester was purified by distillation b.p. 60°/0.1 mm. and identified as 4-isopropyl-1-carbomethoxycyclohept-3(4)-ene(112) by g.l.c. comparison

with the authentic sample obtained in (a) R_t = 11.5 min., 13.4 min. on 5% Q.F.1 at 100°.

1-Dimethylamino-5-methylhexanone-3 (107)

This Mannich base was prepared according to the method of Mousseron[79]. The physical data is discussed in Part II, p.134.

2-(5'-Methyl-3'-oxohexyl)cyclopentanone (105)

The Mannich base (107) (4.5 gm., 0.03 m.) and cyclopentanone (7.5 gm., 0.09 m.) were heated together at reflux temperature for 2 hours. Standard work up procedure gave a yellow oil from which the required diketone (105) was obtained, by distillation, as a colourless oil (5 gm., 75%) b.p. 102-4°/0.3 mm. Found: C, 74.00; H, 10.36, $C_{12}H_{20}O_2$ requires C, 73.50; H, 10.27%.

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1738 cm.$^{-1}$ (cyclopentanone) and 1714 cm.$^{-1}$ (chain ketone).

N.M.R.spectrum: 9.1 τ (6 x H doublet, J = 6 c.p.s.).

Treatment of diketone (105) with acid

(a) Hydrochloric acid - glacial acetic acid

The diketone (105) (4.2 gm.) was dissolved in

glacial acetic acid (24 ml.) and concentrated hydrochloric acid (8 ml.) and the mixture heated at reflux temperature for 24 hours. Standard work up procedure gave a neutral fraction (3.6 gm.) and an acidic fraction (90 mgs, 3%).

Distillation of the neutral material gave the major product as a colourless oil b.p. 90-4°/1 mm. (3.2 gm., 70%). R_t = 21.2 min. on 10% A.P.L. at 130°.

The following spectral data identified the product as 4-isopropyl-5-oxo-$\Delta^{4,9}$-tetrahydroindene (108).

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1678 cm.$^{-1}$ ($\alpha\beta$,unsaturated ketone).

U.V. spectrum: $\lambda_{max.}^{EtOH}$ 247 mμ, ε 10,000 (calculated u.v. for (108): $\lambda_{max.}$ 253 mμ).

N.M.R.spectrum: 8.85 τ (6 x H, doublet).

Mass spectrometry gave the molecular weight as 178.

[$C_{12}H_{18}O$ i.e. (108) requires 178].

The 2,4-dinitrophenylhydrazone was recrystallised from ethanol as deep red plates m.p. 155-7°. Found: C, 60.22; H, 5.98; N, 15.73. $C_{18}H_{22}N_4O_4$ requires C, 60.32; H, 6.19, N, 15.63%.

The acidic material (90 mgs.) was esterified with ethereal diazomethane and the resultant ester distilled

b.p. 90°/0.8 mm. as a colourless oil. R_t = 13.5 min., 15.0 min. on 5% Q.F.1 at 100° (1:1). Found: C, 73.81; H, 10.66. $C_{13}H_{22}O_2$ requires C, 74.24; H, 10.54%.

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1738 cm.$^{-1}$ (ester).

N.M.R.spectrum: 6.2 τ (3 x H, singlet) and 8.96 τ (6 x H, doublet).

The above physical data is consistent with 4-isobutyl-1-carbomethoxycyclohept-3(4)-ene (109).

(b) p-Toluene sulphonic acid - ethylene glycol

The diketone (105) (1.5 gm.), was dissolved in ethylene glycol (2.5 gms.) and treated with p-toluene sulphonic acid at reflux temperature for 2 hours. Standard work up procedure gave an acidic material (1.1 gm., 72%) and a neutral fraction (150 mgs.). The neutral material gave 4-isopropyl-5-oxo-$\Delta^{4,9}$tetrahydroindene(108)as a colourless oil (110 mgs.,~7%) on distillation b.p. 91-6°/1 mm. and identified by i.r. and u.v. comparison with the authentic sample obtained in (a). The acidic material was esterified and shown to be identical to the ester (109) obtained in (a). R_t = 13.5 min. and 15.0 min. on 5% Q.F.1 at 100°.

Bis-cyclopentanonylmethane[50,52](56)

2-Dimethylaminomethylcyclopentanone[41] (58) (30 gm., 0.19m.) was dissolved in cyclopentanone (47 gm., 0.57 m.) and the mixture heated at reflux temperature for 90 minutes. Work up as usual gave the desired diketone (56) as a white solid (25 gm., 65%) b.p. 90-2°/0.1mm. m.p. 71-2° (colourless needles from petrol). R_t 34.5 min. on 10% A.P.L. at 150° and 16.25 min. on 10% P.E.G.A. at 170°.

I.R.: $\nu_{C=O}^{CCl_4}$ 1741 cm.$^{-1}$ (cyclopentanone).

10-Hydroxybicyclo-[5,3,0]-decane-5-carboxylic acid lactone (59)[30]

This lactone (59) was prepared by treating the diketone (56) with concentrated hydrochloric acid and glacial acetic acid and isolated as a colourless oil, b.p. 157°/12 mm. in 60% yield.

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1775 cm.$^{-1}$ (lactone).

N.M.R.spectrum: no absorption below 8.3 τ.

5-(α-Hydroxyisopropyl)-10-hydroxybicyclo[5,3,0]decane (61)

Methyl magnesium iodide, prepared from magnesium (30 gm.), methyl iodide (70 gm.) in ether (500 ml.), was added portionwise, with stirring, to a solution of the

lactone (59) (23 gm.) in ether (50 ml.) at 0°. The mixture was stirred for 30 minutes at 0° and at room temperature for a further 12 hours. The Grignard complex was decomposed by pouring the reaction mixture on to a saturated solution of ammonium chloride and ice. The organic phase was separated and the aqueous solution extracted with ether (4 x 50 ml.). The combined ethereal extracts were washed with brine, dried and evaporated to give the required diol (61) as a white solid (24 gm., 90%) m.p. 87-9° (colourless needles from petrol). Found: C, 74.40; H, 11.26. $C_{13}H_{24}O_2$ requires C, 73.54; H, 11.39%. The infra-red spectrum showed intermolecular hydrogen bonding at 3617 $cm.^{-1}$, 3456 $cm.^{-1}$ and 3302 $cm.^{-1}$ (dilution studies showed a decrease in extinction coefficient). N.M.R. spectrum: 8.1 τ (2 x H singlet) and 8.8 τ (6 x H, singlet) (D_2O exchange removed the signal at 8.1 τ). The mass spectrum showed no molecular ion but gave an M-18 ion at 194 m/e. A further facile loss of the 18 m/e frequent gave the M-36 ion at 176 m/e with a metastable at 160 m/e (calculated as 159.9 m/e). The base peak at 136 m/e arose from loss of acetone and water (66 m/e). For a complete fragmentation see Scheme X.

5-Carbomethoxybicyclo-[5,3,0]-$\Delta^{9,10}$-decene (60)

Bis-cyclopentanonylmethane (56) (3 gm.) was dissolved in methanol (60 ml.) acidified with concentrated sulphuric acid (6 ml.). The mixture was refluxed for two days and the solvent evaporated. The residue was flooded with water and extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to give a pale yellow oil (2.9 gm.). Distillation gave the required ester (60) as a colourless oil (2.6 gm., 75%) b.p. 85-90°/0.25 mm. R_t = 7.75 min. on 10% A.P.L. at 175°. Found: C, 74.18; H, 8.89. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.24%

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1738 cm.$^{-1}$ (ester)

N.M.R.spectrum: 6.30 τ (3 x H, singlet). No vinyl proton signal.

5-(α-Hydroxyisopropyl)bicyclo-[5,3,0]-$\Delta^{9,10}$-decane (63)

Methyl magnesium iodide, prepared from magnesium (8.4 gm., 0.14 m.), methyliodide (19.9 gm., 0.14 m.) in ether (180 ml.) was added dropwise, over 30 minutes, to a solution of the ester (60) (6.7 gm., 0.035 m.) in dry ether (10 ml.) at 0°. The reaction mixture was stirred for 15 minutes at 0° and for a further 3 hours at room

temperature. The Grignard complex was decomposed by pouring the reaction mixture on to a saturated solution of ammonium chloride at 0°. The organic pahse was separated and the aqueous layer extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to afford the required alcohol (63) as a white solid (6 gm. 90%) m.p. 54-54.5° (colourless needles on sublimation). Found: C, 80.28; H, 11.31. $C_{13}H_{22}O$ requires C, 80.35, H, 11.41%.

I.R. spectrum : $\nu_{max.}$ 3500 cm.$^{-1}$ (hydroxyl non bonded; no change in extinction coefficient on dilution).

N.M.R.spectrum: 6 x H singlet at 8.85 τ, 1 x H singlet at 8.3 τ.

5-Isopropyl-1,2,3,6,7,8-hexahydroazulene (62).

(a) From the diol (61)

The diol (61) (1 gm.) was treated with 20% sulphuric acid (15 ml.) and the mixture heated at reflux temperature, with stirring, for 30 minutes. The cooled residue was poured on to ice and extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to give a pale yellow oil (900 mgs.). Distillation gave

the required diene (62) as a colourless oil (800 mgs., 85%) b.p. 95-6°/1 mm. R_t = 14.50 min. on 1% O.V. 17 at 75° and 5.90 min. on 25% dyano B at 75°.

U.V. spectrum : $\lambda_{max.}^{EtOH}$ 263 mμ, ε 4,500 (calculated for (62) as $\lambda_{max.}$ 263 mμ).

N.M.R.spectrum: 4.5 τ (1 x H, singlet), 9.02 τ (6 x H, doublet, J = 6 c.p.s. and 6.55 τ (1 x H, subsplit quartet, J = 6 c.p.s.).

(b) From the alcohol (63)

The tertiary alcohol (63) (1 gm.) was treated with 20% sulphuric acid (20 ml.) at reflux temperature for 30 minutes. Work up as in (a) gave a pale yellow oil (900 mgs.). Distillation gave the required diene (62) as a colourless oil (750 mg., 80%) b.p. 88-90°/1 mm. Rt = 4.25 min. on 1% O.V. 17 at 75° and 5.90 min. on 25% cyano B at 75°.

U.V. spectrum: $\lambda_{max.}^{EtOH}$ 263 mμ, ε 4,500

N.M.R.spectrum: 4.5 τ (1 x H, singlet), 9.02 τ (6 x H doublet, J = 6 c.p.s.) and 6.55 τ (1 x H, subsplit quartet, J = 6 c.p.s.).

i.e. spectral data identical to diene obtained in (a).

5-Isopropyl azulene (64)

5-Isopropyl-1,2,3,6,7,8-hexahydroazulene (62) (1 gm.) ans selenium powder[55] (1.5 gm.) were heated together at 300° in a Wood's metal bath for 15 minutes. A deep blue oil condensed on the condenser and hydrogen selenide was evolved. The cooled residue was dissolved in ethanol, filtered and evaporated to give a dark green oil (800 mgs.). Chromatography on silica and elution with petroleum ether gave unreacted diene (62) (600 mgs.) followed by a deep blue volatile liquid (8 mgs.) u.v. spectrum: $\lambda_{max.}^{EtOH}$ 239 mμ, ε 3,000, and $\lambda_{max.}^{EtOH}$ 276 mμ ε 7,000 (see Fig.VII[56,57]), i.e. characteristic of 5-isopropylazulene.

Ozonolysis of ester (60)

The ester (34) (1 gm.) was dissolved in ethyl acetate (15 ml.) and the solution cooled to -70°. A slow stream of ozone was bubbled through the solution for 4 hours whichwas then brought to room temperature. The ozonide was decomposed by treatment with zinc (2 gm.) in acetic acid (5 ml.) with stirring at room temperature for 12 hours. The zinc was removed by filtration and the solvent evaporated under reduced pressure to give the crude ozonolysis product as a yellow oil (950 mgs.). Distillation gave the major component as a colourless oil (750 mgs.).

b.p. 120-5°/0.5 mm. R_t = 5.48 min. on 1% Q.F.1 at 150°.

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1735 cm.$^{-1}$ (ester) and 1670 cm.$^{-1}$ (α,β-unsaturated ketone).

U.V, spectrum : $\lambda_{max.}^{EtOH}$ 245 mμ, ε 12,000.

N.M.R.spectrum: 6.3 τ (3 x H, singlet) (no vinylic protons).

The 2,4-dinitrophenyl hydrazone was obtained as deep red needles m.p. 192-4° (ethanol). Found: C, 55.90; H, 4.96; N, 14.55. $C_{18}H_{20}N_4O_6$ requires C, 55.67; H, 5.19; N, 14.43%. U.V. spectrum: $\lambda_{max.}^{EtOH}$ 257 mμ, ε 14,000 and 367 mμ, ε 20,000. The above physical data is consistent with a $\Delta^{9,10}$-keto-octalin carbomethoxylated at either C_6 or C_8 (73).

Hydrolysis of the octalin (73)

The keto octalin (73) (300 mgs.) was dissolved in methanolic potassium hydroxide (500 mgs. in 10 ml.). The mixture was stirred at room temperature for 12 hours and the methanol removed under reduced pressure. The residue was dissolved in water and the aqueous solution extracted with ether and the ethereal extracts discarded. The aqueous layer was acidified and extracted with ether and the combined ethereal extracts brine washed, dried and evaporated

to give a white solid (200 mgs.). Recrystallisation from benzene gave the acid as colourless needles, m.p. 145-6°. Found: C, 67.85; H, 7.27. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.37%.

Mass spectrum : Molecular ion at 194 m/e showing a facile loss of 45 m/e to give the base peak at 149 m/e.

I.R. spectrum : Carboxylic acid absorption bands at 2800 - 3300 $cm.^{-1}$ and 3530 $cm.^{-1}$ (non-bonded). $\nu_{C=O}^{CCl_4}$ 1710 $cm.^{-1}$ (carboxylic acid) and 1670 $cm.^{-1}$ (α,β-unsaturated ketone).

U.V. spectrum : $\lambda_{max.}^{EtOH}$ 247 mμ, ε 11,200 (calculated for (74) as $\lambda_{max.}$ 249 mμ).

The above spectral data is consistent with 1-oxo-6-carboxy-$\Delta^{9,10}$-octalin (78).

2,3-Cyclopentenobicyclo-[3,2.1]-oct-2-en-8-one (57)

p-Toluene sulphonic acid (2 gm.) and anhydrous toluene (50 ml) were refluxed in a Dean and Stark water separator for 2 hours. Bis-cyclopentanonyl methane (56) (2 gm.) in dry toluene (5 ml.) was added to the cooled solution and the

mixture refluxed for 2 hours. The cooled residue was neutralised with anhydrous potassium carbonate overnight. The toluene was evaporated under reduced pressure (0.5 mm.) to give a brown oil (1.8 gm.). Chromatography on silica, and distillation gave the required bicyclic ketone[30] (57) as a colourless oil (1.6 gm.) b.p. 80-5°/0.5 mm. Infra-red spectrum: $\nu_{C=O}^{CCl_4}$ 1758 cm.$^{-1}$ (strained carbonyl).

Ozonolysis of the bicyclic ketone (57)

2,3-Cyclopentenobicyclo-[3,2,1]-oct-2-en-8-one (57) (2.2 gm.) was dissolved in ethyl acetate (25 ml.) and the solution cooled to -70°. A slow stream of ozone was bubbled through the solution for 4 hours and work up as before gave the ozonolysis product as a white solid (2 gm.) m.p. 146-7° (colourless needles from benzene). The ozonolysis product was identified as 1-oxo-6-carboxy-$\Delta^{9,10}$-octalin (40) by comparison of spectral data with that of the authentic sample obtained from the ozonolysis of the ester (60), (mixed m.p. = 145°).

U.V. spectrum : $\lambda_{max.}^{EtOH}$ 247 mμ, ε 11,200.

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1710 cm.$^{-1}$, 1670 cm.$^{-1}$.

Mass spectrum : Molecular ion at 194 m/e and base peak at 149 m/e.

The 2,4-dinitrophenyl hydrazone was obtained as brick-red needles m.p. 245-7° (dioxan-methanol). Found: C, 54.28; H, 5.01; N, 14.80. $C_{17}H_{18}N_4O_6$ requires C, 54.54; H, 4.85; N, 14.97%. U.V. spectrum: $\lambda_{max.}^{EtOH}$ 250 mμ, ε 14,000 and $\lambda_{max.}^{EtOH}$ 368 mμ, ε 17,000.

The acid obtained from ozonolysis of the bicyclic ketone (57) was esterified with diazomethane and identified as 1-oxo-6-carbomethoxy-$\Delta^{9,10}$-octalin (77) by comparison with the authentic sample obtained by ozonolysis of the ester (60). R_t = 5.48 min. on 1% Q,F.1 at 150°. The 2,4-dinitrophenyl-hydrazone was obtained as a deep red solid, m.p. 195-6° (ethanol). Found: C, 55.71; H, 5.09; N,14.00. $C_{18}H_{20}N_4O_6$ requires C, 55.67; H, 5.19; N, 14.43% U.V. spectrum: $\lambda_{max.}^{EtOH}$ 257 mμ, ε 11,000 and 366 mμ, ε 17,000.

2-(2'-Cyclopentanonylmethyl)cyclohexanone (88)

2-Dimethylaminomethylcyclopentanone (58) (9 gm., 0.06 m.) was dissolved in cyclohexanone (24 gm., 0.25 m.) and the mixture heated at reflux temperature, with stirring, for 2 hours. Standard work up procedure gave a colourless oil from which the required diketone was obtained by distillation (6 gm., 45%) b.p. 120-5°/1.5 mm. R_t = 14.0 min. on 10% P.E.G.A. at 175°. Found: C, 73.68; H, 9.63. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.34%.

2,3-Cyclohexeno-6,7-dihydro, 5H, pyrindine[80] (89)

The diketone (88) (500 mgs.) was dissolved in absolute ethanol (5 ml.) and the solution treated with hydroxylamine hydrochloride (500 mgs.) at 50° for 15 minutes. The warm solution was poured on to dilute sodium hydroxide and the alkaline solution extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to give the pyrindine (89) as a pale yellow oil (300 mgs., 60%). The picrate was obtained as bright yellow needles, m.p. 155-7° (ethanol). Found: C, 53.67; H, 4.55; N, 13.78. $C_{18}H_{18}N_4O_7$ requires C, 53.73; H, 4.51; N, 13.92%. N.M.R. spectrum: 2.8 τ (1 x H, singlet).

Acid treatment of diketone (88)

The diketone (88) (4 gm.) was dissolved in glacial acetic acid (25 ml.) and concentrated hydrochloric acid (8 ml.) and the mixture refluxed for 24 hours. Standard work up procedure gave a neutral fraction as a yellow oil (3.6 gm.) and a negligible amount of acidic material. G.l.c. investigation showed the neutral material to contain starting diketone (R_t = 14.0 min. on 10% P.E.G.A. at 175° ~ 5%) together with three other components (R_t = 4.25 min., 7.25 min., and 17.00 min. (~1:2:5). The crude neutral

mixture (2 gm.) was adsorbed on to silica and elution with ethyl acetate-petroleum ether gave the non-polar component as a colourless oil (900 mgs.), ($\nu_{C=O}^{CCl_4}$ 1758 cm.$^{-1}$ and 1722 cm.$^{-1}$), the starting diketone (88) (50 mgs.) and the polar component as a colourless oil (750 mgs.).

(a) Polar component

b.p. = 80°/0.5 mm. R_t = 17.00 min. on 10% P.E.G.A. at 175°. Found: C, 74.37; H, 9.60. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.34%.

I.R. spectrum : 1778 cm.$^{-1}$ (lactone).

N.M.R.spectrum: broad unresolved region at 7.8 - 8.2 τ. No signal at ~5.0 τ i.e. γ-lactone at a ring junction.

The above physical data is consistent with11-hydroxy-bicycl-[5,4,0]-undecane-6-carboxylic acid lactone (90).

(b) Non-polar component

G.l.c. analysis showed this material to be a mixture of two similar compounds. R_t = 4.25 min., 7.25 min. on 10% P.E.G.A. at 175°. The mixture (900 mgs.) was dissolved in dilute acid and refluxed for 3 days. Standard work up procedure gave only a neutral product, shown by

g.l.c. to be a mixture of two components (R_t = 4.25 min. and 17.00 min.). The mixture was adsorbed on to silica and elution with ethyl acetate-petrol gave a non-polar component (c) (250 mgs.) and a polar component (d) (400 mgs.).

(c) Non-polar component

Isolated as a colourless oil, b.p. 60°/0.01 mm. R_t = 4.25 min. on 10% P.E.G.A. at 175°. Found: C, 81.17; H, 9.65. $C_{12}H_{16}O$ requires C, 81.7; H, 9.15%.

Mass spectrum : parent ion at 176 m/e.

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1722 cm.$^{-1}$.

N.M.R.spectrum: 7.5 τ (2 x H, multiplet); 8.2 τ (6 x H, multiplet and 8.5 τ (8 x H, multiplet).

The above physical data is consistent with 2,3-cyclopentenobicyclo-[3,3,1]-non-2-ene-9-one (92).

(d) Polar component

Isolated as a colourless oil, b.p. 85-90°/0.7 mm. R_t = 17.00 min. on 10% P.E.G.A, at 175°. Infra-red spectrum: 1778 cm.$^{-1}$ (lactone). 1.e.11-hydroxy-bicyclo-[5,4,0]-undecane-6-carboxylic acid lactone (90). Thus the non-polar component from which this was derived must have been 1,2-cyclohexenobicyclo-[3,2,1]-oct-2-en-8-one (91).

2-Methylcyclopentanone

This compound was prepared by cyclisation of diethyladipate and subsequent alkylation of the 2-carbethoxycyclopentanone as described by Nicole.[81] It was isolated in 70% yield as a colourless oil b.p. 140°/760 mm.

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1740 cm.$^{-1}$

N.M.R.spectrum: 8.73 τ (6 x H, doublet).

2-Methyl-2-(β-dimethylaminomethyl)cyclopentanone (116)

This compound was prepared as described in Part II, p.133, and used without further purification.

2-Methyl-5-(2'-cyclopentanonylmethyl)cyclopentanone (83)

(a) From the Mannich base (116)

The Mannich base (116) (9.9 gm., 0.07 m.) was reacted with cyclopentanone (17.64 gm., 0.21m.) as described in Part II, p.141. The required diketone (83) was isolated as a colourless oil, b.p. 105-8°/0.5 mm. R_t = 12.05 min. on 10% A.P.L. at 175°. Found: C, 73.98; H, 8.98. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.34%.

I.R. spectrum: $\nu_{C=O}^{CCl_4}$ 1740 cm.$^{-1}$ (cyclopentanone)

The N.M.R. spectrum showed the methyl protons as two overlapping doublets at 8.95 τ (6 c.p.s.).

(b) From the Mannich base (58)

The Mannich base (58) (6.5 gm., 0.06 m.) and 2-methylcyclopentanone (18 gm., 0.18 m.) were heated at reflux temperature for 90 minutes. Standard work up procedure gave a pale yellow oil from which the required diketone (83) was obtained as a colourless oil (5.2 gm., 50%), b.p. 110°/0.5 mm. R_t = 12.05 min. on 10% A.P.L. at 175°.

2,3-(2'-Methylcyclopenteno)-6,7-dihydro-5H-pyrindine (85)

The diketone (83) (500 mgs.) in ethanol (10 ml.) was treated with hydroxylamine hydrochloride (500 mgs.) and the mixture heated at 50° for 15 minutes. The warm solution was poured on to dilute sodium hydroxide (5 ml.) and extracted with ether (3 x 5 ml.). The combined ethereal extracts were brine washed, dried and evaporated to give the required pyrindine derivative as a pale unstable oil. The mass spectrum gave the molecular weight as 173.12026 m/e ($C_{12}H_{15}N$ requires 173.12044 m/e). N.M.R. spectrum: 2.7 τ (1 x H, singlet), 8.7 τ (6 x H, doublet, J = 6 c.p.s.).

1-Methyl-2,3-cyclopentenobicyclo-[3,2,1]-oct-2-en-8-one (86)

p-Toluene sulphonic acid (500 mgs.) was dissolved in dry toluene (20 ml.) and the mixture refluxed for 2 hours in a Dean and Stark water separator. The diketone (83) (500 mgs.) in dry toluene (2 ml.) was added to the cooled solution and the mixture refluxed for 3 hours. The cooled residue was neutralised by standing over solid potassium carbonate for 12 hours. The solid was filtered and washed with hot benzene. The solvents were evaporated to give a pale yellow oil (480 mgs.). Chromatography on silica with 30% benzene-petrol gave the required bicyclic ketone (86) as a colourless oil (260 mgs., 60%), b.p. 82-4°/0.9 mm. R_t = 2.9 min. on 1% A.P.L. at 150°. Found: C, 81.49; H, 8.39. $C_{12}H_{16}O$ requires C, 81.49; H, 8.15%.

I.R. spectrum : $\nu_{C=O}^{CCl_4}$ 1758 cm.$^{-1}$ (strained cyclopentanone).

U.V. spectrum : $\lambda_{max.}^{EtOH}$ 208 mμ, ε 6,000

N.M.R.spectrum: 8.95 τ (6 x H, singlet).

The above physical data is consistent with the bicyclic ketone (86).

Treatment of bicycle (86) with selenium dioxide[63,65]

The bicyclic ketone (86) (100 mgs.) was dissolved in ethanol (5 ml.) and treated with freshly sublimed selenium dioxide (80 mgs.). The mixture was heated at reflux temperature for 3 hours and the precipitated selenium removed by filtration through glass paper. The ethanol was evaporated to give a pale yellow oil. U.V. and g.l.c. investigation showed this to be returned starting material. Also the allylic oxidation was unsuccessful by using the recommended[64] higher boiling solvents (benzene, toluene, xylene or acetic anhydride).

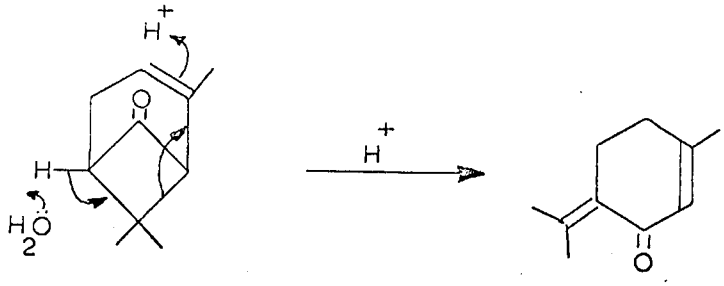
2-(3'-Methyl-2'-oxocyclopentylmethyl)cyclohexan-1,3-dione (87)

Cyclohexane-1,3-dione (11 gm., 0.1 m.) was dissolved in 2-methyl-2-dimethylaminomethylcyclopentanone[116] (4.65 gm., 0.04 m.) and the mixture refluxed with stirring for 6 hours. Standard work up procedure gave the required triketone (87) as a white solid, m.p. 115-6° (petrol).

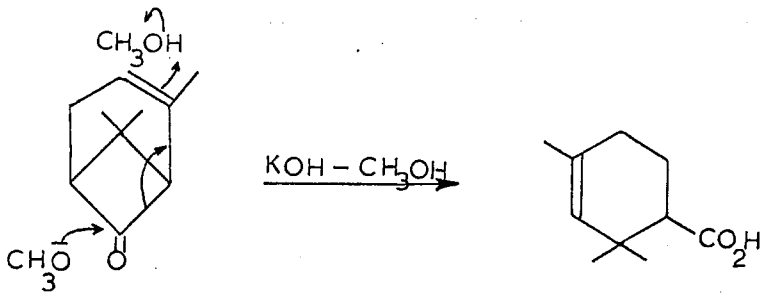
For the spectral data see Part II, p.141 .

Attempted cyclisation of the triketone (87)

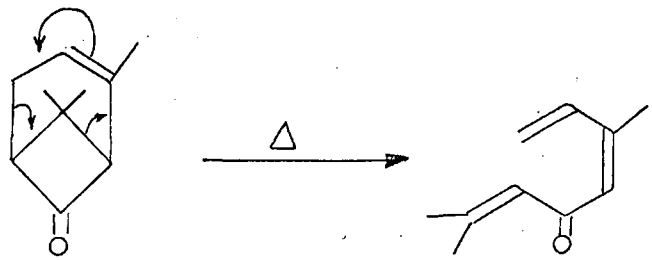
p-Toluene sulphonic acid (1 gm.) was dissolved in dry toluene (40 ml.) and the mixture refluxed in a Dean and Stark water separator for 3 hours. The triketone (1 gm.) in toluene (5 ml.) was added to the cooled solution, and the mixture refluxed for 4 hours. The cooled residue was neutralised with anhydrous potassium carbonate, filtered and evaporated to give a white solid identified as returned triketone (87) by mixed m.p. (116°).



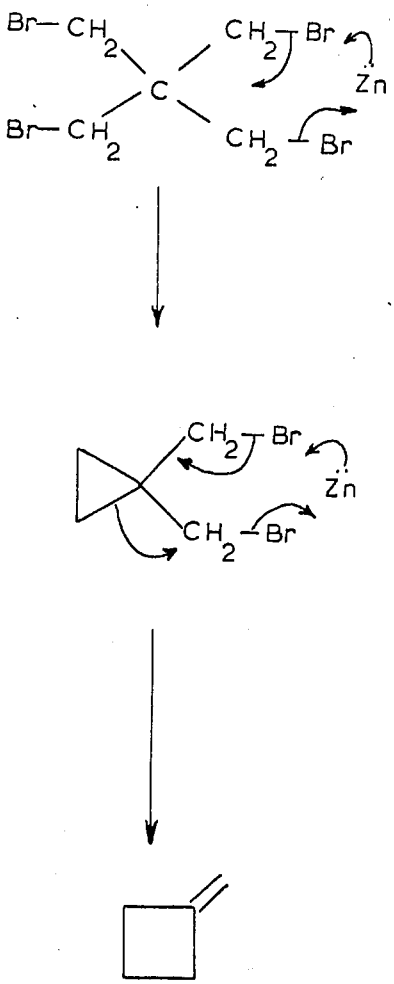
Scheme I



Scheme II



Scheme III



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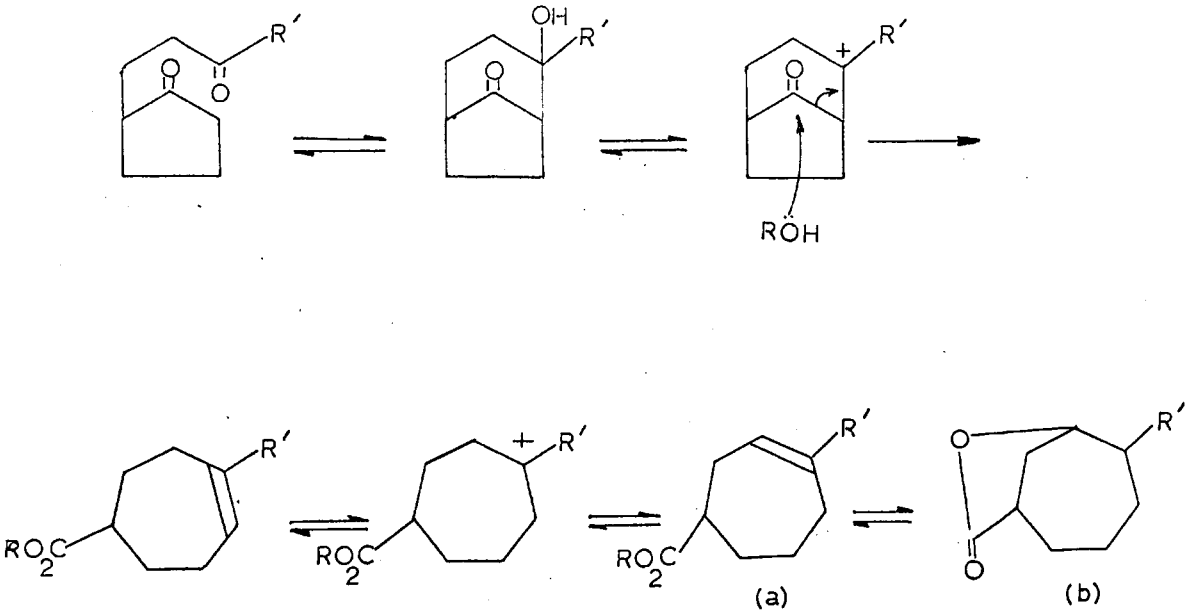
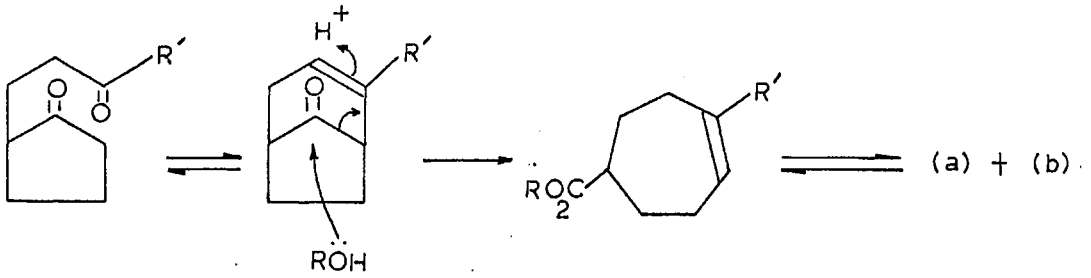


Scheme V



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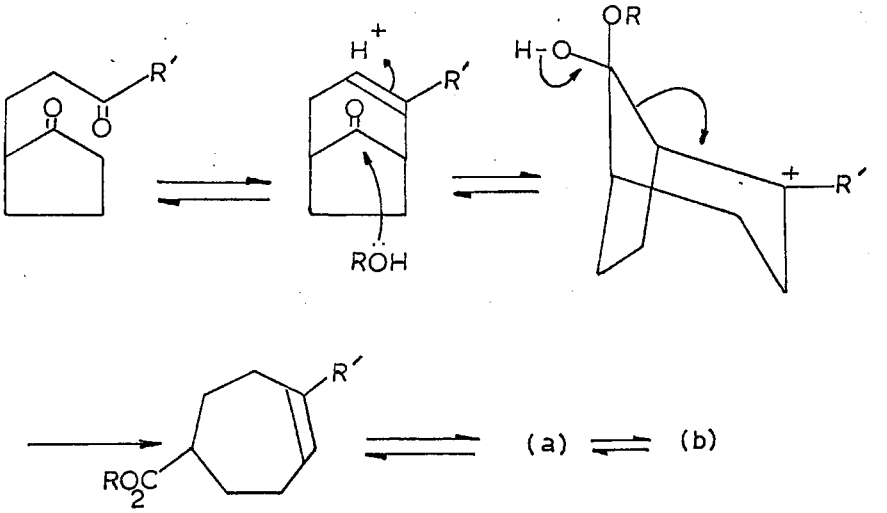

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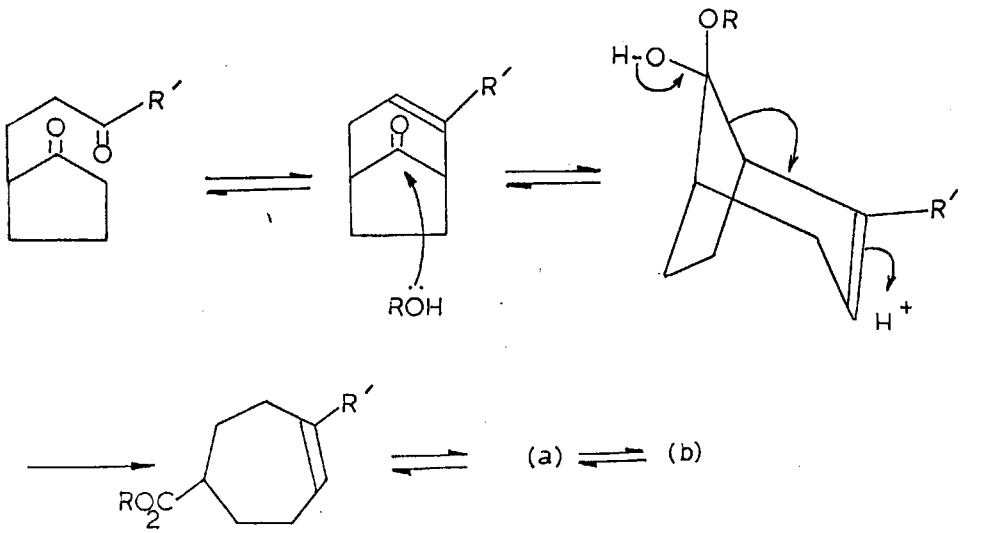
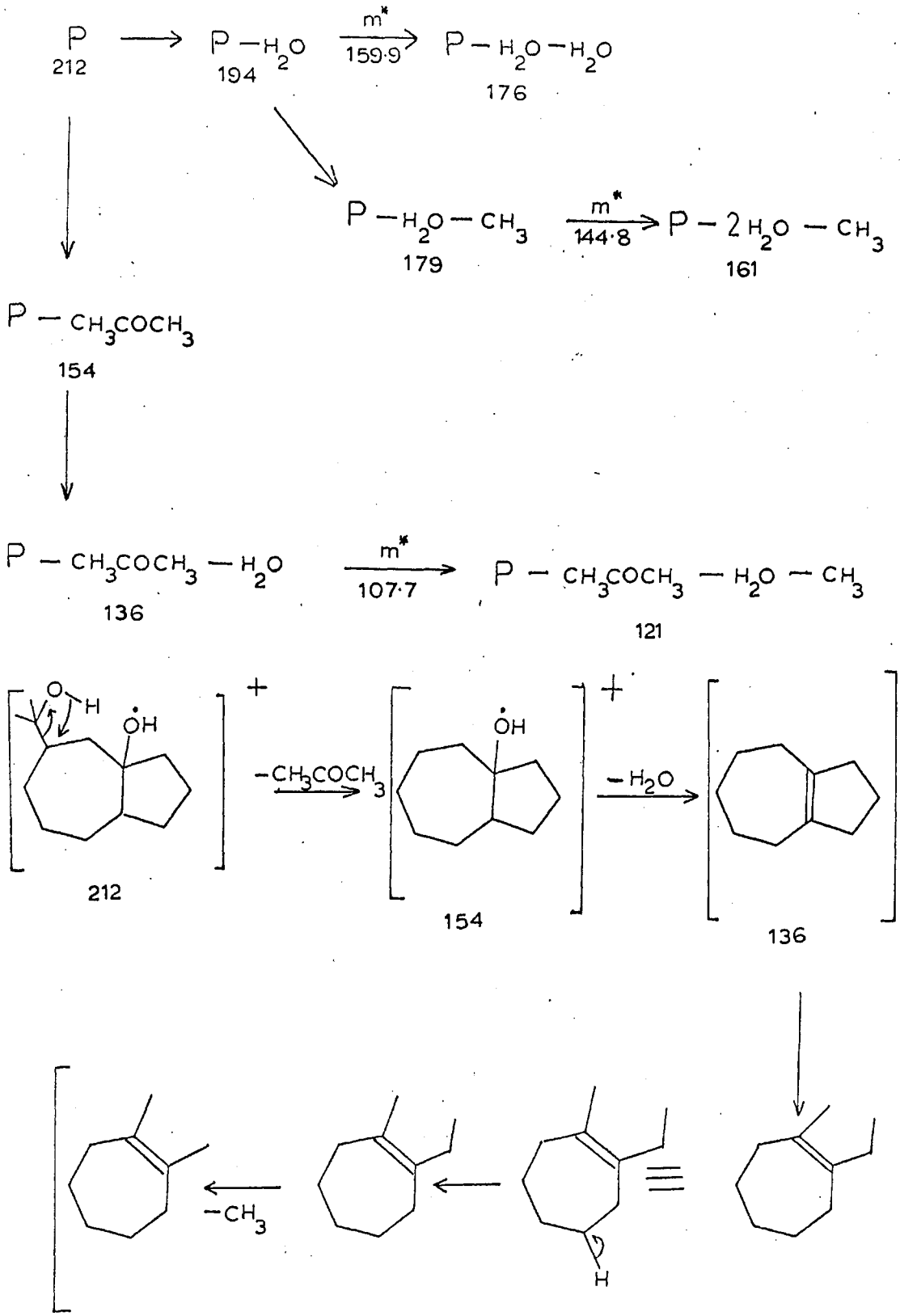
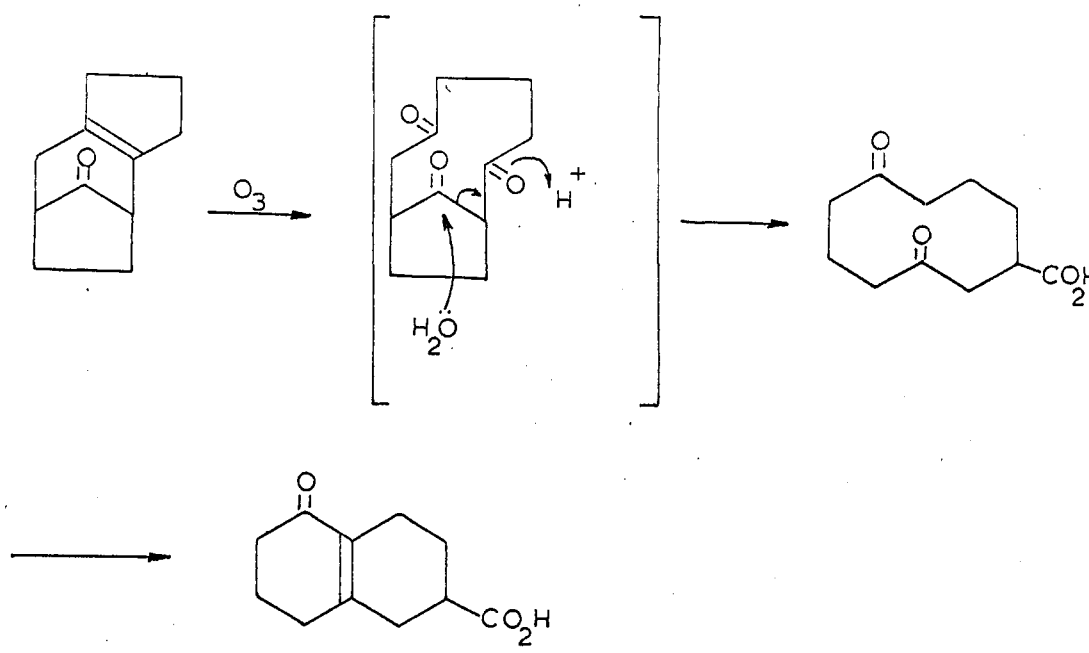


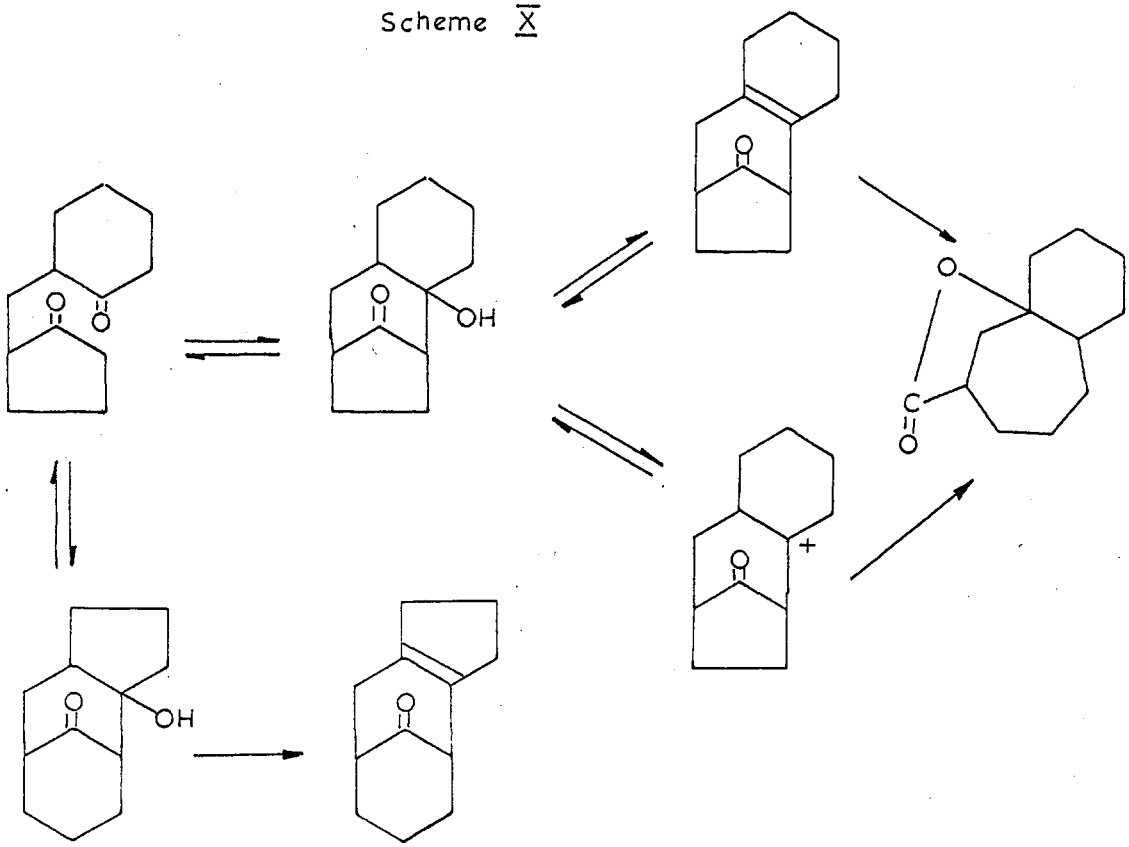
Scheme VIII


P
212
P − H2O
194
m*
159·9
P − H2O − H2O
176
P − H2O − CH3
179
m*
144·8
P − 2H2O − CH3
161
P − CH3COCH3
154
P − CH3COCH3 − H2O
136
m*
107·7
P − CH3COCH3 − H2O − CH3
121
212
−CH3COCH3
154
−H2O
136
−CH3

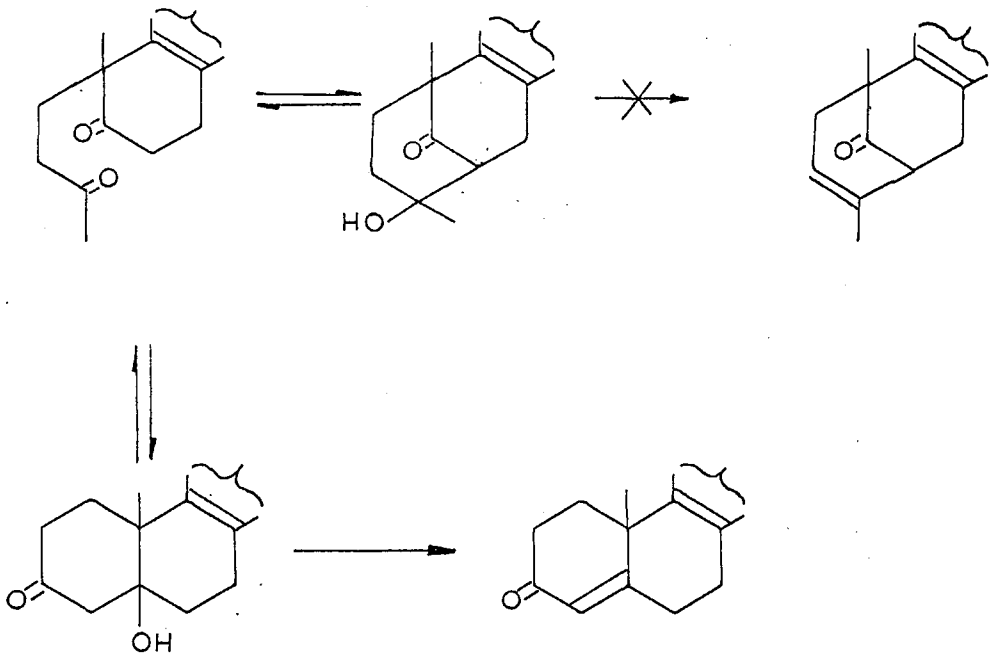
Scheme IX



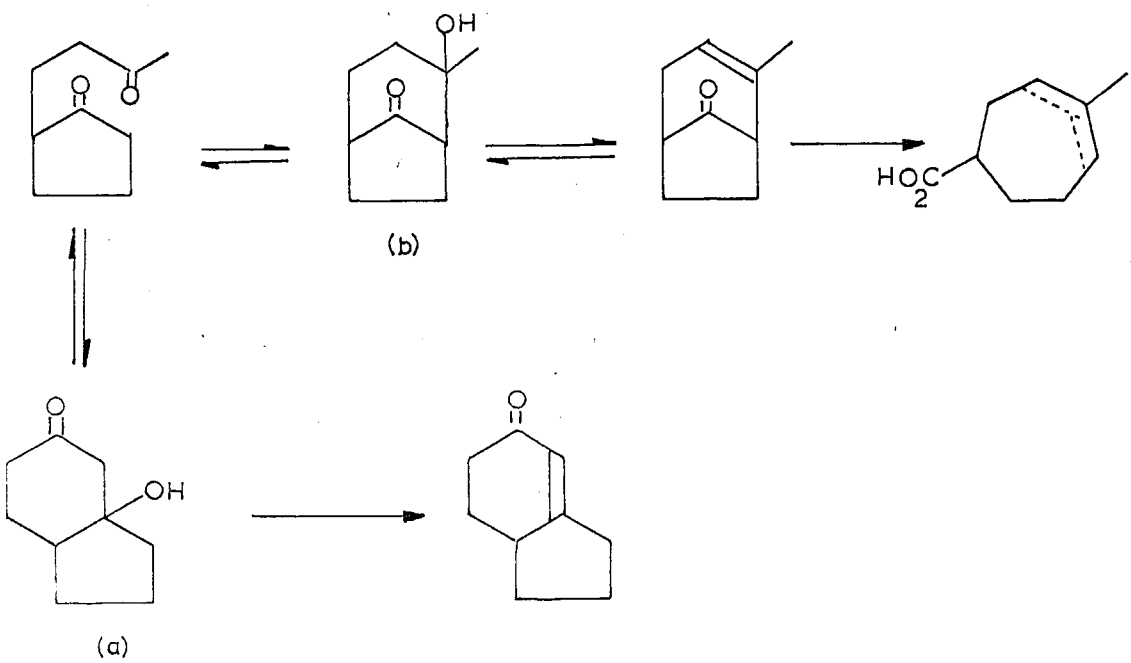
Scheme X



Scheme XI



Scheme XII



Scheme XIII

REFERENCES

1. Dewar, Nature, 1945, 155, 50.
2. Dewar, Nature, 1945, 155, 151.
3. Cook and Sommerville, Nature, 1949, 163, 410.
4. Nozoe, Proc. Jap. Acad., 1950, 26, 38.
5. Johnson, Bartels-Keith and Taylor, Chem. and Ind., 1951, 337.
6. Van Tamelen et al., Tet., 1961, 14, 8.
   Eschenmoser et al., Helv.Chim.Acta, 1961, 540.
   Nakamura et al., Chem.Pharm.Bull., 1960, 8, 843; 1961, 9, 81,; 1962, 10, 281.
   Woodward, 'The Harvey Lectures', 1965.
7. Erdtman and Gripenberg, Nature, 1948, 161, 719.
8. Willstraed, Ber., 1935, 68, 333.
9. Plattner and St. Pfau, Helv.Chim.Acta, 1936, 19, 858.
10. Karrer, Ruckstuhl and Zbinden, Helv.Chim.Acta, 1945, 28, 1176.
11. Stahl, Ber., 1954, 87, 505.
12. Ruzicka et al., Helv.Chim.Acta, 1926, 9, 499.
13. Cope et al., J.Amer.Chem.Soc., 1962, 84, 4865.
14. Ziegler, Eberle and Ohlinger, Annalen, 1933, 504, 94.
15. Prelog et al., Helv.Chim.Acta, 1947, 30, 1741.

16. Prelog, 'Centenary Lecture', J.Chem.Soc., 1950, 420.

17. Rapaport and Campion, J.Amer.Chem.Soc., 1951, 73, 2239.

19. Lowenthal, J. Chem. Soc., 1961, 1421.

20. Gutsche, J.Amer.Chem.Soc., 1951, 73, 786.

21. Martel, Huynh and Toromanoff, J.Org.Chem., 1965, 30, 1753.

22. Scott et. al, Tet., 1965, 21, 3005.

23. Burger and Mossettig, J.Amer.Chem.Soc., 1930, 52, 3456.

24. Doering and Knox, J.Amer.Chem.Soc., 1950, 72, 2305.

25. Craig, Chem.Soc.Spec.Pub., 1958, 12, 343.

26. Dodson, Parham and Soeder, J.Amer.Chem.Soc., 1962, 84, 1755.

27. Birch, Proc. Chem. Soc., 1962, 282.

28. Fassnacht, Nelson and Piper, J.Amer.Chem.Soc., 1959, 81, 5009.

29. Chapman and Fitton, J.Amer.Chem.Soc., 1961, 83, 1005.

30. McLay, Ph.D. Thesis (Glasgow), 1965.

31. Cope, Graham and Marshall, J. Amer. Chem. Soc., 1964, 76, 6159

32. Buchanan et.al., J. Chem. Soc., 1965, 833.

33. Buchanan and McLay, Tet., 1966, 22, 1521.

34. Cope and Hermann, J.Amer.Chem.Soc., 1950, 72, 3405.

35. Buchanan et. al., Tet., 1965, 21, 3273.

36. Foote and Woodward, Tet., 1964, 20, 687.

37. Blanchard, Chem. and Ind., 1958, 293.

38. Lipp et. al., Ber., 1931, 64, 2823.

Coops et.al., Rec. Trav. Chim., 1951, 70, 1033.

39. Shand, Shomaker and Fischer, J. Amer. Chem. Soc., 1944, 66, 636.

Roberts and Sauer, J.Amer.Chem.Soc., 1949, 71, 3925.

40. Conia et. al., Bull. Soc. Chim. Fr., 1961, 1803.

41. Gill et. al., J.Amer.Chem.Soc., 1952, 74, 4923.

42. Blicke and Maxwell, J.Amer.Chem.Soc., 1942, 64, 428.

43. Gordy, J. Chem. Phys., 1940, 8, 516.

44. Ginsberg, Lederman and Papa, J.Amer.Chem.Soc., 1957, 75, 4587

45. Cheney, Fitzgibbon and Wheatley, J. Amer. Chem. Soc., 1954, 76, 4490.

46. Aycock and Stamper, J. Amer. Chem. Soc., 1954, 76, 2786.

47. Hahn, Kapper and Ludewig, Ber., 1934, 67, 696.

48. Buchanan et. al., Tet,,1964, 20, 1449.

49. Dauben and McFarland, J.Amer.Chem.Soc., 1960, 82, 4245.

50. Nun and Rapson, J.Chem.Soc., 1949, 825.

51. Dreux, Delplace and Cologne, Bull. Soc. Chim. Fr., 1956, 1638.

52. Mousseron, Jacquier and Boyer, Bull. Soc. Chim. Fr., 1957, 346.

53. Ruzicka and Rudolph, Helv.Chim.Acta., 1926, 9, 118.

54. Ruzicka and Hagen Smit, Helv.Chim.Acta., 1931, 14, 1104.

55. Herout, Dolejs and Sorm, Chem. and Ind., 1956, 1237.

56. Heilbronner and Plattner, Helv.Chim.Acta., 1948, 804.

57. Plattner et.al., Helv.Chim.Acta., 1954, 37, 275.

58. De Mayo, Chem. Comm., 1967, 89.

59. Marshall and Andersen, Tet Lets., 1967, 17, 1611.

60. Plattner and St. Pfau, Helv.Chim.Acta., 1940, 23, 768.

61. Ruzicka and Hagen Smit, Helv.Chim.Acta., 1931, 14, 1122.

62. Plattner and Magyer, Helv.Chim.Acta., 1941, 241, 191.

63. Barbier, Helv.Chim.Acta., 1940, 23, 524, (1477).

64. Dupont et.al., Bull.Soc.Chim. Fr., 1933, 53, 600.

65. Dupont et.al., Compte Rend., 1934, 199, 363.

66. Johnson et. al., J.Amer.Chem.Soc., 1960, 82, 4245.

67. Buchanan and McLay, Chem. Comm., 1965, 20, 587.

68. Ross and Levine, J.Org.Chem., 1964, 29, 2341.

69 Rapaport et. al., J.Amer.Chem.Soc., 1954, 76, 3693.

70. Rapaport, Campion and Gordon, J.Amer.Chem.Soc., 1955, 77, 2389.

71. Vogel, Practical Org. Chem., 1948, 694.

72. Ungnade and Morriss, J.Amer.Chem.Soc., 1948, 70, 1898.

73. Perkin, J. Chem. Soc., 1904, 85, 424.

74. Padfield and Tomlinson, J.Chem.Soc., 1950, 2273.

75. Baker, J. Chem. Soc., 1933, 1381.

76. Anschutz and Scholl, Ann. 1911, 379, 333.

77. McCrae, Ph.D. Thesis (Glasgow), 1966.

78. Birch, J. Chem. Soc., 1944, 430.

79. Jacquier, Boyer and Mousseron, Bull.Soc.Chim.Fr., 1956,1653.

80. Stobbe, J. Prakt. Chim., 1912, 86, 241.

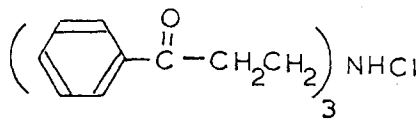
81. Nicole and Beslinguet, Canad. J. Chem., 1962, 40, 353.

82. Org. Syn., Coll. Vol. II, 1943, 476.

83. Vogel, Practical Org. Chem., 1948, 302.

PART II

STUDIES IN THE MANNICH REACTION



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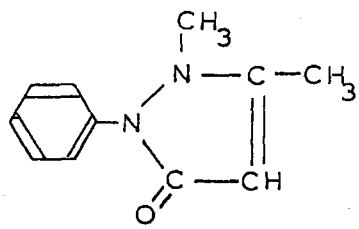

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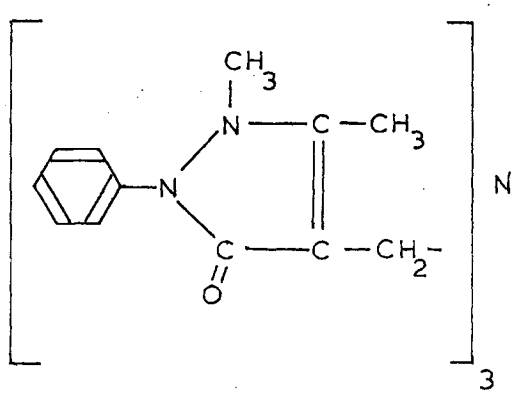
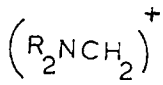


3

INTRODUCTION

Although it is over fifty years since the Mannich reaction was first discovered, it still continues to provide much challenging chemistry and despite the simplicity of the reaction, it has been the subject of a lengthy review[1], a book[2] and a great many controversial articles published as recently as 1967.

When a compound containing an active hydrogen atom is treated with formaldehyde and ammonia, (or a primary or secondary amine), the active hydrogen is replaced by an aminomethyl group, thus providing a satisfactory method for the introduction of a single carbon atom. The first observation of a condensation of this type, now known as the Mannich reaction, was made by Tollens[3] in 1903, when he isolated the tertiary amine (1) from the reaction of acetophenone with ammonia and formaldehyde. This reaction was also studied by Petrenko[4] in 1909, but it was not until 1912 that it was recognised as a general reaction when Mannich[5] undertook a detailed systematic study of the raaction following his discovery that antipyrinesalicylate (2), formaldehyde, and ammonium chloride reacted to form a tertiary amine (3).



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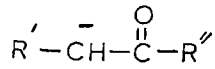

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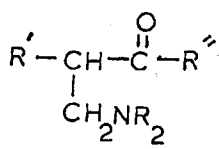

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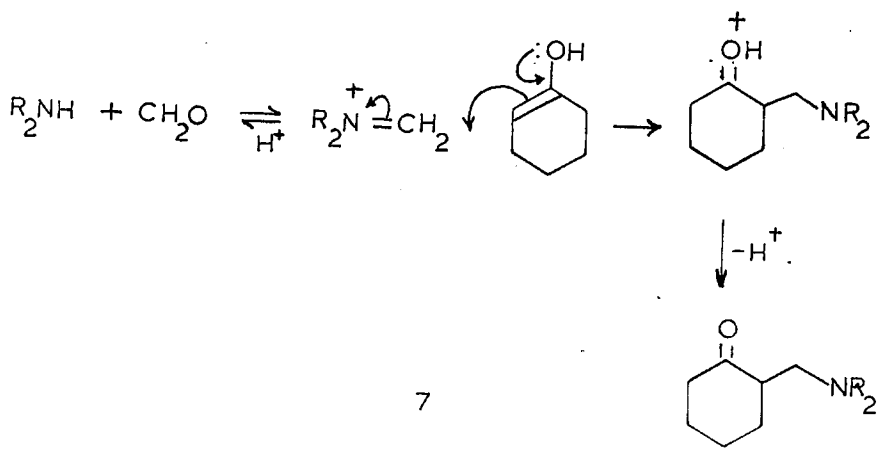

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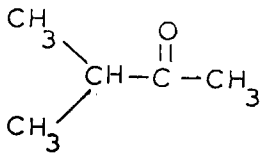
The range of active hydrogen containing compounds, that take part in the Mannich reaction, is vast and includes ketones, aldehydes, acids, esters, phenols and acetylenes.

The mechanism of the Mannich reaction has been the subject of considerable discussion and during the period 1930 to 1960, four mechanistic schemes were proposed. In 1933, Bodendorf and Korelewski[6] concluded from their experiments that neither the condensation of the formaldehyde with the amine, nor with the active hydrogen compound, to yield the corresponding methylols, showed the true course of the reaction. Liebermann[7] presented an attractive mechanism involving the formation of a carbonium ion (4), from the amine and formaldehyde, and a carbanion (5), formed by removal of a proton from the active hydrogen compound, and then proposed a final irreversible step involving the combination of the carbonium ion and the carbanion with formation of the Mannich base (6). This mechanism was shown to be erroneous by Alexander and Underhill[8], who carried out a kinetic study of the Mannich reaction. Their experiments showed third order kinetics with no primary salt effects, thus contradicting the mechanism of Liebermann which postulated the final and rate controlling step as the reaction between two ions which should show a



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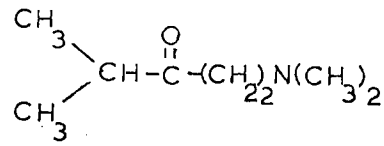

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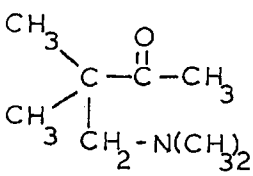

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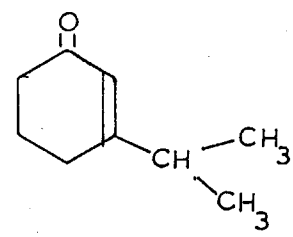

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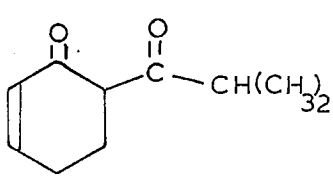

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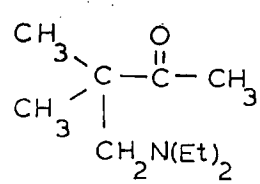


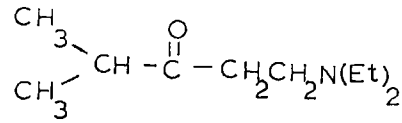
13

primary salt effect. Cummings and Shelton[9], in 1960, showed that under the usual slightly acidic reaction conditions, the mechanism of the Mannich reaction involves an electrophilic attack by an iminuim salt on the enol of an active methylene compound as shown in (7).

Although symmetrical ketones (e.g. acetone, cyclohexanone and cyclopentanone) form Mannich bases with predictable and indisputable structures, ambiguity regarding orientation in the Mannich reaction can arise with unsymmetrically substituted ketones (e.g. isopropylmethyl ketone, 2-methylcyclohexanone and 2-methylcyclopentanone). Thus the Mannich base of isopropylmethyl ketone (8) has been described with conviction as 5-dimethylamino-2-methylpentanone-3[10](9), 3-dimethylaminomethyl-3-methylbutanone-2[11](10) and as a mixture of both.[12] Only the structure (9) explains the findings of Mousseron et al.[10] who, in 1956, isolated a homogeneous picrate from the Mannich base of isopropylmethyl ketone and assigned this structure on the evidence that condensation of the methiodide with ethylacetoacetate gave 1-isopropylcyclohex-1-en-3-one (11). These findings were supported by Lions[13] who used the same process in his carvenone synthesis and moreover by Mousseron[10], when he

showed the Mannich base to react with butadiene under Diels-Alder conditions to furnish the diketone (12). This structure (9) was accepted until 1962 when Brown[11] presented NMR. spectral evidence (3 H singlet) at 7.93 τ and a (6 H singlet at 8.9 τ) inconsistent with structure (9) but compatible with the isomeric structure (10). Four years later, Haynes and Timmons[12] investigating the homologous diethylamino Mannich base presented evidence in favour of a mixture of isomeric bases [(13), 75% and (14) 25%]. Although Mannich bases are not particularly heat stable, these workers separated the isomers by distillation (with confirmation by GLC.) and assigned structure by infra-red spectroscopy (ε CH_3/ε N-CH_2). The impressive chemical evidence of Mousseron could only be compatible with the spectral evidence of Brown, if either a rearrangement were occurring during the classical Michael condensation, or if such chemical evidence related to the minor component of an isomeric mixture undetectable by NMR. spectroscopy. However, the occurrence of a mixture has been proved in only one case[12] and the question of an intervening rearrangement has never been settled.

With respect to cyclic unsymmetrical ketones (e.g. 2-methylcyclohexanone and 2-methylcyclopentanone), the



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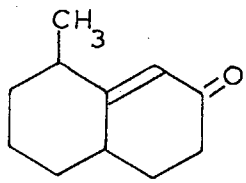

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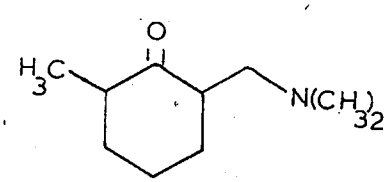

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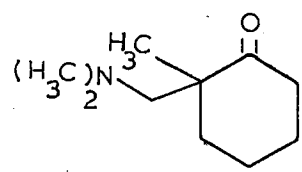

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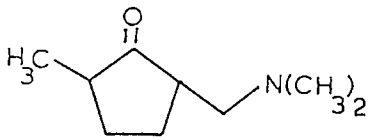
situation is equally confusing with chemical evidence in favour of one isomeric Mannich base and spectral evidence in favour of the other. Robinson[14] and his co-workers isolated 3-keto-5-methyl-$\Delta^{4,10}$-octalin (15) from the alkylation of ethylacetoacetate with the methiodide of the Mannich base of 2-methylcyclohexanone and thus proposed the structure of the base to be 2-dimethylaminomethyl-6-methylcyclohexanone (16) with further proof offered independently by Frank[15] who, in his octahydro coumarin synthesis, successfully alkylated ethyl malonate with the Mannich base methiodide. This combined proof, together with the successful conversion of the Mannich base into 2,6-dimethylphenol by Robinson[14], was recognised as sufficient evidence to assign structure (16), until in 1964 House[16] re-investigated this base using NMR. spectroscopy. The NMR. spectrum showed a singlet methyl signal at 8.9 τ and a doublet methyl signal at 8.95 τ and by measuring the areas under C-methyl peaks he proposed the Mannich base of 2-methylcyclohexanone to be a mixture of 2-dimethylaminomethyl-6-methylcyclohexanone (16) [30%] and 2-dimethylaminomethyl-2-methylcyclohexanone (17) [70%] which could explain the findings of Robinson as being related to the minor component of an isomeric mixture. However the subject



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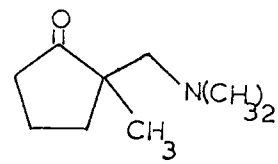

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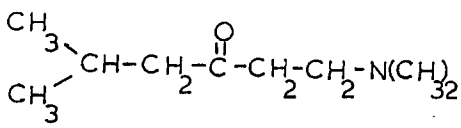

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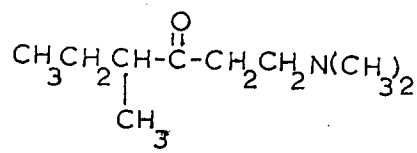

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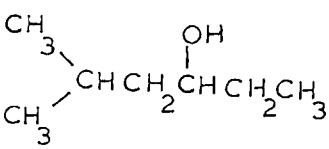

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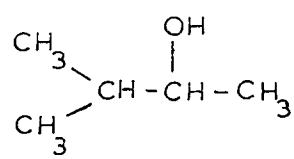

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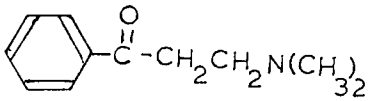
is still open to doubt because House failed to separate the isomeric bases and hence the extraneous methyl doublet at 8.95 τ, which was interpreted as being evidence for structure (16), could be due to traces of 2-methylcyclohexanone formed by decomposition of the Mannich base. Although the mixture hypothesis explains the chemical evidence of Robinson and Frank, it is possible that a rearrangement could intervene during the alkylation reactions or during the purification of the base.

This ambiguity arising from conflicting chemical and spectral evidence is not restricted to isopropylmethyl ketone and 2-methylcyclohexanone. The Mannich base of 2-methylcyclopentanone was shown by Robinson[14] to be 2-methyl-5-dimethylaminomethylcyclopentanone (18) on the basis of chemical evidence, whereas House[16] proposes a mixture of isomeric bases (18) and (19) from NMR. studies. The iodoform reaction has been used with conviction to assign the structure of the Mannich bases of isobutylmethyl ketone[10] and 3-methylpentanone-2[17] as (20) and (21) respectively. Structures have been assigned to the Mannich bases of isobutylmethyl ketone[10] and ethylmethyl ketone[10] by hydrogenolysis to and comparison with the known alcohols (22) and (23) respectively.

However, in view of the doubtful status of chemical evidence as cited above, these assignments require verification spectroscopically.

The most useful property of β-amino ketones, and in particular their hydrochlorides, is their ability to decompose on heating, on steam distillation or on treatment with alkali, to form the corresponding vinyl ketone. The use of such vinyl ketones is limited by the disadvantage of ready polymerisation in the presence of catalysts. To offset this disadvantage, Robinson[14] found that the methiodides of β-amino ketones liberated the corresponding α,β unsaturated ketones in minimal concentrations when treated with sodium ethoxide in the presence of a nucleophilic substrate thus allowing a classical Michael condensation to occur in acceptable yields. Although much of the credit for this reaction goes to Robinson, it was Abdullah[18] in 1935 who first reported that β-dimethylaminopropiophenone (24) took part in a classical Michael condensation with ethylacetoacetate in the presence of sodium ethoxide to give 3-carbethoxy-6-phenylhexanedione-2,6 (25) which further reacted to give 3-phenylcyclohex-2-enone (26). More recently, Wilds[19], Downes[20], and Novello[21] have employed the Mannich base



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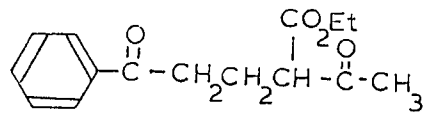

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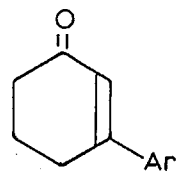

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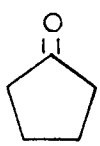

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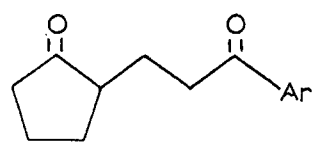


28

hydrochlorides and quaternary salts to overcome the experimental difficulty of instability of the free bases. Gill[22] extended this reaction in 1952 when he discovered that a ketonic Mannich base (e.g. 24) heated in excess of a substrate incorporating a keto methylene system (e.g. 27) underwent β-acylethylation by a thermal Michael reaction with formation of a 1,5-diketone (e.g. 28) in acceptable yield.

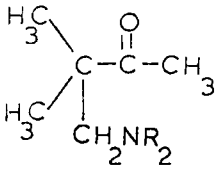
Because of our extensive use of Mannich bases in the thermal Michael reaction (Part I), we felt a need to clarify the structure situation still further and one of the objectives of this work is to re-examine the structures of Mannich bases of unsymmetrical ketones.

DISCUSSION

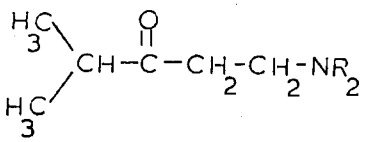
CHAPTER (a)

Recent n.m.r. evidence presented by House[16] has indicated that a mixture of isomeric bases arises from the Mannich reaction of 2-methylcyclohexanone. Infra-red studies by Haynes[12] on the diethylamino Mannich base of isopropyl methyl ketone has provided positive proof for the existence of a mixture of isomers. Such combined evidence raises the question — is an isomeric mixture always formed in a Mannich reaction involving an unsymmetrical ketone, and if so why ? To answer this question, and to substantiate the findings of House and Haynes, attempts have been made to separate and examine, by n.m.r., the isomeric bases arising from a Mannich reaction.

A chromatographic technique was developed to effect this separation, thus offsetting the disadvantage of thermal instability of Mannich bases implicit in a separation by distillation or preparative g.l.c. The mixture of bases derived from isopropyl methyl ketone, paraformaldehyde and diethylamine hydrochloride separated into a non-polar component (75%) and a more polar component (25%); both showing amino-ketone functionalities in the infra-red ($\nu_{C=O}^{CCl_4}$ 1713 cm.$^{-1}$ and $\nu_{N-CH_2}^{CCl_4}$ 2800-2900 cm.$^{-1}$, 3 bands).

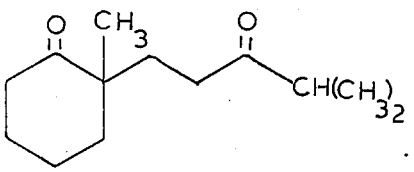


1.



2.

$R = CH_3$



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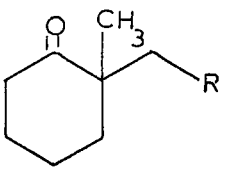
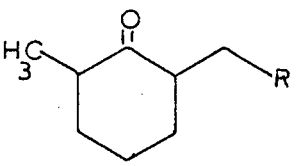
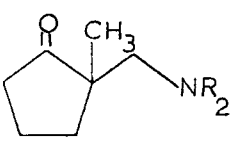




4. $R = N(CH_3)_2$ = R 6.

5. $R = \overset{+}{N}(CH_3)_3\,\bar{I}$ = R 7.



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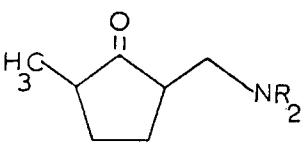
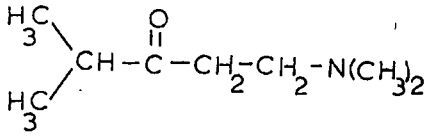


9.

$R = CH_3$

The picrates were examined by n.m.r. indicating the non-polar component to be 3-dimethylaminomethyl-3-methylbutanone-2 (1) (6H singlet at 8.6 τ) and the polar component to be 5-dimethylamino-2-methylpentanone-3 (2) (6H doublet at 8.85 τ and 2H triplet at 6.7 τ). Application of this separation technique to the mixture arising from the Mannich reaction of 2-methylcyclohexanone, failed to effect a complete separation because of the similarities in R_f values (t.l.c.) of the isomeric bases. However, a separation into one pure isomer was achieved by sacrificial recrystallisation of a quaternary salt. The crude (1 recrystallisation) methiodide showed 2-dimethylaminomethyl-2-methylcyclohexanone methiodide (5) (3H singlet at 8.5 τ) together with the isomer 2-dimethylaminomethyl-6-methylcyclohexanone methiodide (7) (3H doublet at 8.9 τ) (~20%), whereas repeated recrystallisation gave (5) as a homogeneous methiodide (3H singlet at 8.5 τ). Similar success was achieved with the picrate; the crude picrate (1 recrystallisation) showed both isomers (3H singlet at 8.7 τ and 3H doublet at 9.1 τ) whereas repeated recrystallisation gave a homogeneous picrate (3H singlet at 8.7 τ).

This unambiguous proof of the existence of isomeric Mannich bases arising from isopropl methyl ketone and from



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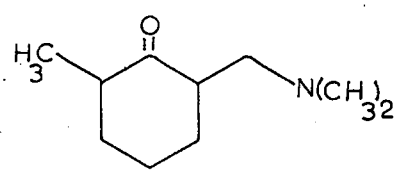


6.

2-methylcyclohexanone suggests that most Mannich bases, from unsymmetrical ketones, are mixtures, the major component of which can be obtained pure via a crystalline salt. The chemical proof offered by Mousseron[10] and Robinson[14] in favour of structures (2) and (6) respectively, must therefore relate to the minor component of an isomeric mixture or involve a molecular rearrangement. This question will be discussed later (Chapter 6). The existence of a mixture of isomeric Mannich bases, arising from the Mannich reaction of unsymmetrical ketones, can be interpreted in terms of Cummings'[9] mechanistic scheme for this reaction, which involves the combination of an imminium salt with the enol form of the ketone. A study of acid catalysed enolisation by Cardwell[23] produced a general rule for predicting the predominant direction of enolisation. " In the acid catalysed enolisation of an unsymmetrical ketone (acyclic or monocyclic), the proton will be lost most readily from the carbon whose adjacent carbon atom carries the largest number of hydrogen atoms". From other investigations, isopropyl methyl ketone, and 2-methylcyclohexanone are known to enolise predominantly at the more heavily substituted carbon atom and this is in agreement with the orientation found in the Mannich reaction.

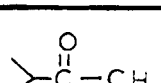
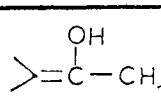
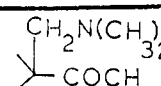
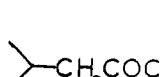
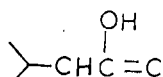
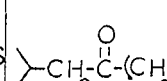
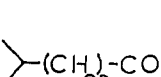
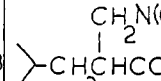
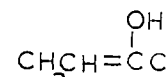
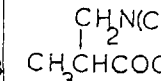
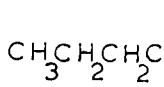
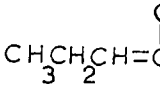
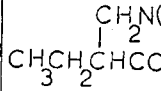
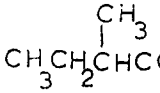
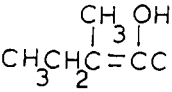
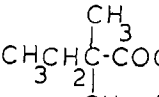
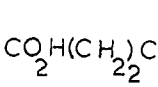
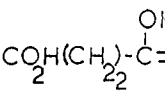
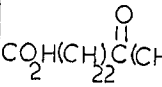
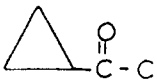
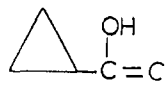
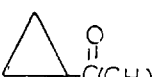
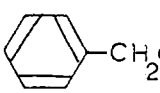
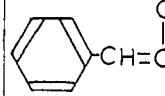
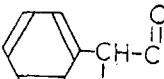
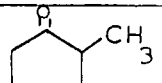
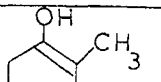
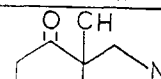
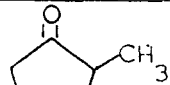
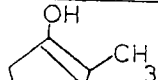
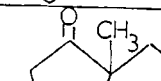
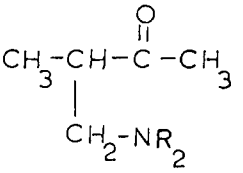
Ketone	Enol (predominant)	Ref	Mannich Base (predominant)	n.mr of free base CH_3CO	n.mr of free base CH_3CHCO
		23		7·81 τ	8·9 τ (s)
		26		blank	—
		23		7·90 τ	—
		23		7·89 τ	8·95 τ (d)
		23		7·80 τ	—
		23		7·81 τ	8·85 τ (s)
		26		blank	—
		23		blank	—
		23		8·00 τ	—
		23		—	8·90 τ (s)
		23		—	9·08 τ (s)

Table I



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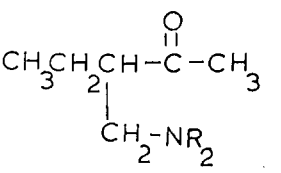
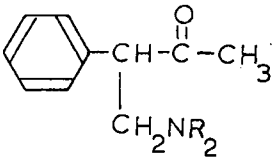


$R = CH_3$

11.



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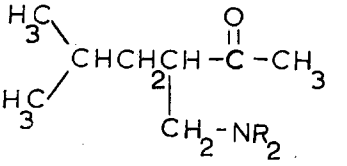

$R = CH_3$

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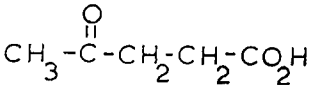

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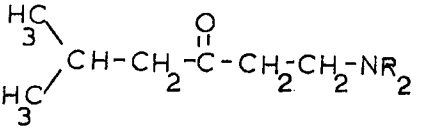

$R = CH_3$

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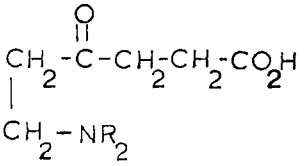

$R = CH_3$

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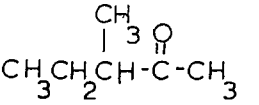
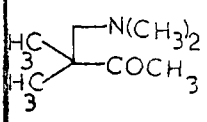
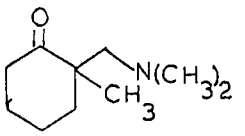
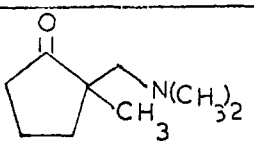
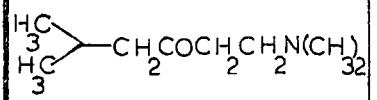
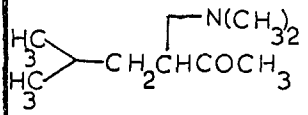
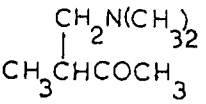
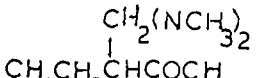
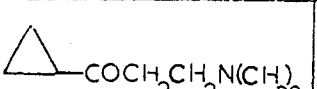
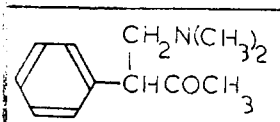


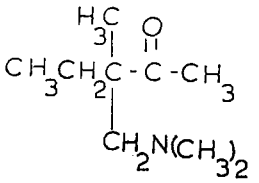
17.

The existence of both enol forms, in acid, explains the formation of an isomeric mixture in the Mannich reaction. By application of Cardwell's 'Rule', it should be possible to predict the predominant isomer produced in the Mannich reaction of an unsymmetrical ketone. However, since the chemical evidence presented in favour of (2) and (6) is now known to be misleading, we have re-investigated the structures of a number of Mannich bases using n.m.r., and Table I shows a comparison of the predominant Mannich base formed with the experimentally determined predominant direction of enolisation. Thus the Mannich bases prepared from methyl ethyl ketone, methyl n-propyl ketone, phenyl acetone, and methyl iso-amyl ketone are as predicted by theory and have been correctly formulated by Mousseron as (10) - (13). Both the bases and their picrates show 3H singlets in the range 7.72 - 7.9 τ together with other expected signals. The Mannich bases derived from iso-butyl methyl ketone and laevulinic acid (14) are (15) and (16) respectively; neither showing a 3H singlet, and the 7.7 to 7.9 τ region being blank in each case. These structures are as expected from enolisation studies,[26] if not from Cardwell's rule, and are in agreement with the literature formulations.[10,27] 3-Methylpentanone-2 (17) gave the

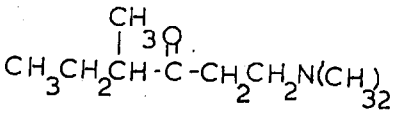
Mannich Base	Free Base (τ)		Picrate (τ)		Δτ	
	α*	α'*	α	α'	α	α'
	7·80	7·60	7·05	6·60	0·75	1·00
	7·80	7·50	7·00	6·70	0·80	0·80
	7·81	7·62	7·15	6·63	0·66	0·99
	7·88	7·75	7·01	6·80	0·87	0·95
	7·82	7·45	7·08	6·80	0·75	0·65
	7·83	7·45	7·09	6·80	0·74	0·65
	7·75	7·35	7·05	6·60	0·70	0·75
	7·75	7·50	7·04	6·80	0·71	0·70
	7·84	7·70	7·04	6·60	0·80	1·10

* $\alpha = NCH_3$, $\alpha' = NCH_2$-

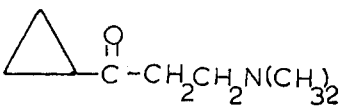
Table II



18.

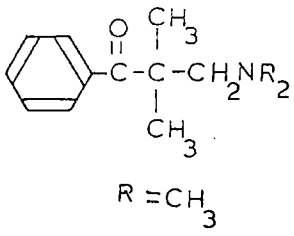


19.



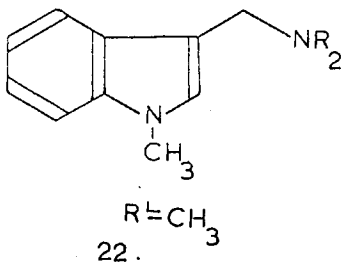
20.

Mannich base 3-dimethylaminomethyl-3-methylpentanone-2 (18) (3H singlet at 7.8 τ and 2H singlet at 7.35 τ) as would be predicted from enolisation studies[23] thus the existing structure (19) by Reichert[17] is erroneous. Cyclopropyl methyl ketone gave the Mannich base (20) (blank region at 7.7 to 7.9 τ; 2H triplet at 7.3 τ). No enolisation data is available for this ketone and, as it does not conform to enolisation theory, it can be regarded as a special case because of steric factors. The most distinguishing feature in the n.m.r. of the Mannich base, for assigning a structure, is the presence or absence of a $C\underline{H}_3CO$ signal at 7.7 to 7.9 τ, but in many cases such a signal was found to be enveloped by a stronger $N\text{-}C\underline{H}_3$ signal at 7.8 to 7.85 τ. A comparative n.m.r. study of a series of bases and their salts, in the same medium demonstrated a known[28] but little studied phenomenon. Table II shows that the formation of the picrate causes a downfield shift of 0.66 - 0.87 ppm. for the α_{CH_3} proton signal and 0.55 - 1.1 ppm. for the α_{CH_2} proton signal. Protons more remote from the nitrogen suffered smaller shifts ($\Delta\tau$ 0.1 - 0.3 ppm.), the effect becoming less marked with distance from the quarternised centre. A similar study of other salts (hydrochloride and methiodide) could not be used comparatively, with the free bases, because of their insolubility in a common organic solvent.



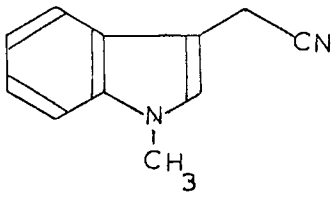
R = CH_3

21.



R = CH_3

22.



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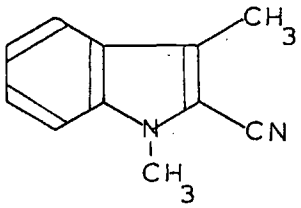

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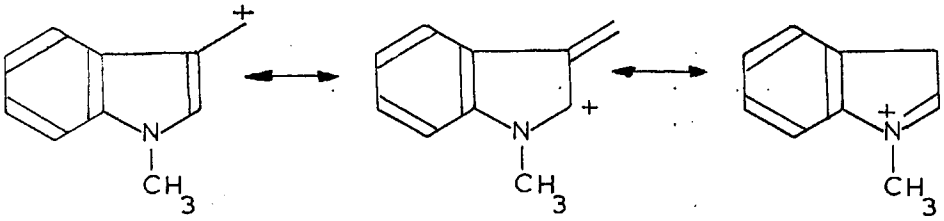

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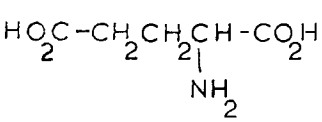
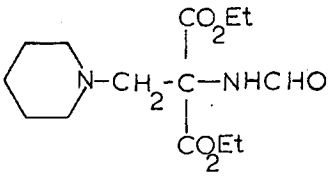


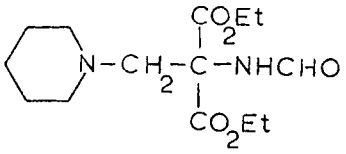
26.



27.

CHAPTER (b)

β,β-Disubstituted Mannich bases, unable to suffer amine elimination, have been observed in several instances to enter into alkylation reactions by substitution[29,30] (quaternary salt) or by transaminomethylation[31-34] (free base). Snyder and Brewster[30] found that the β-amino ketone α,α-dimethyl-β-dimethylaminopropiophenone (21) failed to react with diethyl malonate in the presence of solid sodium hydroxide in boiling xylene but under acid conditions, they observed a reverse Mannich reaction with regeneration of α,α-dimethylacetophenone and proposed mechanism (A). In hot aqueous sodium hydroxide they found the corresponding quaternary salt gave benzoic acid by mechanism (B). The same workers also found that the quaternary salt of the β,β-disubstituted Mannich base N-methylgramine (22) entered into a substitution reaction with aqueous potassium cyanide giving the products (23 and (24); both arising from the intermediate carbonium ion (25). Hellman's synthesis of glutamic acid (26) involved a successful alkylation of diethyl malonate with the Mannich base piperidinomethylformamido malonic ester (27) in boiling xylene catalysed by solid sodium hydroxide. Hellman introduced the term 'transaminomethylation' for the rearrangement of this



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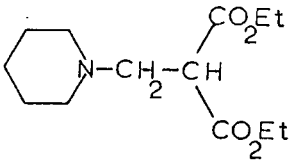

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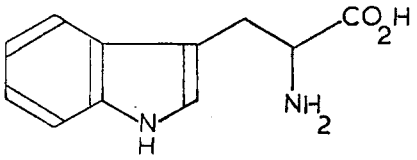

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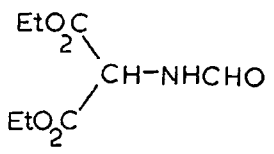

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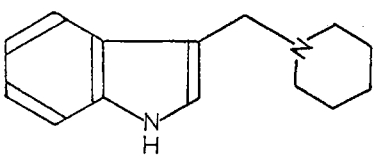

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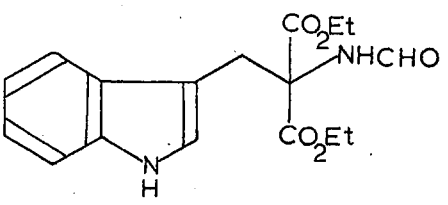

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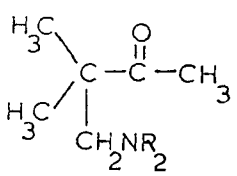
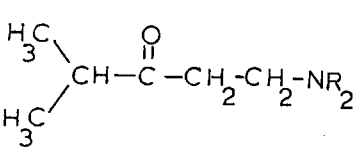


1

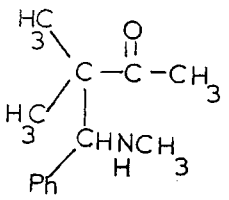
R = CH_3



2

Mannich base (27) with formation of diethylpiperidino methyl malonate (28) and diethylformamido malonate (29). Proof for such a rearrangement was provided by his synthesis of tryptophan[32] (30), where the Mannich base (27) reacted with indole with the initial formation of β-piperidino methyl indole (31) and diethylformamido malonate (29) which then reacted by amine elimination to give the substituted indole (32). Hellman found this transaminomethylation reaction to be most successful with β,β-disubstituted Mannich bases which, under alkaline conditions, gave rise to an anion stabilised by several resonance forms (mechanism C). An attempt to extend the reaction to include quaternary salts was found to give no identifiable products.

The transaminomethylation experiments of Hellman were restricted to non-ketonic Mannich bases and were always catalysed by solid sodium hydroxide at elevated temperatures. We chose to examine the possibility of an analogous rearrangement in ketonic β,β-disubstituted Mannich bases under milder conditions. Indeed we had observed that attempted distillation of 3-dimethylaminomethyl-3-methylbutanone-2 (1) gave a product which showed a new 6H doublet at 8.85 τ (~ 10%). Such a signal could arise from the isomeric base (2), formed



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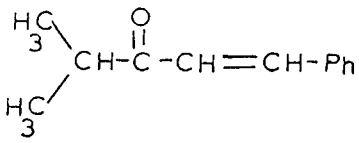

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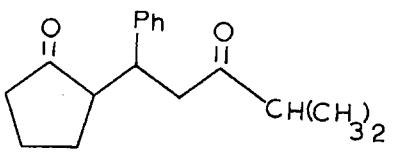

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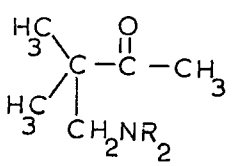
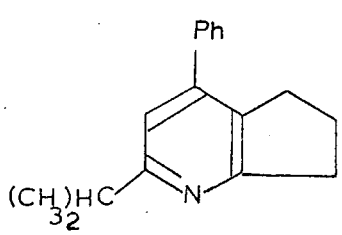


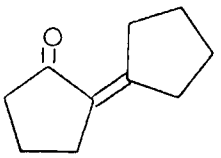
$R = CH_3$

1



36.

by a rearrangement, or from isopropyl methyl ketone, the reverse Mannich reaction product. That a rearrangement was, in fact, possible was demonstrated by thermal conversion of 4-phenyl-3,3-dimethyl-4-methylaminobutanone-2 (33) into 5-phenyl-2-methylpent-4-enone-3 (34) identified by its infra-red ($\nu_{C=O}^{CCl_4}$ 1670 cm.$^{-1}$), u.v. ($\lambda_{max.}^{EtOH}$ 289 mμ, ε 23,000; lit.[53] $\lambda_{max.}^{EtOH}$ 288 mμ, ε 24,000) and by comparison of its 2,4-dinitrophenylhydrazone derivative with an authentic sample. An attempt to isolate isopropyl vinyl ketone from (1), by heat, was unsuccessful; only polymer was formed. To offset this disadvantage, the possible scope of the rearrangement was examined by employing the thermal Michael reaction in which vinyl ketones, produced from Mannich bases with labile β-hydrogens, react with active methylene components to give stable 1,5-diketones. This reaction has been more fully discussed in section I. 4-Phenyl-3,3-dimethyl-4-methylaminobutanone-2 (33) reacted with cyclopentanone giving 2-(1'-phenyl-4'-methyl-3'-oxopentyl)cyclopentanone (35) in 30% yield. The infra-red showed carbonyl absorption at 1735cm.$^{-1}$ (cyclopentanone) and 1712 cm.$^{-1}$ (chain ketone). This 1,5-diketone was further characterised as its pyrindine derivative (36). The picrate was isolated as yellow needles analysing



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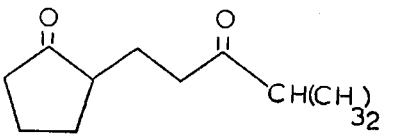

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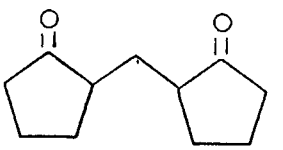

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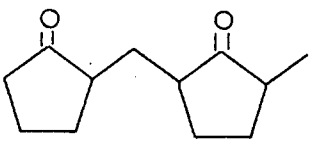

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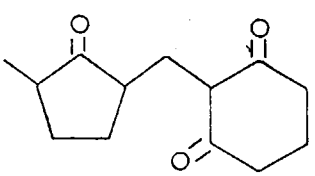

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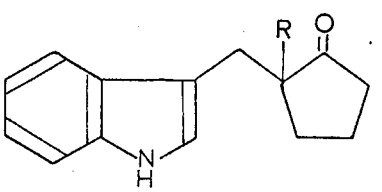
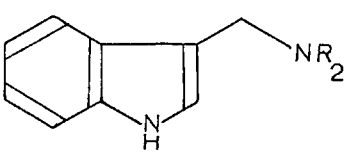


R = CO_2Et

42.

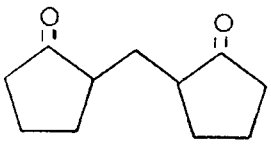


R = CH_3

43.

for $C_{23}H_{22}N_2O_7$ i.e. 2-isopropyl-4-phenyl-6,7-dihydro-5H-pyrindine picrate. The n.m.r. showed a 6H doublet at 8.85 τ (isopropyl methyl protons); a 5H singlet at 2.2 τ (aromatic protons) and a 1H doublet at 2.4 τ (aromatic proton at C_3 on pyrindine ring).

Treatment of the Mannich base of isopropyl methyl ketone with cyclopentanone under reflux gave three producfs (g.l.c. on 1% P.E.G.A. at 135°) which were separated by chromatography on fine silica. The non-polar material (∼ 6%) was identified as cyclopentylidene cyclopentanone (37) by its i.r. ($\nu_{C=O}^{CCl_4}$ 1690 cm.$^{-1}$); u.v. ($\lambda_{max.}^{EtOH}$ 258 mμ, ε 28,000, mass spectrum (m/e 150) and by comparison of its 2,4-dinitrophenyl-hydrazone derivative with an authentic sample.[36] The major component was isolated as a colourless oil analysing for $C_{11}H_{18}O_2$ and shown to be 2-(4'-methyl-3'-oxopentyl)cyclopentanone (38) by its n.m.r. (6H doublet at 8.9 τ), its infra-red ($\nu_{C=O}^{CCl_4}$ 1714 cm.$^{-1}$ and 1738 cm.$^{-1}$) and by the parent ion in the mass spectrum (m/e 182). The polar component was isolated as a white solid (∼5%) and identified as bis-cyclopentanonyl-methane (39) by comparison with an authentic sample (R_t = 34.5 min. on 10% A.P.L. at 150° and 16.5 min. on 1% P.E.G.A. at 135°). The isolation of cyclopentylidene cyclopentanone (37)



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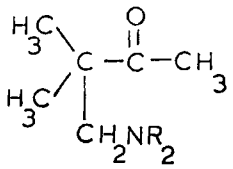

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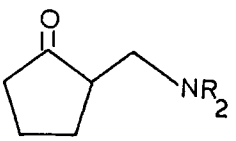

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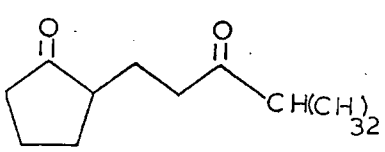

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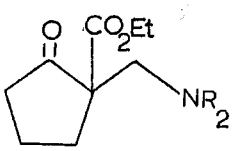
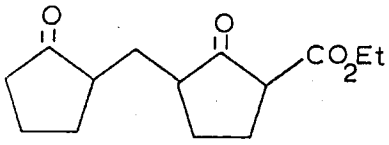


44.

can be interpreted as a self-condensation product of cyclopentanone, catalysed by dimethylamine, and not related to any rearrangement process. The second minor component, bis-cyclopentanonyl methane (39), is an important consequence of a rearrangement of the β,β-disubstituted Mannich base (1) with formation of 2-dimethylaminomethylcyclopentanone (47) which then undergoes a thermal Michael condensation with cyclopentanone giving (39). Such a sequence could only arise if an inter-molecular rearrangement intervened, whereas the formation of the major product 2-(4'-methyl-3'-oxopentyl)cyclopentanone (38) could be interpreted in terms of either an inter- or an intra-molecular rearrangement.

To distinguish between intra- and intermolecular mechanisms, cyclopentanone was alkylated with 2-carbethoxy-2-dimethylamino methyl cyclopentanone (44). The product was isolated as a colourless oil analysing for $C_{14}H_{20}O_4$ (i.e. bis-cyclopentanonyl methane carbethoxylated at either C_2 or C_5). The infra-red showed bands at 1733 $cm.^{-1}$ (ester) and 1738 $cm.^{-1}$ (cyclopentanone) but the ultra-violet spectrum showed bands characteristic of an enolisable β-keto ester system ($\lambda_{max.}^{EtOH}$ 219 mμ, ε 12,000; with a bathochromic shift in alkali). Although the u.v. suggests the product of



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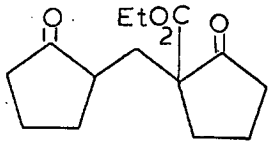

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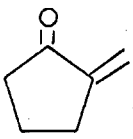

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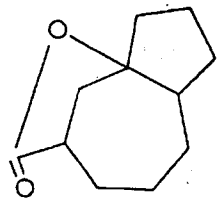


49.

rearrangement to be 5-carbethoxy-2-(2'-oxocyclopentylmethyl)-cyclopentanone (45), the diketone failed to give a C-benzoate,[38] an O-benzoate[39] or to form a pyrindine,[35] i.e. more characteristic of the isomer (46). Authentic 2-carbethoxy-2-(2'-oxocyclopentylmethyl)cyclopentanone (46) was prepared by a base catalysed Michael condensation[40] of 2-methylene cyclopentanone with 2-carbethoxy cyclopentanone, and compared with the product of rearrangement. The retention times on three g.l.c. columns were found to be identical (R_t = 5.5 min. on 5% Q.F.1 at 225°; 14.25 min. on 10% P.E.G.A. at 175° and 13.12 min. on 10% A.P.L. at 175°). To explain the anomolous u.v. results the diketone was treated with alkali under the conditions used in the u.v. determination — i.e. standing for 3 minutes in cold ethanolic sodium hydroxide — and the acidic and enolic products isolated. The acidic material was decarboxylated to bis-cyclopentanonyl methane (g.l.c. comparison). The enol was shown (i.r., u.v. and g.l.c.) to be 2-carbethoxycyclopentanone (R_t = 2.25 min. on 5% Q.F.1 at 225°; 2.75 min. on 10% P.E.G.A. at 175° and 8.01 min. on 10% A.P.L. at 175°). Thus the rearrangement product (46) undergoes rapid hydrolysis and cleavage to an enolisable β-keto ester. This experiment accounts for the anomolous u.v. data. The formation of 2-carbethoxy-2-(2'-

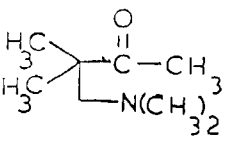
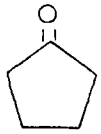
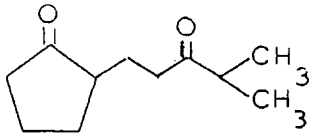
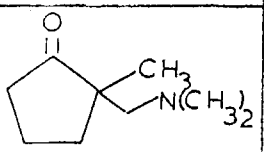
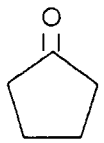
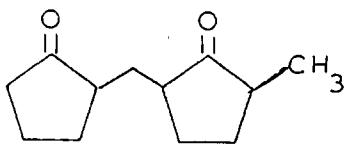
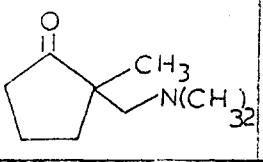
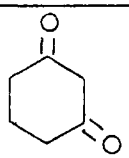
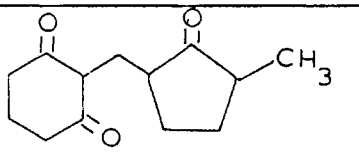
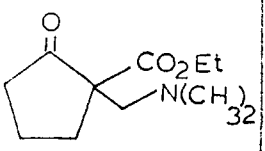
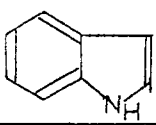
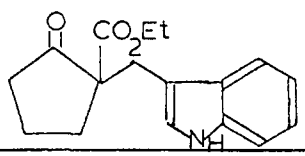
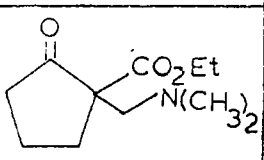
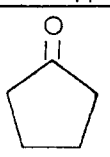
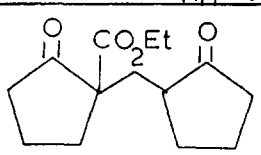
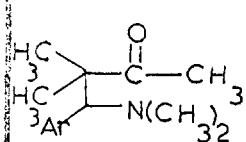
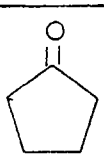
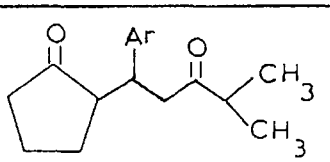
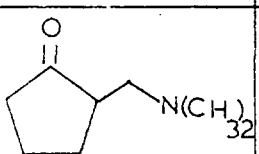
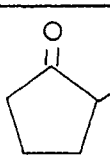
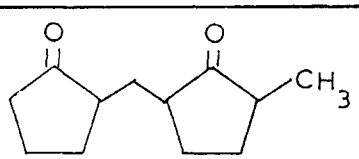
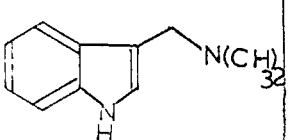
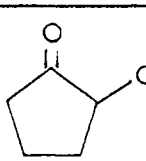
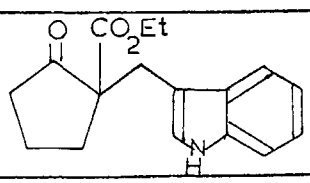
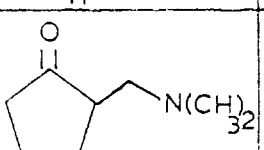
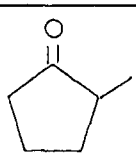
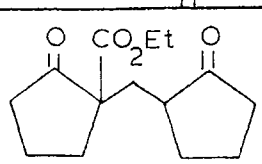
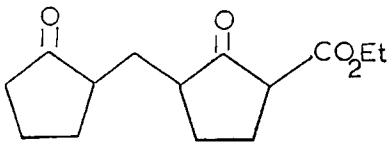
Mannich Base	Substrate	Product	Yield
			53%
			40%
			55%
			65%
			48%
			25%
			50%
			70%
			45%

Table III



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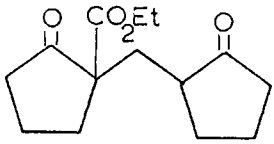

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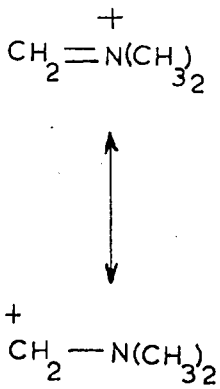

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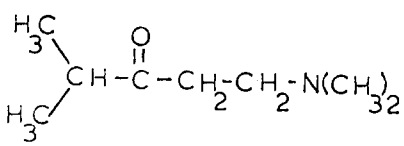

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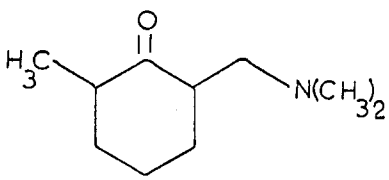
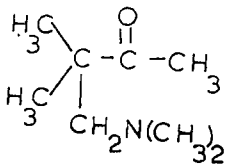


6

oxocyclopentylmethyl)cyclopentanone (46) can be interpreted as unequivocal evidence for intermolecular rearrangement; had intramolecular rearrangement occurred, the product would have been 5-carbethoxy-2-(2'-oxocyclopentylmethyl)cyclopentanone (45).

A possible mechanistic scheme (D) for the rearrangement, based on the above findings, incorporates the imminium ion (50) used by Cummings in his mechanisms for the Mannich reaction and by Hellman in his transaminomethylation reaction mechanism. The scope of this rearrangement has been examined by applying it, under the above conditions, to a series of β,β-disubstituted Mannich bases and active methylene compounds. The results are shown in Table III together with alternative routes, where possible, to the 1,5-diketones obtained by rearrangement.

Having firmly established a rearrangement of β,β-disubstituted Mannich bases under thermal Michael conditions, the question arises — can we account for the chemical evidence presented by Mousseron[10] and by Robinson,[14] in support of structures (2) and (6), by postulating a rearrangement ? Or are their products derived solely from trace amounts of (2) and (6) present in the crude Mannich bases ? This poses the question — do quaternary methiodides of β,β-disubstituted Mannich bases rearrange under alkaline conditions ? To examine



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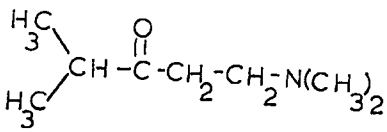

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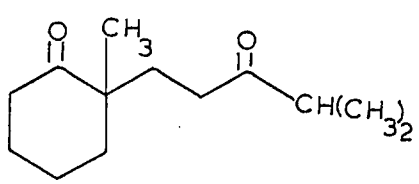


3

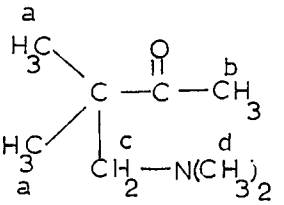
this last possibility, the crude Mannich base methiodide from isopropyl methyl ketone [i.e. (1) + (2)], was treated with the sodium salt of 2-methylcyclohexanone, in ether, under reflux.[12] This reaction gave the diketone 2-methyl-2-(4'-methyl-3'-oxopentyl)cyclohexanone (3) in 10% yield. The n.m.r. showed 6 methyl protons as a doublet at 8.94 τ and 3 methyl protons as a singlet at 8.96 τ. The reaction was repeated using the homogeneous methiodide of (1) (i.e. no 6H doublet at 8.7 τ) and in this instance no diketone corresponding to (3) could be detected by g.l.c. This resistance to alkylate, together with the findings of Hellman on quaternary salts, is sufficient to establish that a rearrangement by transamino methylation does not intervene during the reaction of a quaternary salt under Robinson-Michael conditions and hence, the findings of Robinson and Mousseron retain their validity as far as the minor component is concerned.

EXPERIMENTAL

Part II

3-Methyl-3-dimethylaminomethylbutanone-2(1)

This compound was prepared from isopropylmethyl ketone, paraformaldehyde and dimethylamine hydrochloride according to the method of Mousseron[10] and isolated in 60% yield as a colourless oil. The methiodide was recrystallised from ethanol as white plates m.p. 184-5°. The picrate was recrystallised from ethanol as yellow plates m.p. 145-7°.



1.

Free base	Picrate	Methiodide(in D_2O)
Ha 8.9 τ (6H, s.)	Ha 8,6 τ (6H, s.)	Ha 8.6 τ (6H, s.)
Hb 7,81 τ (3H, s.)	Hb 7.78 τ (3H, s.)	Hb 7.54 τ (3H, s.)
Hc 7.6 τ (2H, s.)	Hc 6.6 τ (2H, s.)	Hc 6.1 τ (2H, s.)
Hd 7.80 τ (6H, s.)	Hd 7.05 τ (6H, s.)	Hd 6.78 τ (9H, s.)

Separation of 5-dimethylamino-2-methylpentanone-3 (2) and 3-dimethylaminomethyl-3-methylbutanone-2 (1).

The isomeric mixture of bases (1) and (2) (180 mgs.) was separated by adsorption on to a preparative chromatographic plate and developed in 14% diethylamine-benzene, into a non-polar component (1) (130 mgs.) and a polar component (2) (30 mgs.). Both isomers showed N-CH_2 bands in the infra-red at 2800 $cm.^{-1}$ and 2850 $cm.^{-1}$. The picrate of the non-polar component was recrystallised from ethanol as yellow plates m.p. 145-7° and the N.M.R. showed a 6H singlet at 8.6 τ. The picrate of the polar component was recrystallised from ethanol as yellow needles m.p. 143-5° and the N.M.R. showed a 6H doublet at 8.85 τ and a 2H triplet at 6.7 τ.

2-Methyl-2(4'-methyl-3'-oxopentyl)cyclohexanone (3).

(a) 2-Methylcyclohexanone (22.4 gm., 0.2 m.) in dry ether (25 ml.) was added portionwise with stirring to a suspension of sodamide (7.8 gm. 0.2 m.) in dry ether (25 ml.). A suspension of unpurified 3-dimethylaminomethyl-3-methylbutanone-2-methiodide (57 gm., 0.2m.) in pyridine (30 ml.) was added at room temperature to this preformed sodium salt and the mixture stirred at room temperature for 12 hours and

refluxed for 1 hour. The cooled residue was flooded with water and acidified and the organic phase separated. The aqueous layer was extracted with ether and the combined ethereal extracts were washed with dilute hydrochloric acid, brine, dried ($Mg._2SO_4$) and evaporated to a yellow oil which yielded the required diketone (3) as a colourless oil (3.2 gm., 8%) on distillation b.p. 100-4°/0.6 mm. (R_t = 45.3 min. on 10% P.E.G,A. at 125°) $\nu_{C=O}^{CCl_4}$ 1712 $cm.^{-1}$. The N.M.R. showed 6 methyl protons as a doublet at 8.94 τ and 3 methyl protons as a singlet at 8.96 τ.

The bis- 2,4-dinitrophenylhydrazone was recrystallised from chloroform-ethanol as an orange powder m.p. 198-200° (lit. 200-1°).[12,41]

The bis-semicarbazone was recrystallised from methanol as white plates m.p. 210-2° (Found: C, 55.25; H, 8.53. $C_{15}H_{28}N_6O_2$ requires: C, 55.53; H, 8.70%).

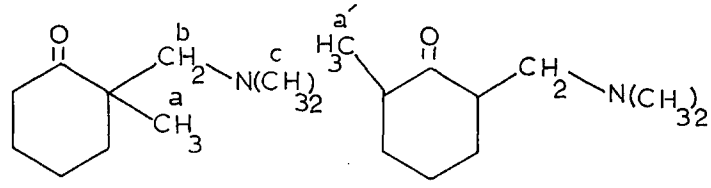
(b) The experiment was repeated using recrystallised methiodide (28 gm.), 2-methylcyclohexanone (11.2 gm.) and sodamide (3.8 gm.). The resultant gum showed no identifiable products on G.L.C. examination (10% P.E.G.A. at 125°).

2-Methyl-2(β-dimethylaminomethyl)cyclohexanone (4) and 6-methyl-2(β-dimethylaminomethyl)cyclohexanone (6).

This isomeric mixture was prepared from 2-methyl-cyclohexanone according to the method of House[16] and isolated in 50% yield as a colourless oil. $\nu^{CCl_4}_{N-CH_2}$ 2800 cm.$^{-1}$ and 2850 cm.$^{-1}$.

The methiodide was recrystallised from ethanol as white needles m.p. 198-200°.

The picrate was recrystallised from ethanol as yellow needles m.p. 124-5°.



4. 6.

Free base	Methiodide (D_2O)	Picrate
Ha 8.9 τ (singlet)	Ha 8.5 τ (3H, s.)	Ha 8.6 τ (3H, s.)
Ha' 8.95 τ (doublet)	–	–
Hb 7.5 τ (2H, s.)	Hb 6.15 τ (2H, s.)	Hb 6.7 τ (2H, s.)
Hc 7.8 τ (6H, s.)	Hc 6.75 τ (9H, s.)	Hc 7.00 τ (6H, s.)

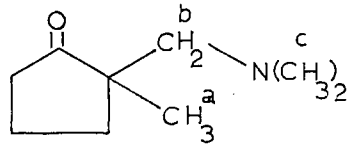
Measurement of areas under Ha (singlet) and Ha' (doublet) gave ratio of (4) and (6) as 4:1.

2-Methyl-2(β-dimethylaminomethyl)cyclopentanone (8) and 5-methyl-2(β-dimethylaminomethyl)cyclopentanone (9).

This isomeric mixture was prepared from 2-methyl-cyclopentanone according to the method of House[16] and isolated as a colourless oil in 60% yield. $\nu_{C=O}^{CCl_4}$ 1735 cm.$^{-1}$; $\nu_{N-CH_2}^{CCl_4}$ 2800 and 2850 cm.$^{-1}$.

The methiodide was recrystallised from ethanol-petroleum ether as white needles m.p. 216-8°.

The picrate was recrystallised from ethanol as yellow needles m.p. 152-4° (Found: C, 47.08; H, 5.24; N, 14.60. $C_{15}H_{20}N_4O_8$ requires: C, 46.88; H, 5.25; N, 14.58%).



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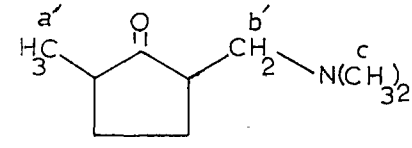


9.

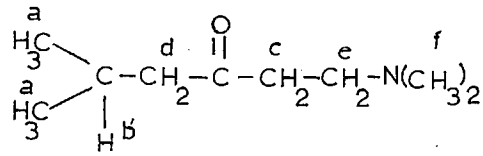
Free base	Methiodide (D_2O)	Picrate
Ha 9.08 τ (singlet)	Ha 8.70 τ (3H, s.)	Ha 8.89 τ (3H, s.)
Ha' 8.9 τ (doublet)	–	–
Hb 7.62 τ (2H, s.)	Hb 6.32 τ (2H, s.)	Hb 6.63 τ (2H, s.)
Hc 7.81 τ (6H, s.)	Hc 6.70 τ (9H, s.)	Hc 7.15 τ (6H, s.)

A measurement of the areas under the C-methyl peaks Ha (singlet) and Ha' (doublet) gave the ratio of (8) to (9) as 9:1.

1-Dimethylamino-5-methylhexanone-3 (15).

This compound was prepared from isobutylmethyl ketone according to the method of Mousseron[10] and isolated as a colourless oil in 55% yield.

The picrate was recrystallised from ethanol as yellow plates m.p. 127-9°.

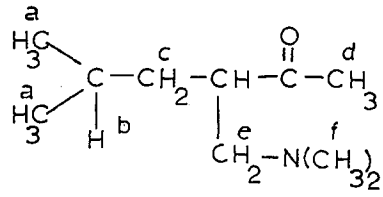


15.

Free base	Picrate
Ha 9.15 τ (6H, doublet 6 cps.)	Ha 9.1 τ (6H, doublet 6 cps.)
Hb 7.98 τ (1H, multiplet)	Hb 7.90 τ (1H, multiplet)
Hc 7.5 τ (2H, multiplet)	Hc 7.5 τ (2H, multiplet)
Hd 7.5 τ (2H, multiplet)	Hd 7.6 τ (2H, doublet)
He 7.75 τ (2H, multiplet)	He 6.8 τ (2H, multiplet)
Hf 7.88 τ (6H, singlet)	Hf 7.01 τ (6H, singlet)

3-Dimethylaminomethyl-5-methylhexanone-2 (13)

This compound was prepared from isoamylmethyl ketone according to the method of Mannich[42] and isolated in 60% yield as a colourless oil. The picrate was recrystallised from ethanol as yellow needles m.p. 127-9°.

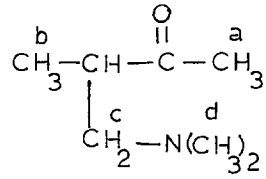


13.

Free base		Picrate	
Ha 9.1	τ (6H, doublet)	Ha 9.1	τ (6H, doublet)
Hb 8.1	τ (6H, multiplet)	Hb 8.1	τ (6H, multiplet)
Ho 8.65	τ (2H, multiplet)	Hc 8.6	τ (2H, multiplet)
Hd 7.9	τ (3H, singlet)	Hd 7.8	τ (3H, singlet)
He 7.45	τ (2H, multiplet)	He 6.8	τ (2H, multiplet)
Hf 7.82	τ (6H, singlet)	Hf 7.08	τ (6H, singlet)

3-Dimethylaminomethylbutanone-2 (10)

This compound was prepared from ethylmethyl ketone according to the method of Cardwell[42] and isolated as a colourless oil in 55% yield. The picrate was recrystallised from ethanol as yellow needles m.p. 145-7°

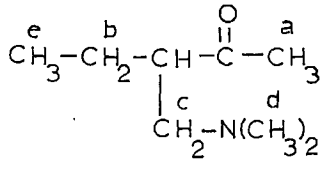


10.

Free base	Picrate
Ha 7.89 τ (3H, singlet)	Ha 7.74 τ (3H, singlet)
Hb 8.95 τ (3H, doublet)	Hb 8.72 τ (3H, doublet)
Hc 7.45 τ (2H, multiplet)	Hc 6.8 τ (2H, multiplet)
Hd 7.83 τ (6H, singlet)	Hd 7.09 τ (6H, singlet)

3-Dimethylaminomethylpentanone-2 (11).

This compound was prepared from n-propylmethyl ketone according to the method of Mannich[42] and isolated as a pale yellow oil in 70% yield. The picrate was recrystallised from ethanol as yellow plates m.p. 123-5°.

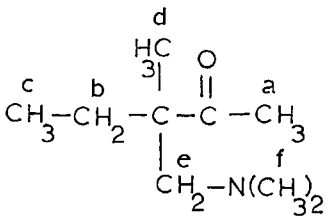


11.

Free base	Picrate
Ha 7.8 τ (3H, singlet)	Ha 7.72 τ (3H, singlet)
Hb 8.5 τ (2H, multiplet)	Hb 8.3 τ (2H, multiplet)
Hc 7.35 τ (2H, multiplet)	Hc 6.8 τ (2H, multiplet)
Hd 7.75 τ (6H, d.,1 cps.)	Hd 7.05 τ (6H, d.,1 cps.)
He 9.1 τ (3H, triplet)	He 9.1 τ (3H, triplet)

3-Dimethylaminomethyl-3-methylpentanone-2 (18)

This compound was prepared from 3-methylpentanone-2 by the method of Reichart[17] and isolated as a colourless oil in 60% yield.



18.

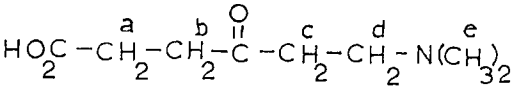
Free base

Ha 7.81 τ (3H, singlet)
Hb 8.6 τ (2H, quartet)
Hc 9.15 τ (3H, multiplet)
Hd 8.85 τ (3H, singlet)
He 7.35 τ (2H, singlet)
Hf 7.75 τ (6H, singlet)

6-Dimethylamino-4-oxo-n-caproic acid hydrochloride (16)

Levulinic acid (11.6 gm., 0.1 m.) and dimethylamine hydrochloride (8 gm., 0.1 m.) were heated together at 110° until a homogeneous solution was obtained. Paraformaldehyde (3 gm.) was added and the mixture heated at 110° for 1 hour under a reduced pressure of 14 mm. The cooled residue was poured into ethanol (10 ml.) and acetone (40 ml.) added gradually to precipitate the Mannich base hydrochloride

(12 gm., 60%) as white needles m.p. 112-20° (ethanol)



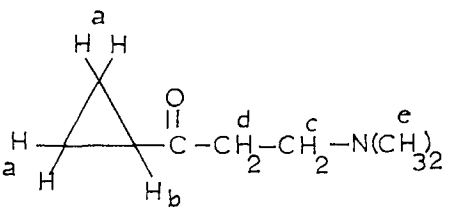
16.

Hydrochloride (in D_2O)

Ha 7.05 τ (2H, multiplet)
Hb 7.5 τ (2H, multiplet)
Hc 6.65 τ (2H, triplet)
Hd 6.45 τ (2H, triplet)
He 6.95 τ (6H, singlet)

2-Dimethylaminoethylcyclopropyl ketone (20)

This compound was prepared from cyclopropylmethyl ketone according to the method of Smith[45] and isolated as a colourless oil in 90% yield. $\nu^{CCl_4}_{N-CH_2}$ 2800 cm.$^{-1}$ and 2850 cm.$^{-1}$. The picrate was recrystallised from ethanol as yellow needles m.p. 120-2°.



20.

Free base

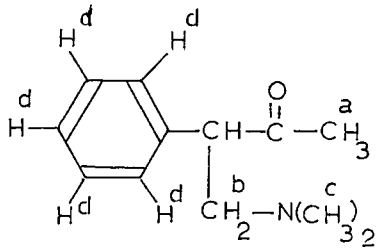
Ha 9.0 τ (4H, multiplet)
Hb 8.0 τ (1H, multiplet)
Hc 7.5 τ (2H, multiplet)
Hd 7.3 τ (2H, triplet)
He 7.75 τ (6H, singlet)

Picrate

Ha 8.95 τ (4H, multiplet)
Hb 8.0 τ (1H, multiplet)
Hc 6.8 τ (2H, multiplet)
Hd 6.65 τ (2H, triplet)
He 7.04 τ (6H, singlet)

4-Dimethylamino-3-phenylbutanone-2 (12)

This compound was prepared from phenylacetone using the method of Wilson[46] and isolated as a colourless oil in 55% yield. The picrate was recrystallised from ethanol as yellow needles m.p. 155-6°.



12.

Free base	Picrate
Ha 8.0 τ (3H, singlet)	Ha 7.91 τ (3H, singlet)
Hb 7.7 τ (2H, doublet)	Hb 6.6 τ (2H, doublet)
Hc 7.84 τ (6H, singlet)	Hc 7.04 τ (6H, singlet)
Hd 2.88 τ (5H, singlet)	Hd 2.6 τ (5H, singlet)

2-(4'-Methyl-3'-oxopentyl)cyclopentanone (38)

3-Dimethylaminomethyl-3-methylbutanone-2 (1) (5.5 gm., 0.04 m.) was treated with cyclopentanone (10 gm., 0.12 m.) under reflux with stirring for 4 hours. The cooled residue was acidified with glacial acetic acid, extracted with ether and the ethereal solution brine washed, dried and evaporated to afford a yellow oil (3.5 gm.) (after removal of excess

cyclopentanone). T.l.c. and g.l.c. analysis showed one major and two minor components [R_t = 8 min., 16.5 min (major) and 51.2 min. on 1% P.E.G.A. at 135°].

The mixture (3 gm.) was adsorbed on to fine silica and elution with ethylacetate-petroleum ether gave cyclopentylidenecyclopentanone (37) as a colourless oil (100 mgs.). $\nu_{C=O}^{CCl_4}$ 1690 cm.$^{-1}$ (α,β-unsaturated carbonyl); $\lambda_{max.}^{EtOH}$ 258 mμ ε 28,000 (predicted $\lambda_{max.}^{EtOH}$ 258 mμ). Mass spectrum showed a parent ion of m/e 150. R_t = 8.1 min. on 1% P.E.G.A. at 135°. The 2,4-dinitrophenylhydrazone was recrystallised from ethanol as red needles m.p. 227-9° (mixed m.p. 228-9°[36]).

Further elution gave 2-(4'-methyl-3-oxopentyl)cyclopentanone (38) as a colourless oil (2.2 gm.) $\nu_{C=O}^{CCl_4}$ 1714 cm.$^{-1}$ (chain ketone) and 1738 cm.$^{-1}$ (cyclopentanone). Mass spectrum showed a parent ion of m/e 182: R_t = 7.2 min. on 10% P.E.G.A. at 125°, 16.5 min. on 1% P.E.G.A. at 135° and 11.6 min. on 5% Q.F.I. at 150°. (Found: C, 72.36; H, 9.92. $C_{11}H_{18}O_2$ requires: C, 72.42; H, 9.95%). N.M.R. showed 8.9 τ (6H, doublet 6 cps.) and 7.4 τ (2H, triplet). The second minor component, bis- cyclopentanonylmethane (39), was isolated as a white solid (50 mgs.) on further elution with ethylacetate-petrol. The diketone (39) was recrystallised

from petrol as white needles m.p. 71-2° (mixed m.p. 70-72°[37]). R_t = 34.5 min. on 10% A.P.L. at 150° and 16.5 min. on 1% P.E.G.A. at 135°. $\nu_{C=O}^{CCl_4}$ 1740 cm.$^{-1}$ (cyclopentanone).

5-Methyl-2(2'-oxocyclopentylmethyl)cyclopentanone (40)

2-Methyl-2-dimethylaminomethylcyclopentanone (8) (9.9 gm., 0.07 m.) was dissolved in cyclopentanone (17.64 gm., 0.21 m.) and the mixture refluxed with stirring for 3 hours. Standard work up procedure gave the required diketone (40) as a colourless oil (2.5 gm., 40%) on distillation b.p. 105-8°/ 0.5 mm. R_t = 12.05 min. on 10% A.P.L. at 135°. (Found: C, 73.98; H, 8.98. $C_{12}H_{18}O_2$ requires: C, 74.19; H, 9.34%). $\nu_{C=O}^{CCl_4}$ 1742 cm.$^{-1}$ (cyclopentanone). N.M.R. 8.95 τ (2 overlapping doublets J = 6 cps.).

2-(3'-Methyl-2'-oxocyclopentylmethyl)cyclohexan-1,3-dione (41)

Cyclohexane-1,3-dione (11 gm., 0.1 m.) was dissolved in 2-methyl-2-dimethylaminomethylcyclopentanone (4.65 gm., 0.04 m.) (8) and the mixture refluxed with stirring for 6 hours. Standard work up procedure gave the required 1,5-diketone (41) as white solid (5 gm., 55%) on distillation. b.p. 140-5°/0.1 mm. m.p. 115-6° (petrol). (Found: C, 70.58; H, 7.70. $C_{13}H_{18}O_3$ requires: C, 70.24; H, 8.10%).

The mass spectrum showed a parent ion at 208 m/e. $\nu_{C=O}^{CCl_4}$ 1738 cm.$^{-1}$ (cyclopentanone) and 1710 cm.$^{-1}$ (dione). U.V. showed $\lambda_{max.}^{EtOH}$ 263 mμ ε 22,000 with bathochromic shift to $\lambda_{max.}^{EtOH}$ 291 in alkali. N.M.R. showed 8.85 τ (3H, doublet).

2-Carbethoxy-2-dimethylaminomethylcyclopentanone (44)

This compound was prepared from 2-carbethoxycyclopentanone[50] according to the method of Mannich[48] and isolated as a colourless oil in 50% yield. N.M.R. showed 6.5 τ (2H, quartet); 7.8 τ (6H, singlet) and 8.8 τ (3H, triplet).

2-(β-Indolemethyl)-2-carbethoxycyclopentanone (42)

(a) From 2-carbethoxy-2-dimethylaminomethylcyclopentanone (44)

The Mannich base (44) (2.13 gm., 0.01 m.) and indole (3.51 gm., 0.03 m.) were heated at 130° with stirring for 2 hours. Work up as before gave the required ketone (42) as a white solid (2 gm. 65%) on distillation b.p. 220-5°/0.8 mm., m.p. 74-5° (aq. ethanol). $\nu_{C=O}^{CCl_4}$ 1720 cm.$^{-1}$ (ester) and 1742 cm.$^{-1}$ (cyclopentanone). U.V. : $\lambda_{max.}^{EtOH}$ 283 mμ ε 6,000; $\lambda_{max.}^{EtOH}$ 291 mμ ε 5,000 and $\lambda_{max.}^{EtOH}$ 225 mμ ε 18,000. N.M.R. showed 2.91 τ (4H, multiplet); 3 τ (1H, multiplet; 5.8 τ (2H, quartet); 6.5 τ (2H, singlet) and 8.8 τ (3H, triplet).

(Found: C, 71.25; H, 6.91; N, 4.90. $C_{17}H_{19}NO_3$ requires C, 71.56; H, 6.71; N, 4.91%).

(b) From β-(dimethylaminomethyl)indole[49] (43)

The Mannich base (3.4 gm., 0.02 m.) was dissolved in carbethoxycyclopentanone (9.36 gm., 0.06 m.) and the mixture refluxed with stirring for 2 hours. Work up as before gave the required ketone (42) as a white solid (4gm., 70%) b.p. 220-5°/0.8 mm. m.p. 74-5° (mixed m.p. 74-5°). $\nu_{C=O}^{CCl_4}$ 1720 and 1742 cm.$^{-1}$.

2-Carbethoxy-2-(2'-oxocyclopentylmethyl)cyclopentanone (46)

(a) From 2-carbethoxy-2-dimethylaminomethylcyclopentanone (44)

The Mannich base (44) (2.13 gm., 0.01m.) was dissolved in cyclopentanone (2.52 gm., 0.03 m.) and the mixture refluxed with stirring for 2 hours. Work up as before gave the desired diketone (46) as a colourless oil (1.5 gm., 48%) b.p. 115-9°/0.1 mm. R_t = 5.5 min. on 5% Q.F.1 at 225°; 14.25 min. on 10% P.E.G.A. at 175° and 13.12 min. on 10% A.P.L. at 175°. (Found: C, 66.28; H, 7.68. $C_{14}H_{20}O_4$ requires: C, 66.65; H, 7.99%). $\nu_{C=O}^{CCl_4}$ 1733 cm.$^{-1}$ (ester) and 1740 cm.$^{-1}$ (cyclopentanone). N.M.R. showed 5.8 τ (2H, quartet);

8.75 τ (3H, triplet). The U.V. showed characteristic β-keto ester bands at $\lambda_{max.}^{EtOH}$ 219 mμ ε 12,000 with a bathochromic shift to $\lambda_{max.}^{EtOH}$ 284 mμ in alkali.

(b) From 2-dimethylaminomethylcyclopentanone (47)

The Mannich base (47) (3 gm., 0.021 m.) was dissolved in carbethoxycyclopentanone (5.3 gm.,0.063 m.) and the mixture refluxed for 90 minutes. Standard work up procedure gave the required diketone (46) as a colourless oil (2.5 gm., 45%) b.p. 155°/1 mm. R_t = 5.5 min. on 5% Q.F.1 at 225° and 14.25 min. on 10% P.E.G.A. at 175°. $\lambda_{max.}^{EtOH}$ 219 mμ, ε 9,500 with a bathochromic shift to $\lambda_{max.}^{EtOH}$ 284 mμ in alkali.

(c) From 2-methylenecyclopentanone[51] (48)

Recrystallised 2-β-dimethylaminomethylcyclopentanone-hydrochloride (5 gm.) was heated gradually under reduced pressure (12 mm.) to 200° and the required ketone (48) distilled at 60°/12 mm. (2.5 gm., 88%).

The vinyl ketone (48) (2 gm., 0.02 m.) was dissolved in 2-carbethoxycyclopentanone (9 gm., 0.06 m.) and the mixture basified with triethylamine (1.18 gm., 0.02 m.) and refluxed with stirring for 90 minutes. The cooled residue was treated with glacial acetic acid and extracted into ether.

The ethereal solution was brine washed, dried and evaporated to afford the required diketone (46) as a colourless oil (3.2 gm., 60%) on distillation b.p. 150-2°/1 mm. R_t = 5.5 min. on 5% Q.F.1. at 225° and 14.25 min. on 10% P.E.G.A. at 175°. U.V. : $\lambda_{max.}^{EtOH}$ 219 mμ ε 11,000 with a bathochromic shift to $\lambda_{max.}^{EtOH}$ 284 in alkali.

Hydrolysis of 2-carbethoxy-2-(2'-oxocyclopentylmethylcyclopentanone (46):

(a) In Acid

The diketone (46) (1 gm.) was treated with concentrated hydrochloric acid (2 ml.) in water (3 ml.) under reflux with stirring for 24 hours. The cooled residue was extracted with ether and the combined ethereal extracts washed with 4$\bar{N}$ sodium hydroxide, brine, dried and evaporated to a pale yellow oil (800 mgs.) which gave 10-hydroxybicyclo[5,3,0]decane carboxylic acid lactone (49) (Part 1, pp) as a colourless oil (750 mg.) on chromatography (silica and elution with 5% ethyl acetate-petrol) b.p. 157°/12 mm. R_t = 16.12 min. on 10% P.E.G.A. at 175° and 14.49 min. on 10% A.P.L. at 175°. $\nu_{C=O}^{CCl_4}$ 1780 cm.$^{-1}$ (lactone).

(b) Alkali

The diketone (46) (100 mgs.) was dissolved in ethanol (10 ml.), treated with 4$\bar{N}$ sodium hydroxide (5 drops) and the mixture shaken under u.v. irradiation for 5 minutes. The ethanol was evaporated and the residue diluted with water and ether extracted. The combined ethereal extracts were discarded and the aqueous solution acidified, ether extracted, and the combined ethereal extracts washed with sodium bicarbonate, brine, dried and evaporated to afford a colourless oil (20 mgs.) identified as 2-carbethoxycyclopentanone by g.l.c. retention times (2.25 min. on 5% Q.F.I at 225°; 2.75 min. on 10% P.E.G.A. at 175° and 8.01 min. on 10% A.P.L. at 175°) and by u.v. ($\lambda_{max.}^{EtOH}$ 218 mμ ε 8,300 with shifts to $\lambda_{max.}^{EtOH}$ 284 mμ in alkali).

The acidic material was isolated from the bicarbonate washings as a colourless oil (70 mgs.) which was decarboxylated, by heating at 200° for 10 minutes, to bis-cyclopentanonylmethane (39) m.p. 71-3° (mixed m.p. 71-3°[37]). R_t = 16.25 min. in 10% P.E.G.A. at 170° and 34.5 min. on 10% A.P.L. at 150°. $\nu_{C=O}^{CCl_4}$ 1742 cm.$^{-1}$ (cyclopentanone).

4-Phenyl-3,3-dimethyl-4-methylaminobutanone-2[52] (33).

An ice-cold mixture of isopropylmethyl ketone (8.6 gm., 0.1 m.) and benzaldehyde (10.6 gm., 0.1 m.) was treated dropwise with stirring with 33% ethanolic methylamine (10 ml.). The mixture was warmed to room temperature, stirred for 24 hours and then acidified with concentrated hydrochloric acid and ether extracted. The aqueous solution was basified and ether extracted and the ethereal solution brine washed, dried and evaporated to afford the required Mannich base (33) as an unstable yellow oil (2.5 gm., 20%). The i.r. showed $\nu_{N-CH_2}^{CCl_4}$ 2800-2850 cm.$^{-1}$ (3 bands) and the n.m.r. showed 7.8 τ (3H, singlet). Distillation gave 5-phenyl-2-methylpent-4-en-3-one[53] (34) as a colourless oil b.p. 100-5°/0.5 mm. $\nu_{C=O}^{CCl_4}$ 1670 cm.$^{-1}$ (α,β-unsaturated carbonyl). $\lambda_{max.}^{EtOH}$ 289 mμ ε 23,000 (calc. $\lambda_{max.}^{EtOH}$ 288 mμ).

The 2,4-dinitrophenylhydrazone was recrystallised from ethanol as red needles m.p. 157-9° (mixed m.p. 156-7°) $\lambda_{max.}^{EtOH}$ 269 mμ ε 10,000 and $\lambda_{max.}^{EtOH}$ 364 mμ ε 10,700. The semicarbazone was recrystallised from petrol as white plates m.p. 164-6° (mixed m.p. 166-7°).

5-Phenyl-2-methylpent-4-en-3-one[53] (34)

Isopropylmethyl ketone (860 mgs., 0.01 m.) and benzaldehyde (1.06 gm., 0.01 m.) were dissolved in ethanol (3 ml.) and treated with 4$\bar{N}$ sodium hydroxide (3 drops) and allowed to stand at room temperature for 3 hours. The ethanol was evaporated and the residue flooded with water and extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to give the required ketone (34) as a colourless oil (1.6 gm., 88%) b.p. 147-9°/14 mm., $\lambda_{max.}^{EtOH}$ 288 mμ ε 23,000. $\nu_{C=O}^{CCl_4}$ 1670 cm.$^{-1}$. The 2,4-dinitrophenylhydrazone was recrystallised from ethanol as red needles m.p. 154-6° ($\lambda_{max.}^{EtOH}$ 269 mμ ε 10,000 and 364 mμ ε 10,000). The semicarbazone was recrystallised from petrol as white plates m.p. 166-7°.

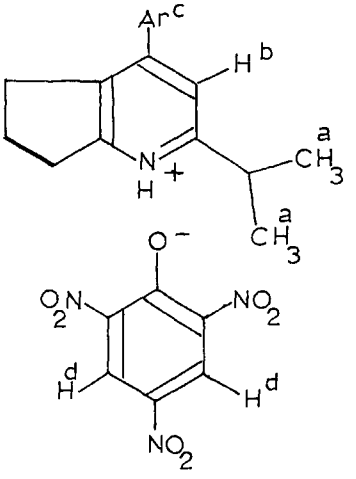
2-(1'-Phenyl-4'-methyl-3'-oxopentyl)cyclopentanone (35)

Undistilled 4-phenyl-3,3-dimethyl-4-methylaminobutanone-2 (33) (4 gm., 0.02 m.) was dissolved in cyclopentanone (5.04 gm., 0.06 m.) and the mixture refluxed for 3 hours, cooled, acidified with glacial acetic acid and extracted with ether. The ethereal solution was brine washed, dried and evaporated to give a pale yellow oil from which the required

diketone (35) was isolated as a colourless oil (1.2 gm., 25%) by distillation b.p. 130-5°/0.1 mm. $\nu_{C=O}^{CCl_4}$ 1735 cm.$^{-1}$ (cyclopentanone) and 1712 cm.$^{-1}$ (chain ketone). The diketone was further characterised as its pyridine derivative (36).

2-Isopropyl-4-phenyl-6,7-dihydro-5H-pyrindine (36)

The diketone (35) (500 mgs.) was dissolved in ethanol (5 ml.) and treated with hydroxylamine hydrochloride (500 mgs.) under reflux for 10 minutes. The warm solution was poured on to dilute sodium hydroxide and the alkaline solution extracted with ether. The combined ethereal extracts were brine washed, dried and evaporated to afford the required pyrindine derivative (36) as a colourless oil (200 mgs., 50%). The picrate was recrystallised from ethanol as yellow needles m.p. 175-6°. (Found: C, 59.65; H, 4.45; N, 12.31, $C_{23}H_{22}N_4O_7$ requires: C, 59.22; H, 4.75; N, 12.01%).



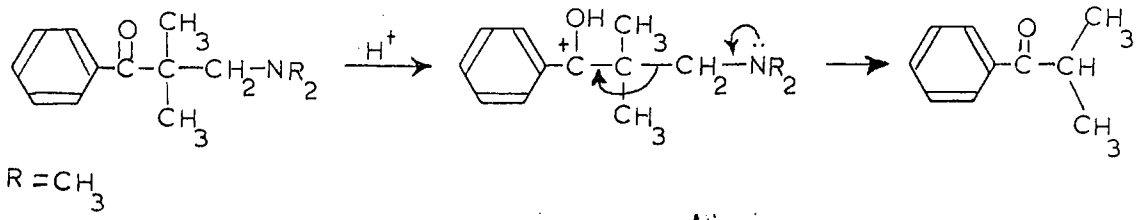
Ha 8.85 τ (6H, doublet)
Hb 2.4 τ (1H, doublet,10 cps.)
Hc 2.2 τ (5H, singlet)
Hd 0.8 τ (2H, singlet)

Effect of heat on 3-dimethylaminomethyl-3-methylbutanone-2 (1)

(a) The Mannich base (1) (1 gm.) was heated to 120° for 1 hour with stirring and the residue treated with ethanolic picric acid. The n.m.r. of the uncrystallised picrate showed 8.6 τ (6H, singlet).

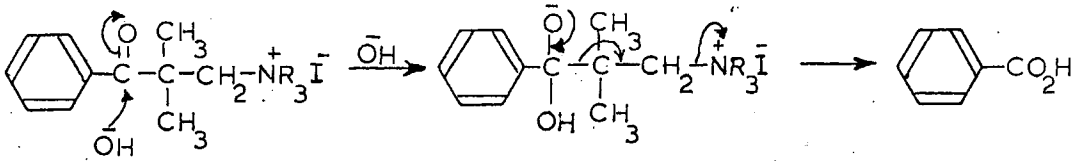
(b) The Mannich base (1) (1 gm.) was dissolved in ethanol (5 ml.) and the mixture heated under reflux with stirring for 1 hour and the cooled residue treated with ethanolic picric acid. The n.m.r. of the uncrystallised picrate showed 8.6 τ (singlet) [~ 90%] and 8.85 τ (doublet) [~ 10%].

(c) Steam distillation and heating (180°)of the recrystallised Mannich base (1) hydrochloride gave no identifiable products.



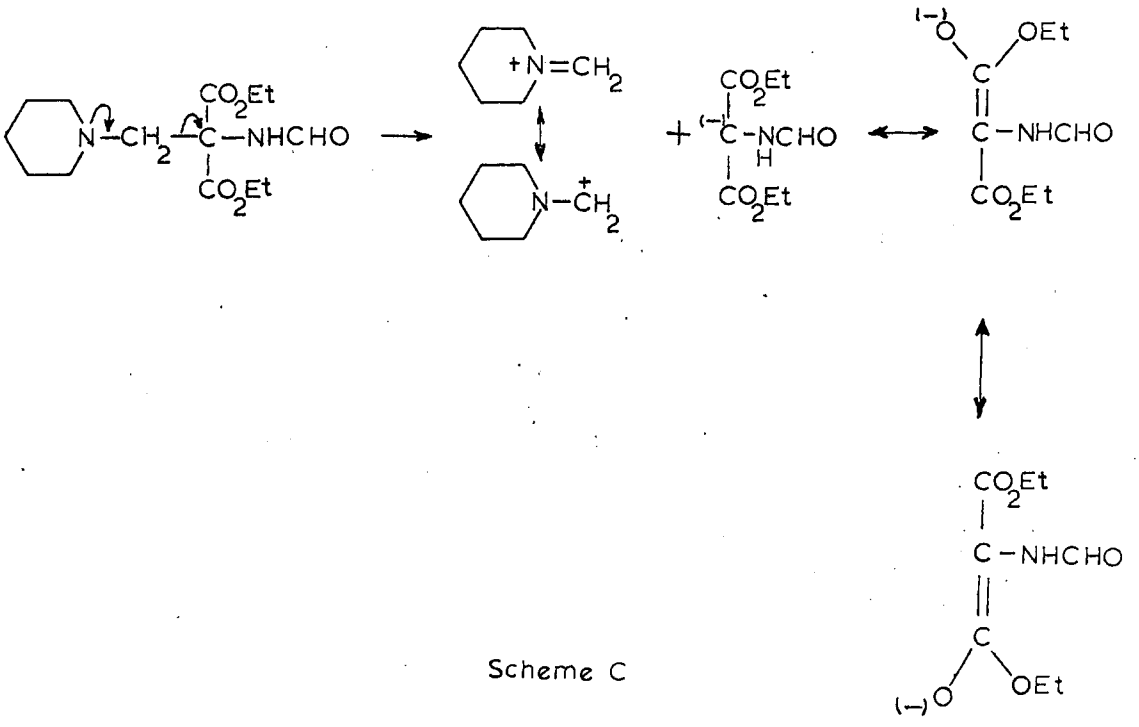
R = CH_3

Scheme A

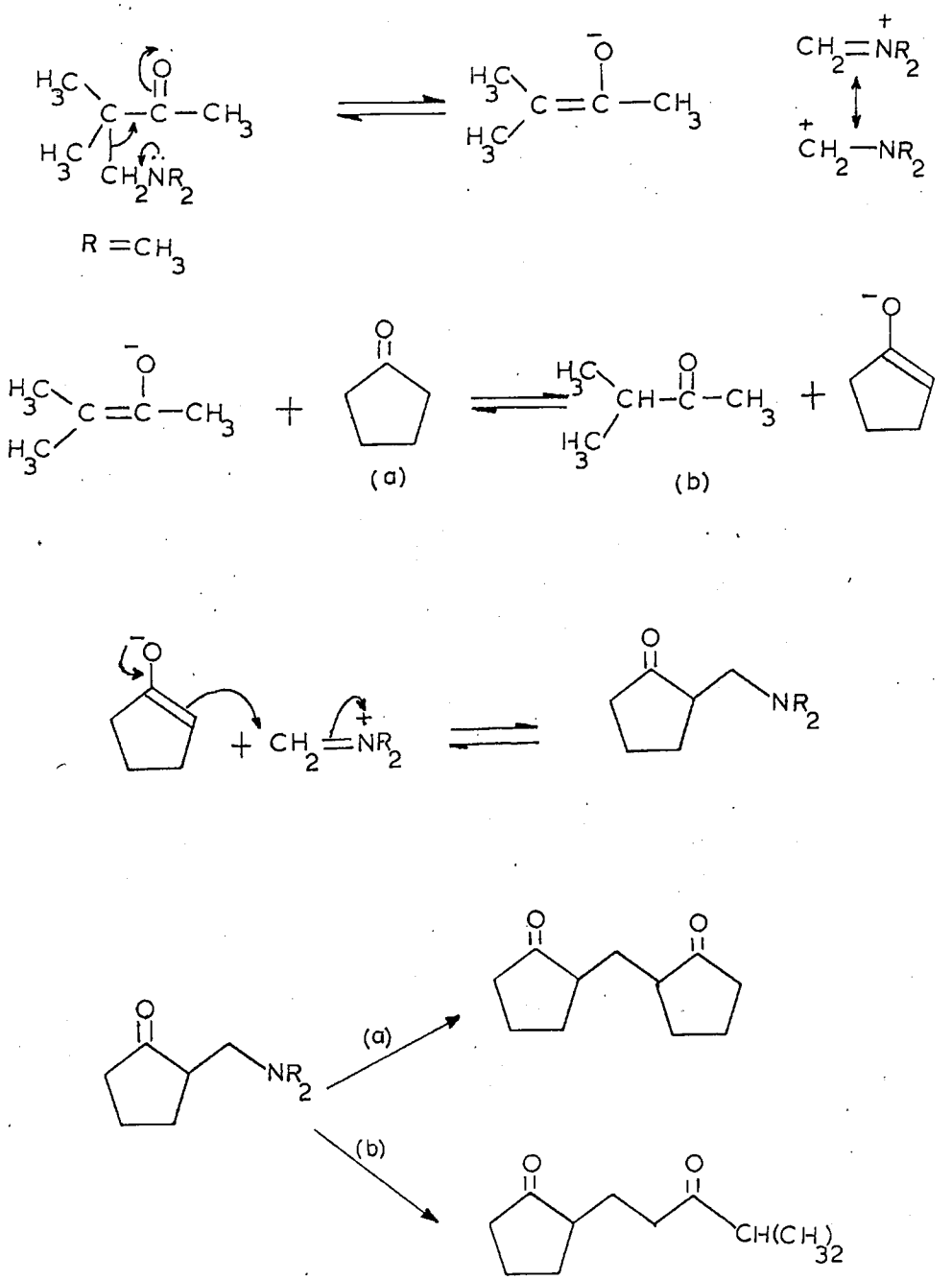


R = CH_3

Scheme B



Scheme C



Scheme D

REFERENCES

1. Blicke, Organic Reactions, 1, 302.
2. Reichert, Die Mannich Reaktion.
3. Marle and Tollens, Ber., 1903, 36, 1351.
   Shafer and Tollens,Ber., 1906, 39, 2181.
4. Petrenko and Zonef,Ber., 1906, 39, 1358; 1909, 42, 3683.
5. Mannich, Arch. Pharm., 1912, 250, 647.
6. Boddendorg, Arch. Pharm., 1933, 271, 101.
7. Liebermann and Wagner, J. Org. Chem., 1949, 14, 1001.
8. Alexander and Underhill, J. Amer.Chem.Soc., 1949, 71, 4014.
9. Cummings and Shelton, J. Org. Chem., 1960, 25, 419.
10. Boyer, Jacquier and Mousseron, Bull.Soc.Chim.Fr., 1956, 1653.
11. Brown and Johnson, J. Org. Chem., 1962, 27, 4706.
12. Haynes and Timmons, J. Chem. Soc., 1966, 224.
13. Downes, Gill and Lions, J. Amer. Chem. Soc., 1950, 72,3464.
14. Du Feu, McQuillin and Robinson, J.Chem.Soc., 1937, 53.
15. Frank and Pierle, J. Amer. Chem. Soc., 1951, 73, 724.
16. House and Trost, J. Org. Chem., 1964, 29, 1339.
17. Reichert and Partenheimer, Arch. Pharm., 1960, 293, 685.
18. Abdullah, J. Ind. Chem. Soc., 1935, 12, 62.
19. Shunk and Wilds, J. Amer. Chem. Soc., 1943, 65, 469.

20. Downes, Aust., J. Sci., 1948, 10, 147.

21. Christie, Novello and Sprague, J.Amer.Chem.Soc., 1953, 75, 1331.

22. Gill, James, Lions and Potts, J. Amer. Chem. Soc., 1952, 74, 4923.

23. Cardwell and Kilner, J. Chem. Soc., 1951, 2430.

24. Frostick, Hauser and Mann, J. Amer. Chem. Soc., 1952, 74, 3228.

25. Borrel and Cornubert, Bull.Soc. Chim..Fr., 1925, 43, 804.

26. Hagemeyer and Hull, Ind. Eng. Chem., 1949, 41, 2920.

27. Mannich and Bauroth, Ber., 1924, 57, 1108.

28. Jackman, Applications of N.M.R. to Org. Chem., P.56.

29. Snyder and Brewster, J.Amer.Chem.Soc., 1949, 71, 1061.

30. Snyder and Elliel, J.Amer.Chem.Soc., 1948, 70, 1857.

31. Hellman, Angew. Chim., 1953, 65, 473.

32. Hellman, Angew, Chim., 1949, 61, 352.

33. Hellman and Renz, Ber., 1951, 84, 901.

34. Hellman et al., Ber., 1953, 86, 1346.

35. Stobbe, J. Prakt. Chim., 1912, 86, 209.

36. Wallach, Ber., 1896, 29, 2955.

37. Nunn and Rapson, J. Chem. Soc., 1949, 825.

38. Wright and McEwan, J. Amer. Chem. Soc., 1954, 76, 4540.

39. McElvain and Kundiger, J. Amer. Chem. Soc., 1942,64,254.

40. Ross and Levine, J. Org. Chem., 1964, 29, 2341.

41. Baisted, J. Chem. Soc., 1956, 2340.

42. Mannich, Arch. Pharm., 1927, 265, 589.

43. Cardwell, J. Chem. Soc., 1950, 1056.

44. Newman and Boothe, J.Amer.Chem.Soc., 1945, 67, 154.

45. Smith and Rogier, J.Amer.Chem.Soc., 1951, 73, 3840.

46. Wilson and Kyi, J. Chem. Soc., 1952, 1321.

48. Mannich, Arch. Pharm., 1942, 280, 361.

49. Snyder et. al., J.Amer.Chem.Soc., 1944, 66, 200.

50. Nicole, J. Canad. Chem. Soc., 1962, 40, 353.

51. Gault and Skoda, Bull.Soc.Chim.Fr., 1946, 13, 308.

52. Noller and Baliah, J.Amer.Chem.Soc., 1948, 70, 3853.

53. Lapworth and Hann, J.Chem.Soc., 1902, 81, 1485.