Studies on the Synthesis of Monoterpene

Alkaloids and Related Compounds

by

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Summary

The chemistry of monoterpene alkaloids is reviewed, and a brief
review of the chemistry of 9-azasteroids is given. The attempted
synthesis of an alkaloid thought to be 6,7-dihydro-7-methyl-5H-2-
-pyrindine is described. Several methods for the construction of a
perhydropyrindine system have been investigated. A synthesis of
2-benzyl-1,2,3,4,7,7a-hexahydro-4-methyl-6H-2-pyrindin-6-one is
described, together with a new synthesis of 1-benzoyl-3-carboethoxy-4-
-piperidone.

Acknowledgements

Contents

All the work reported in this thesis
was carried out by the Author under
the supervision of Dr. G. Jones.

Contents

Nomenclature

Wherever possible, compounds are named according to "Handbook for Chemical Authors", 1961, or "Chemical Abstracts". For the sake of clarity, Arabic numerals have been used in the numbering of compounds.

Introduction

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which was shown to have the structure (1).

Nomenclature

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(1)   (2)   (3)

Since 1959 however, a new class of alkaloids having the cyclopentanoid
monoterpene skeleton (2) have been discovered. These alkaloids can be
considered as derivatives of 5H-2-pyrindine (3).

The structural unit (2) was first discovered in the
nepetalactones (4) and (5) extracted from oil of catnip, a constituent
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cis-trans nepetalactone (4)   trans-cis nepetalactone (5)

In the designation of configuration, the relationship of the
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THE CHEMISTRY OF MONOTERPENE ALKALOIDS

The first monoterpene alkaloid to be discovered was chaksine, which was shown to have the structure (1).[1]
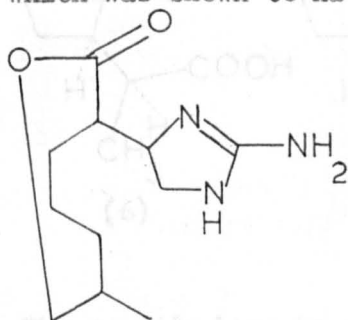
(1)   (2)   (3)
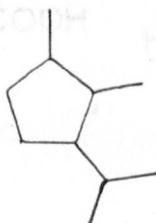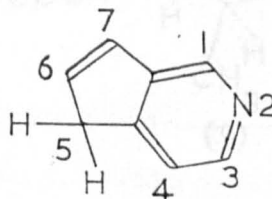
Since 1959 however, a new class of alkaloids having the cyclopentanoid monoterpene skeleton (2) have been discovered.[2] These alkaloids can be considered as derivatives of 5H-2-pyrindine (3).

The structural unit (2) was first discovered in the nepetalactones (4) and (5) extracted from oil of catnip, a constituent of the plant Nepeta cataria.[3]
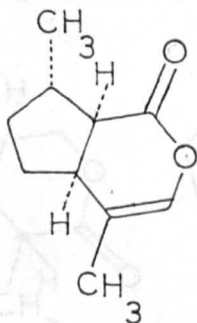
cis-trans nepetalactone (4)   trans-cis nepetalactone (5)
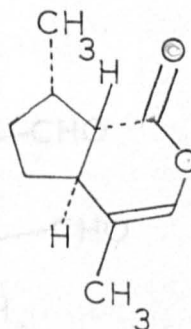
In the designation of configuration, the relationship of the substituents at the ring junction is given first, and that between

the methyl group on the cyclopentane ring and the adjacent ring

structure is given second. The nepetalactones have been converted into

four nepetalinic acids (6) – (9).

(6)　　　　　(7)　　　　　(8)　　　　　(9)
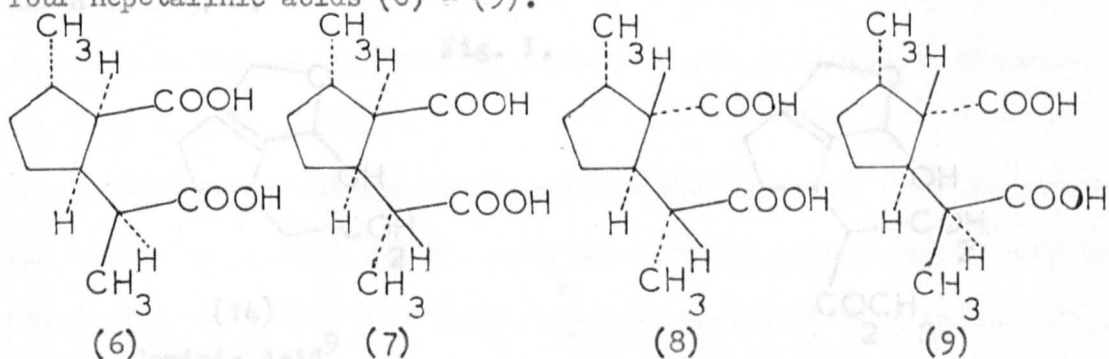
These acids have been used extensively, as reference compounds, in the

correlation of the structure and stereochemistry of the cyclopentanoid

monoterpene alkaloids and other related compounds. The acids (6) and

(7) are present in oil of catnip.

Another class of compounds possessing the cyclopentanoid

monoterpene structure are the ant lactones and related natural products.

Compounds (10) – (13) have been extracted from the glands of Argentinian

and Australian ants.

(10)	(11)	(12)	(13)
Iridomyrmecin	Isoiridomyrmecin	Iridodial	Dolichodial
Ref. 2,4	Ref. 2,4a,5	Ref. 2,6	Ref. 2,6,7
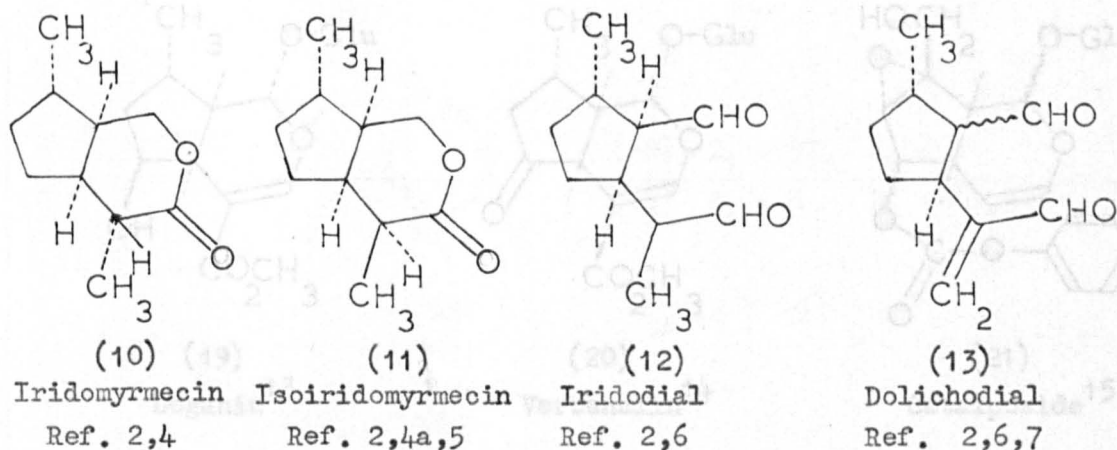
Finally, the cyclopentanoid monoterpene structure is apparent in several plant glycosides and related products. Some of these are shown in Fig. I.[8]

Fig. I.

(14)
Genipic Acid[9]

(15)
Genipinic Acid[9]

(16)
Genepin[10]

(17)
Aucubin[11]

(18)
Asperuloside[12]

(19)
Loganin[13]

(20)
Verbenalin[14]

(21)
Catalposide[15]
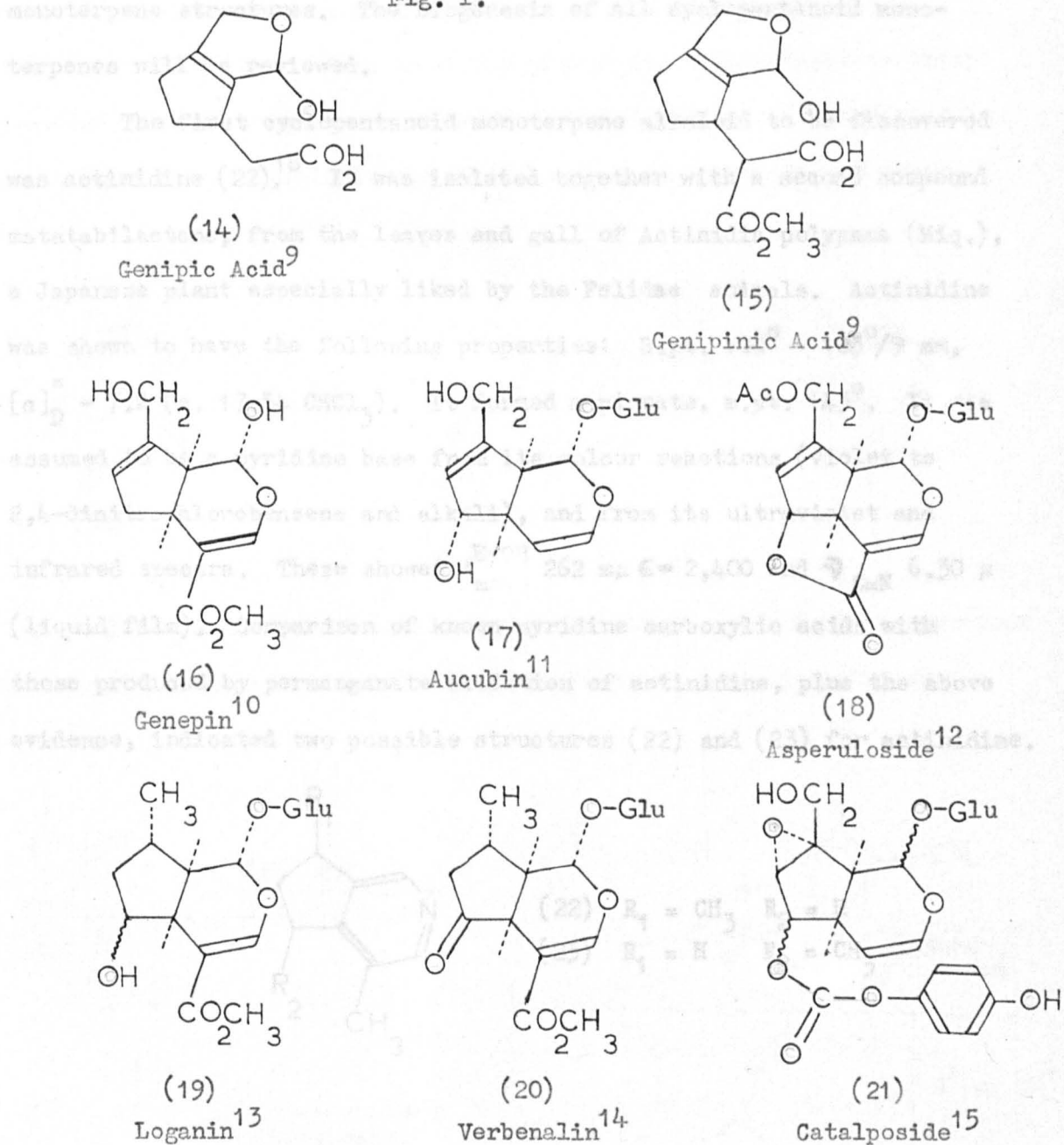
While it is intended to review only the chemistry of the cyclopentanoid monoterpene alkaloids, reference will be made wherever possible to the connections between the alkaloids and other cyclopentanoid monoterpene structures. The biogenesis of all cyclopentanoid monoterpenes will be reviewed.

The first cyclopentanoid monoterpene alkaloid to be discovered was actinidine (22).[16] It was isolated together with a second compound matatabilactone, from the leaves and gall of Actinidia polygama (Miq.), a Japanese plant especially liked by the Felidae animals. Actinidine was shown to have the following properties: B.pt. 100° - 103°/9 mm, $[a]_D''$ - 7.2 (c. 17.54 $CHCl_3$). It formed a picrate, m.pt. 143°. It was assumed to be a pyridine base from its colour reactions (violet to 2,4-dinitrochlorobenzene and alkali), and from its ultraviolet and infrared spectra. These showed λ_{max}^{EtOH} 262 mμ ϵ = 2,400 and $\bar\nu_{C=N}$ 6.30 μ (liquid film). Comparison of known pyridine carboxylic acids with those produced by permanganate oxidation of actinidine, plus the above evidence, indicated two possible structures (22) and (23) for actinidine.

(22) R_1 = CH_3 R_2 = H
(23) R_1 = H R_2 = CH_3

- 4 -
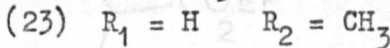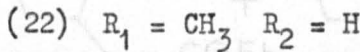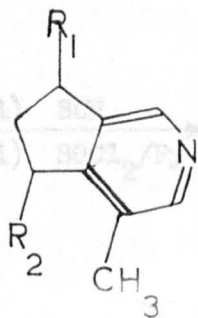
The similarity of structure (22) to the nepetalactone skeleton implies that it is the most likely one for actinidine. This theory was supported by the discovery that matatabilactone, the compound isolated with actinidine, was shown to be a mixture of iridomyrmecin (10) and isoiridomyrmecin (11). Both these structures for matatabilactone imply that (22) is the most likely structure for actinidine. To confirm this, actinidine was synthesised from nepetalinic acid imide (24) as shown below.
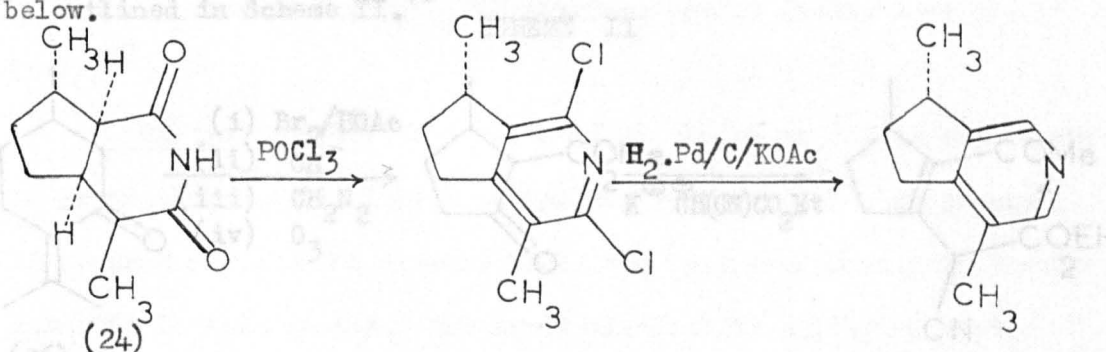
The product was identical with natural actinidine. Two further syntheses of actinidine have been published. The first of these is outlined in Scheme I.[17]

SCHEME I
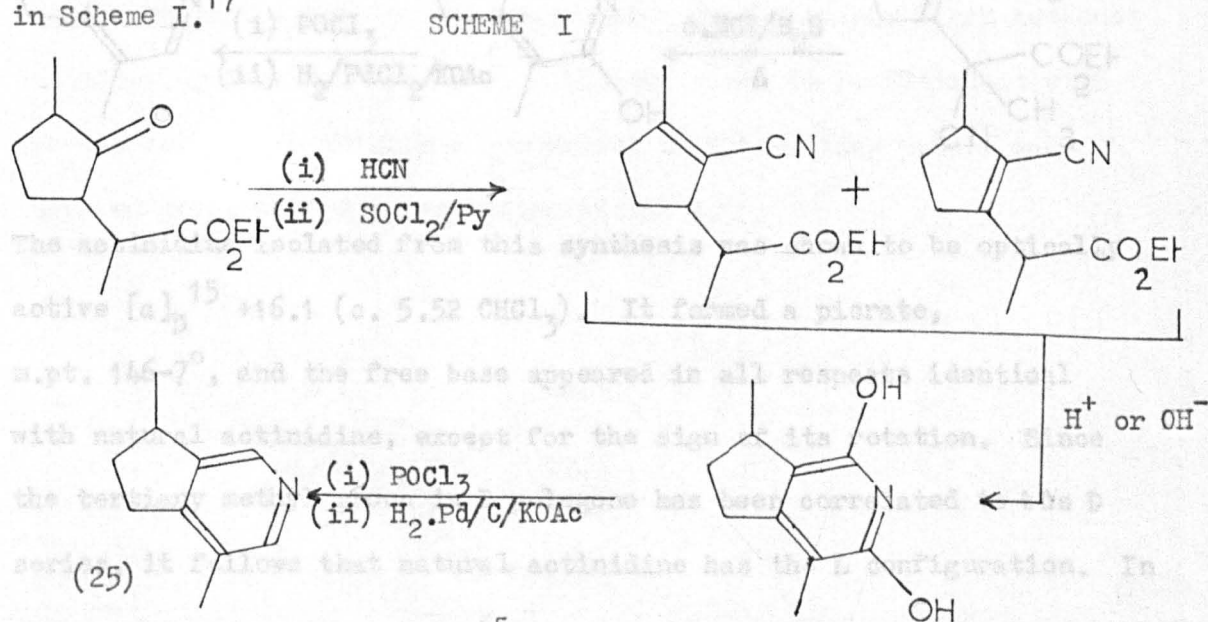
The picrate of D,L-actinidine (25) did not depress the melting point
of natural actinidine picrate. The D,L actinidine was resolved through
its mono salt of dibenzoyl tartaric acid. The less soluble salt in
ethanol yielded, on regeneration of the base, a laevorotatory oil
$[a]_D^{21}$ -8.01 (c. 2.17 CHCl$_3$). The picrate, m.pt. 146 - 7°, did not
depress the melting point of natural actinidine picrate. The second
synthesis started with an optically active compound, D pulegone, (26) and
is outlined in Scheme II.[18]

SCHEME II

(26)
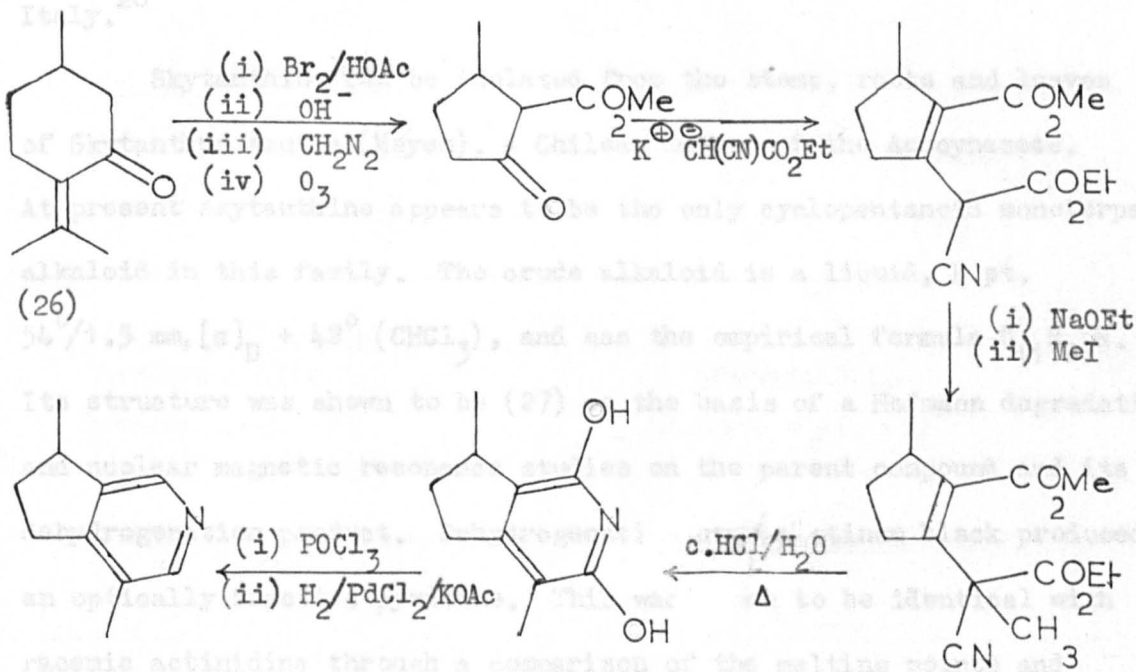
The actinidine isolated from this synthesis was shown to be optically
active $[a]_D^{15}$ +16.1 (c. 5.52 CHCl$_3$). It formed a picrate,
m.pt. 146-7°, and the free base appeared in all respects identical
with natural actinidine, except for the sign of its rotation. Since
the tertiary methyl group in D pulegone has been correlated to the D
series, it follows that natural actinidine has the L configuration. In

the elucidation of the chemistry of iridodial (12), it was found that the
bis 2,4-dinitrophenylhydrazone of natural, optically active
(-)iridodial, was converted quantitatively into optically active
(-)actinidine, by the action of hydrochloric acid in acetic acid
solution.[19]

The second cyclopentanoid monoterpene alkaloid to be discovered
was skytanthine. The chemistry of this alkaloid was studied by
Djerassi, Eisenbraun et al., in America, and by Casinovi et al. in
Italy.[20]

Skytanthine can be isolated from the stems, roots and leaves
of Skytanthus acutus (Meyen), a Chilean member of the Apocynaceae.
At present skytanthine appears to be the only cyclopentanoid monoterpene
alkaloid in this family. The crude alkaloid is a liquid, b.pt.
$54°/1.5$ mm, $[a]_D + 42°$ (CHCl$_3$), and has the empirical formula $C_{11}H_{21}N$.
Its structure was shown to be (27) on the basis of a Hofmann degradation,
and nuclear magnetic resonance studies on the parent compound and its
dehydrogenation product. Dehydrogenation over platinum black produced
an optically inactive pyridine. This was shown to be identical with
racemic actinidine through a comparison of the melting points and
infrared spectra of the respective picrates.

(27)
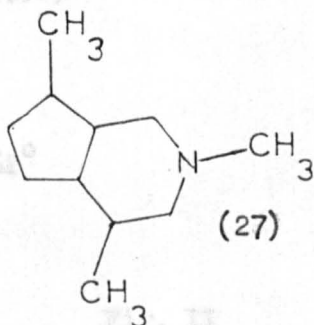
The crude alkaloid mixture has been separated by several chromatographic
techniques (vapour phase, thin layer and silica gel column chromatography),
into three diastereoisomers of skytanthine. The structures of these
diastereoisomers have been correlated with the known nepetalinic acids
(6) – (9).[21] The acids were reduced by lithium aluminium hydride to
the diols and the bis-tosylates of the diols heated under pressure with
methylamine to give the skytanthines. The configuration of the skytanthines
produced is shown in Figure II, (28) – (31).

a-Skytanthine
Picrate m.pt. 120°

β-Skytanthine
Picrate m.pt. 135°

γ-Skytanthine
Picrate m.pt. 162°

δ-Skytanthine
Picrate m.pt. 139°

Fig. II

- 8 -
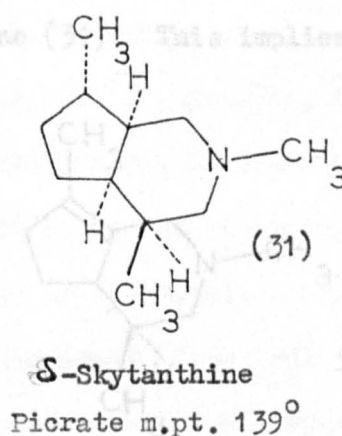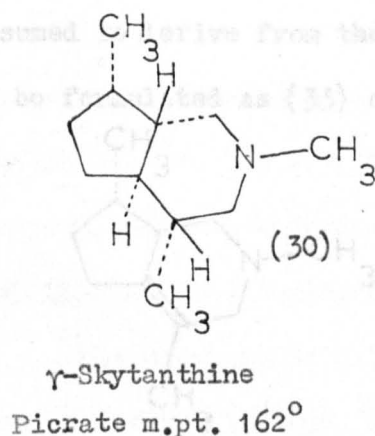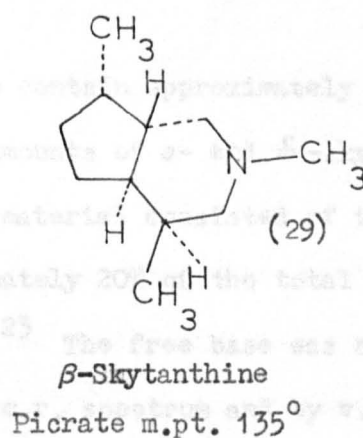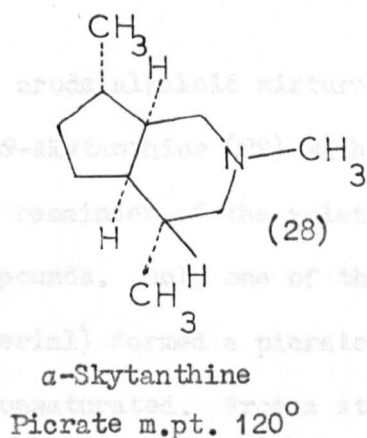
α-Skytanthine (28) has also been prepared from a nepetalic acid (32) and δ-skytanthine (31) has been prepared from iridomyrmecin (10) and from a nepetalic acid.[22]

(32)
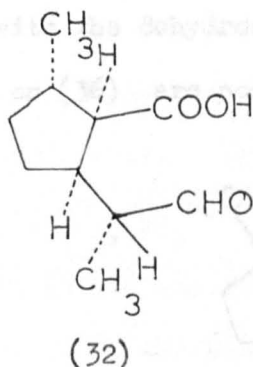
The crude alkaloid mixture was shown to contain approximately 60 - 65% of β-skytanthine (29) with only trace amounts of α- and δ-skytanthines. The remainder of the volatile alkaloid material consisted of two compounds. Only one of these (approximately 20% of the total crude material) formed a picrate, m.pt. 127°.[23] The free base was shown to be unsaturated. From a study of its n.m.r. spectrum and by v.p.c. comparison of its reduction product with the known skytanthines it is presumed to derive from the δ-skytanthine (31). This implies that it can be formulated as (33) or (34).[24]

(33)

(34)
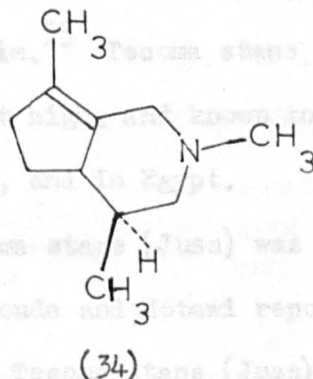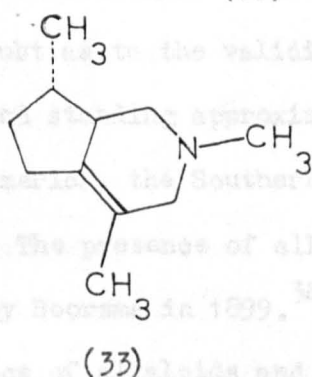
The non-volatile fraction of the extract from Skytanthus acutus yielded a crystalline alkaloid, m.pt. 93°. This compound was shown to be an alcohol. On dehydration with thionyl chloride it gave an unsaturated base, identical with the dehydroskytanthine described above. This implies that either (35) or (36) are possible structures for this alcohol.[24]

(35)   (36)
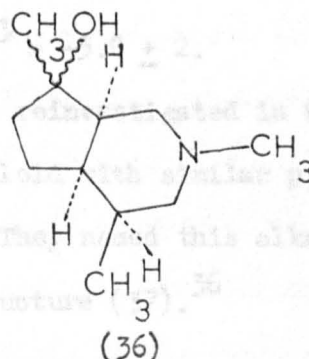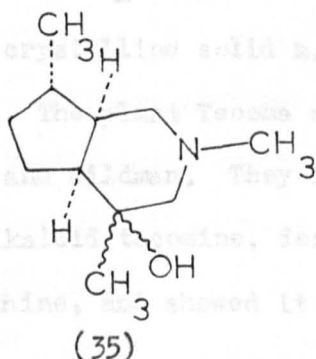
Cyclopentanoid monoterpene alkaloids have also been discovered in the plant Tecoma stans (Juss) belonging to the family Bignoniaceae. The Tecoma species have for a long time been a subject of botanical, chemical and pharmacological interest.[25-31] The leaves of Tecoma mollis (Juss) are widely used by the natives in Mexico as an anti-diabetic drug, and it is claimed they contain alkaloidal material.[32] However, there is some doubt as to the validity of this claim.[33] Tecoma stans (Juss) is a weed standing approximately four feet high, and known to occur in South America, the Southern United States, and in Egypt.

The presence of alkaloids in Tecoma stans (Juss) was first noted by Boorsma in 1899.[34] In 1959 Hammouda and Motawi reported the existence of alkaloids and triterpenes in Tecoma stans (Juss).[35] They isolated two alkaloids. One of these, which they named "Tecomine", was

a liquid base, with the following properties. It formed a methiodide, m.pt. 265°, which corresponded to a molecular formula $C_{12}H_{20}ONI$. It showed a carbonyl group at 1670 cm.$^{-1}$ (nujol) and formed a 2,4-dinitrophenylhydrazone which had a m.pt. 260°. The base also formed a picrate, m.pt. 154°. The methiodide had a specific rotation $[a]_D^{23}$ = -20 ± 2 (in 50% alcohol, concn. 0.5% W/V). The second alkaloid was a crystalline solid m.pt. 275°, $[a]_D^{23}$ = -5.0 ± 2.

The plant Tecoma stans (Juss) was reinvestigated in 1962 by Jones, Fales and Wildman. They isolated an alkaloid with similar properties to the alkaloid tecomine, described above. They named this alkaloid Tecomanine, and showed it to have the structure (37).[36]

(37)
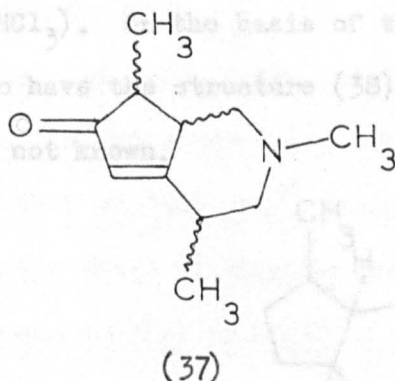
Tecomanine is a colourless unstable liquid. It forms a picrate, m.pt. 179.5 - 180.5°, and a methiodide, m.pt. 240 - 2° (dec.). It is optically active, $[a]_D^{24}$ = -175° (c. 1.17 CHCl$_3$). The infrared spectrum shows peaks at 1700 cm.$^{-1}$ and 1620 cm.$^{-1}$ typical of an $a\beta$ unsaturated cyclopentenone. It has an ultraviolet absorption with λ_{max}^{EtOH} 226 mμ (log$_{10}$ ε 4.10).

Four further alkaloids have been detected in Tecoma stans (Juss).[57]
Only two of these alkaloids were isolated in sufficient quantity to

record their physical properties. One of them was shown to be a pyrindine derivative. It formed a picrate, m.pt. 116–117° which indicated an empirical formula of $C_9H_{11}N$ for the free base. The free base, regenerated from the picrate by the action of lithium hydroxide, showed λ_{max}^{EtOH} 259.5 mμ and 267 mμ ($\log_{10}$ 3.05). The infrared spectrum in the region 900 cm.$^{-1}$ to 650 cm.$^{-1}$ was similar to that of 3,4-lutidine. The n.m.r. spectrum of the picrate showed the presence of 2 a-pyridine protons, a singlet at 8.75 p.p.m., overlying one half of a doublet centred at 8.8 p.p.m. (J = 6 c.p.s.). A β-pyridine proton was detected at 8.0 p.p.m. (J = 6 c.p.s.) and a 3-proton doublet at 1.55 p.p.m. (J = 6.5 c.p.s.). The compound was optically active $[a]_D^{24} = +3°$ (2.34 c in CHCl$_3$). On the basis of the above evidence, the alkaloid is thought to have the structure (38) although its absolute configuration is not known.
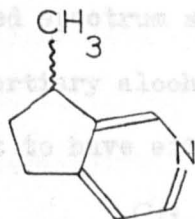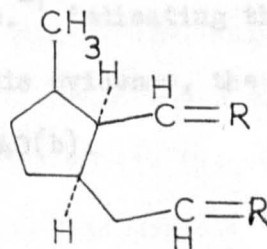
(38)   (39)

Recently this structure has been synthesised.[38] Cis,cis-2-formyl-3-methylcyclopentyl acetaldehyde (39a) R = O obtained as a degradation product from asperuloside (18) was converted into its bis 2,4-dinitro phenylhydrazone (39(b) R = 2,4-(NO$_2$)$_2$C$_6$H$_3$.NH.N=). This on treatment with concentrated hydrochloric acid in glacial acetic acid gave the

compound (38), 6,7-dihydro-7-methyl-5H-2-pyrindine. The picrate of this latter compound had m.pt. 115.5 - 6° and did not depress the melting point of the picrate of the alkaloid from Tecoma stans. The infrared spectra of the two picrates were identical. No figures were supplied for the optical rotation of the **synthetic** compound and thus the configuration of the alkaloid from Tecoma stans is not known.

The remaining alkaloid isolated from Tecoma stans (Juss) by Jones et al. showed the following properties. It formed a picrate, m.pt. 170-170.5° analysis of which indicated $C_{11}H_{21}NO$ as the empirical formula of the free base. Regenerated from the picrate, the base sublimed at 110°/0.25 mm to give a solid m.pt. 91-92°. The n.m.r. spectrum of this compound showed **two** $C - \overset{\overset{C}{|}}{\underset{\underset{H}{|}}{C}} - CH_3$ groups at 0.9 p.p.m. and 1.15 p.p.m. respectively. An N-CH$_3$ group was found at 2.27 p.p.m. The compound was transparent in the ultraviolet above 220 mμ, and the infrared spectrum showed a band at 3609 cm.$^{-1}$ indicating the presence of a tertiary alcohol. On the basis of this evidence, the alkaloid is thought to have either structure 40(a) or 40(b).
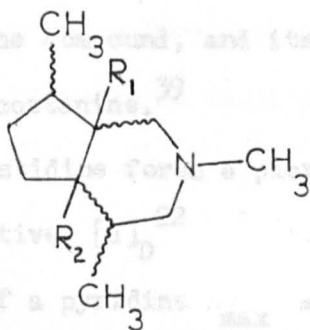
40(a) R$_1$ = H, R$_2$ = OH
40(b) R$_1$ = OH, R$_2$ = H

A short while after its publication, the structure of tecomanine was substantiated by the findings of Hammouda and Le Men.[39] Their investigations on the alkaloids of Tecoma stans (Juss) led them

to identify three alkaloids present in the plant. The crude alkaloid material was separated by thin layer chromatography. One of the alkaloids they obtained was identical with tecomanine. The other alkaloids were shown to have the structures (41) and (42) and were named Tecostanine and Tecostidine respectively.

(41)   (42)
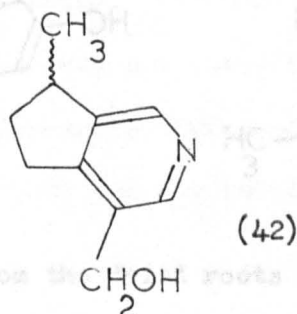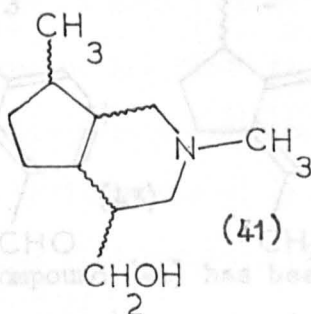
Tecostanine was found to have the following properties. M.pt. 82° $[\alpha]_D^{20} = 0 \pm 2^\circ$ (methanol). It had an I.R. absorption at 3180 cm.$^{-1}$ and formed an acetate. It was transparent in the UV above 215 mμ. Its n.m.r. spectra indicated an N-Me, H-C-CH$_3$, OH and H $-$ C $-$ CH$_2$OH groups. The tosylate was reduced with LiAlH$_4$ to a skytanthine, which formed a picrate, m.pt. 143°. This infers it is not one of the known skytanthine diastereoisomers. The above evidence, combined with that from the mass spectra of the compound, and its degradation products, led to the structure shown for tecostanine.[39]

Tecostidine forms a picrate m.pt. 152-3° and the free base is optically active, $[\alpha]_D^{22}$ -4° (c. 1.221 CHCl$_3$). It has a UV spectrum indicative of a pyridine λ_{max}^{EtOH} = 262 mμ (log$_{10}\mathcal{E}$ = 3.27) and 270 mμ (log$_{10}\mathcal{E}$ = 3.21), showing a hypsochromic shift and increase in intensity on acidification. Infrared measurements showed bands at 3400 cm.$^{-1}$ and 3200 cm.$^{-1}$, indicating a hydroxyl group. These facts, combined with

- 14 -

evidence from the n.m.r. spectra of tecostidine and its deuterated
derivative suggested structure (42) for tecostidine.[40]

The alkaloid structure (43) has been published, although no
information is available concerning the origin of the compound or its
properties.[41]

(43)   (44)   (45)
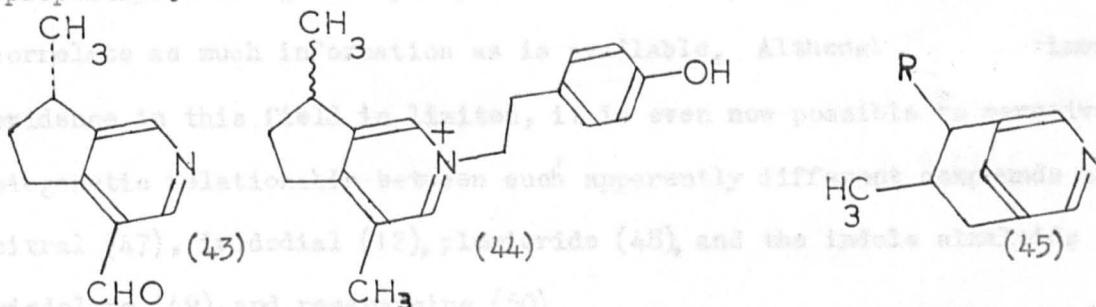
The compound (44) has been isolated from the dried roots of Valeriana
officinalis.[42] It was isolated as the chloride of a crystalline,
optically active base.

The rather unlikely structures (45(a) R = CO_2H) and (45(b)
R = CHO) have been assigned to two alkaloids, named plantagonine and
indicaine respectively.[43] The alkaloids were isolated from the plant
Pedicularis olgae.

Finally, an alkaloid given the name Scholarine, has been
isolated from the mother liquors remaining from the isolation of
echitamine. Scholarine is thought to have the structure shown (46).[43a]

(46)

It is intended to review the biogenesis of all of the natural products possessing the cyclopentanoid monoterpene skeleton, and to correlate as much information as is available. Although the experimental evidence in this field is limited, it is even now possible to perceive a biogenetic relationship between such apparently different compounds as citral (47), iridodial (12), plumieride (48), and the indole alkaloids vindoline (49) and reserpinine (50).
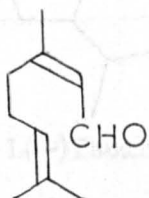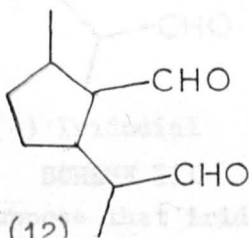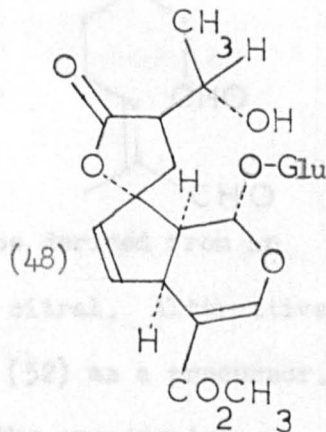
(47)   (12)   (48)
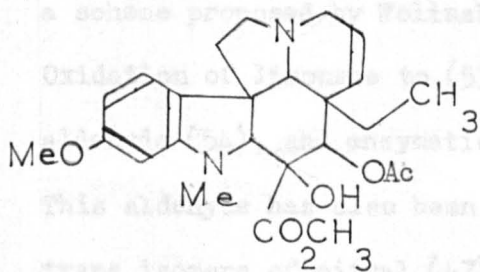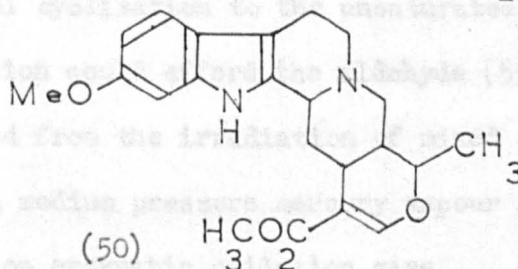
(49)   (50)

The first biogenetic experiments in this field, as in so many others, were performed by Sir Robert Robinson.[44] Starting from L(-) citronellal (51), he synthesised the naturally occurring L(-) iridodial, as shown in Scheme III.

D(+) Iridodial was also synthesised from D(+) citronellal. These compounds, on treatment with warm aqueous (N) sodium hydroxide, gave L(-) isoiridomyrmecin and D(+) isoiridomyrmecin respectively.

L(-)Isoiridomyrmecin   L(-) Iridodial

SCHEME III
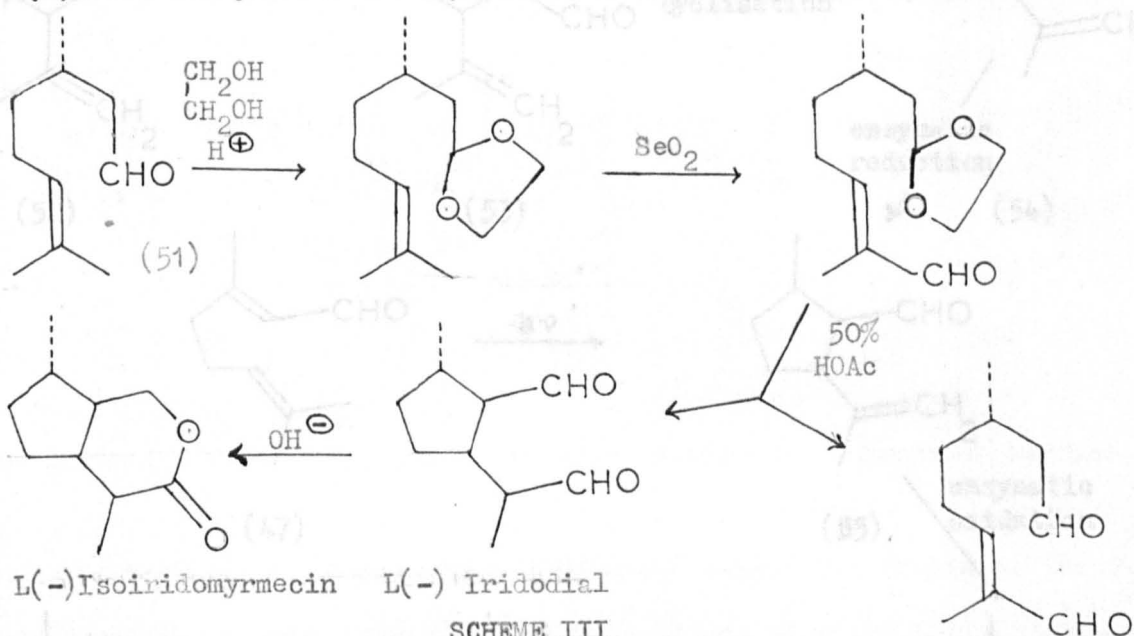
It seems reasonable to suppose that iridodial could be derived from an internal Michael condensation of a partially reduced citral. Alternatively, a scheme proposed by Wolinsky considers (-) limonene (52) as a precursor.[45] Oxidation of limonene to (53), aldol cyclisation to the unsaturated aldehyde (54), and enzymatic reduction could afford the aldehyde (55). This aldehyde has also been obtained from the irradiation of mixed cis and trans isomers of citral (47) with a medium pressure mercury vapour lamp.[46] This aldehyde structure (55) could, on enzymatic oxidation, give dolichidial (13), which after reduction to iridodial and disproportionation would give iridomyrmecin or isoiridomyrmecin. These transformations are shown in Scheme IV.

Oxidation

Aldol cyclisation

(52)

(53)

(54)

enzymatic reduction

(47)

hν

(55)

enzymatic oxidation

disproportionation

reduction

Iridomyrmecin or
Isoiridomyrmecin

Iridodial

SCHEME IV

(13)
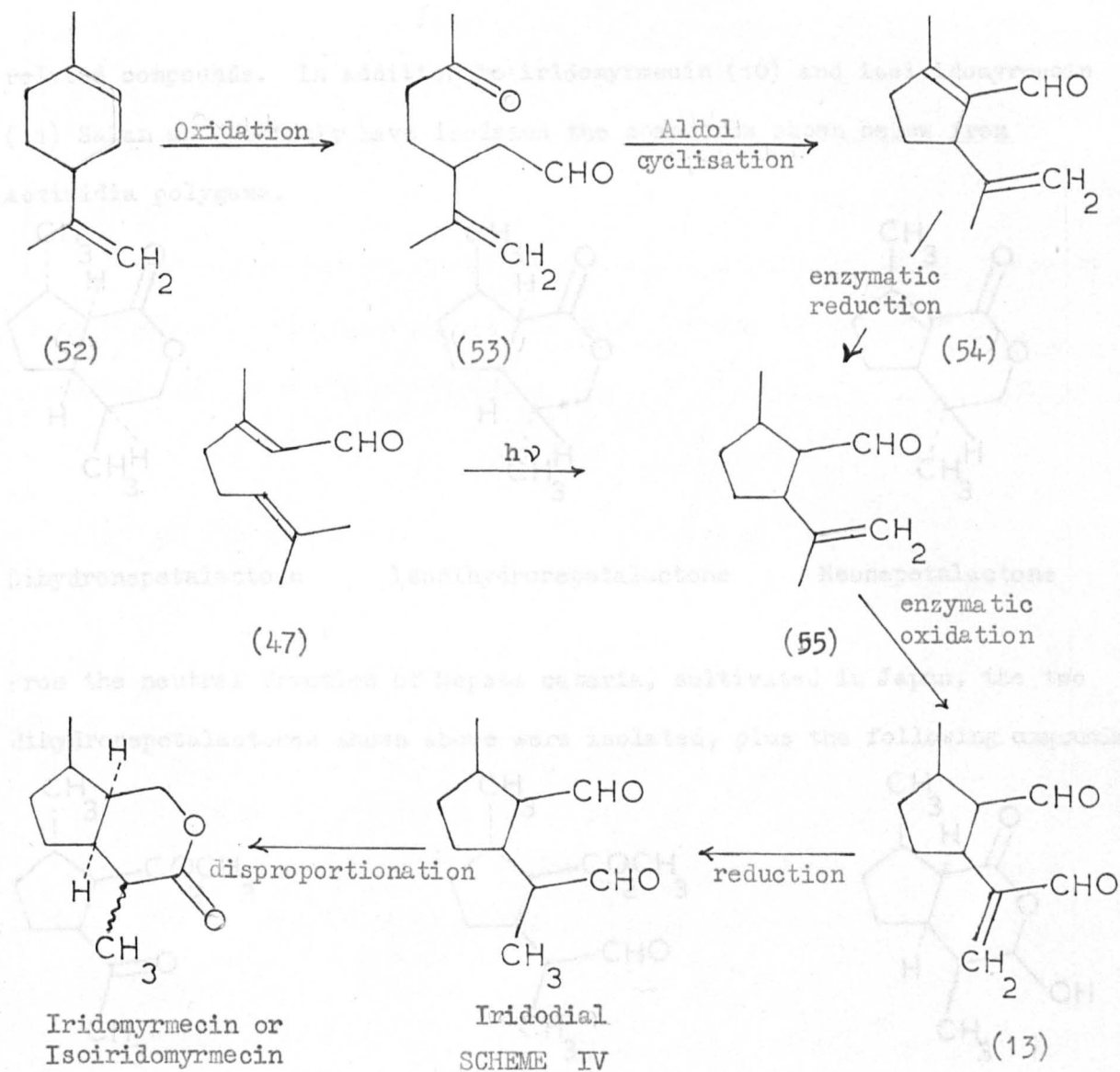
All of these schemes involve **iridodial** as an intermediate in the biogenesis. Until more experimental evidence is available, it seems reasonable to assume that **iridodial** is derived from the cyclisation of two isoprene units with oxidation-reduction reactions occurring either prior to or after the cyclisation.

Iridodial may well be a precursor of the nepetalactones and

- 18 -

related compounds. In addition to iridomyrmecin (10) and isoiridomyrmecin (11) Sakan and Wolinsky have isolated the compounds shown below from Actinidia polygama.
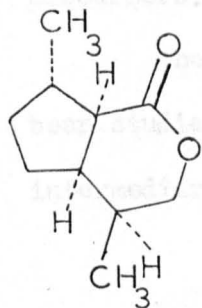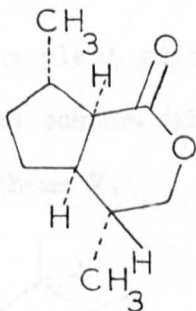
Dihydronepetalactone   Isodihydronepetalactone   Neonepetalactone
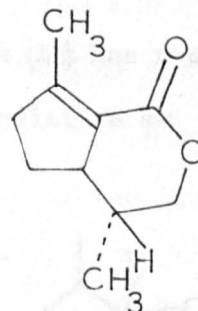
From the neutral fraction of Nepeta cataria, cultivated in Japan, the two dihydronepetalactones shown above were isolated, plus the following compounds.[3(b)]
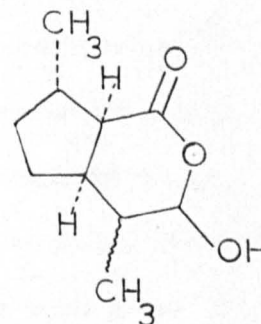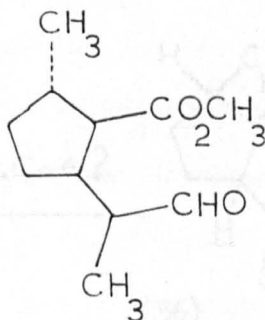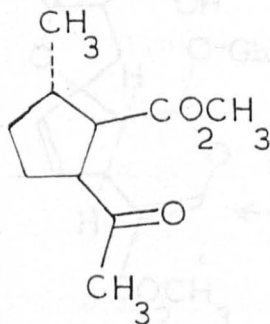
Sakan has also isolated the iridodiols shown below from Actinidia polygama.[47]
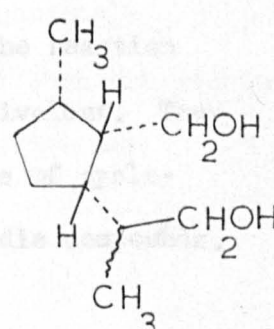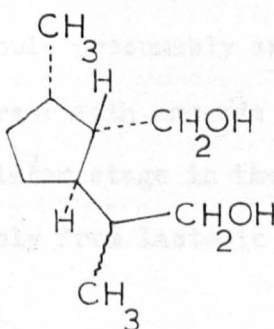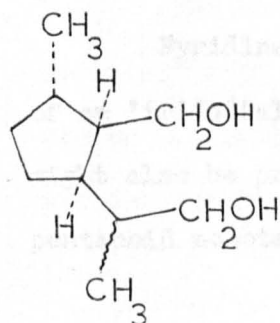
The fact that **iridomyrmecin** and **isoiridomyrmecin** occur with derivatives of the nepetalactones suggests that both the ant lactones and the nepetalactones could originate from one or more closely related precursors.

The biogenesis of the plant glycoside plumieride (48) has recently been studied.[48] The proposed scheme, which invokes iridodial as an intermediary, is shown in scheme V.

Iridodial

$CHCOCHCO.CoA$?
3   2

(48)

(56)
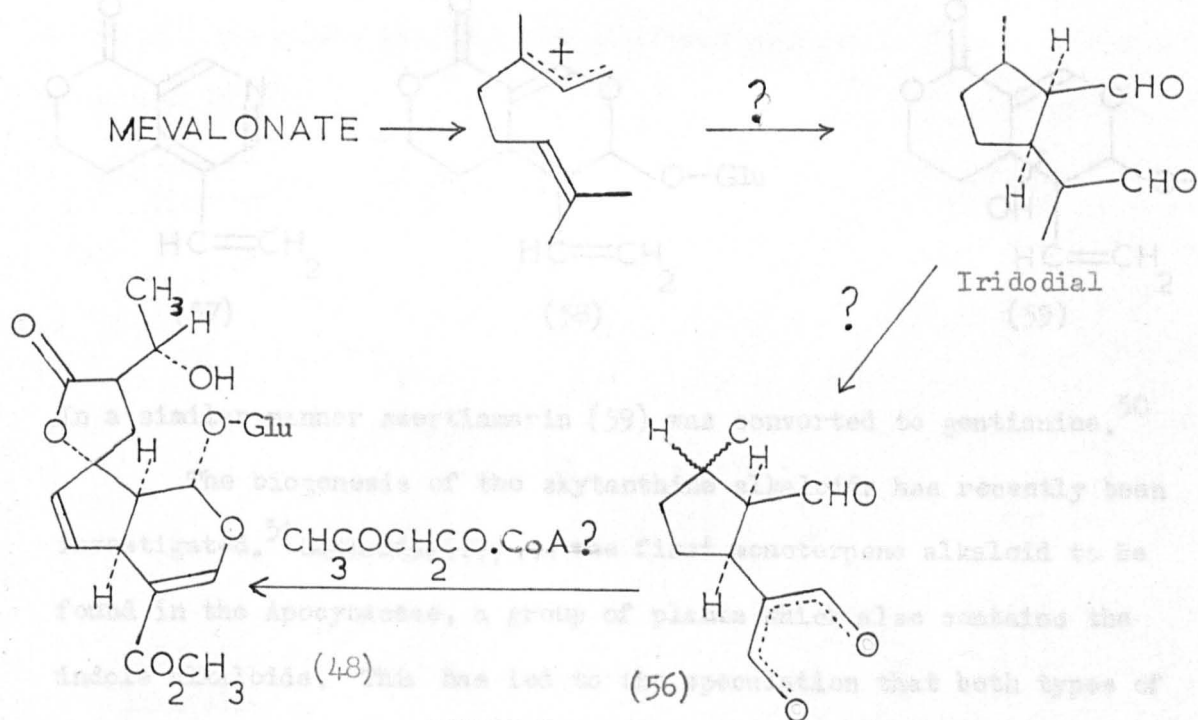
SCHEME V

A compound of the type (56) could lead directly to several of the glycoside structures shown earlier, (P. 8).

Pyridine alkaloids could presumably arise from the reaction of an 'iridodial' type precursor with ammonia or its equivalent. They might also be produced at a later stage in the biogenesis of cyclopentanoid monoterpenes possibly from lactonic or glycosidic compounds.

One cannot exclude the possibility, however, that at least some of the known pyridine alkaloids may be artefacts, produced by the use of ammonia in the isolation of the plant extracts. This has been shown to be the case with the compound gentianine (57).[49] This compound was shown to be produced from the glycoside gentiopicroside (58) by the use of ammonia in the work-up procedure. The use of bicarbonate in place of ammonia, confirmed that no alkaloids were in fact present in the plant.

(57)   (58)   (59)
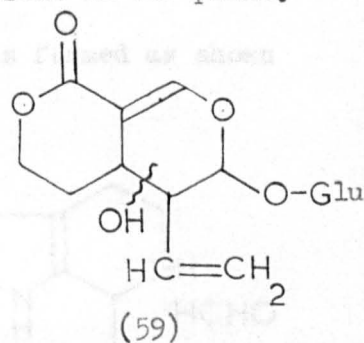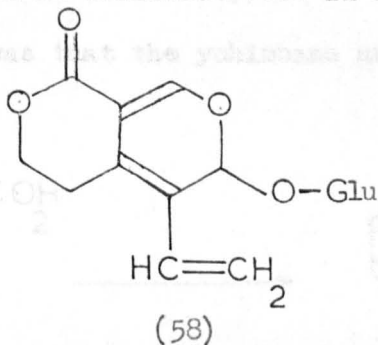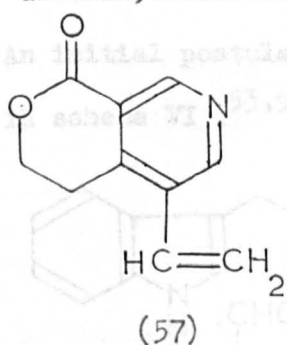
In a similar manner swertiamarin (59) was converted to gentianine.[50]

The biogenesis of the skytanthine alkaloids has recently been investigated.[51] Skytanthine (27) is the first monoterpene alkaloid to be found in the Apocynaceae, a group of plants which also contains the indole alkaloids. This has led to the speculation that both types of alkaloid may derive from a common precursor. Recently indolic bases have been isolated from the plant Skytanthus acutus (Meyen).[20(c)]

The biogenesis of the indole alkaloids is not accurately defined.[52] If one considers the yohimbane skeleton (60) then the section marked (a) is known to derive from a tryptophane moiety, but the precise origin of part (b) is still not resolved.

(60)
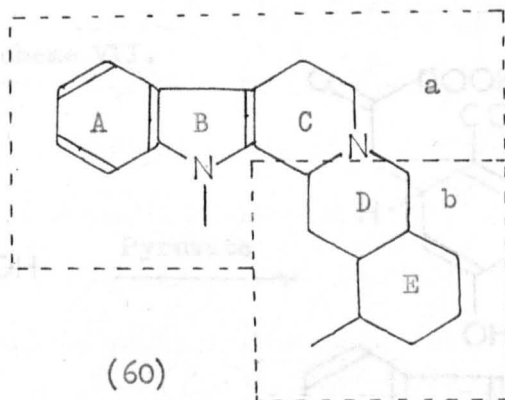
An initial postulate was that the yohimbane nucleus is formed as shown in scheme VI.[53,54]

Yohimbane
Alkaloids
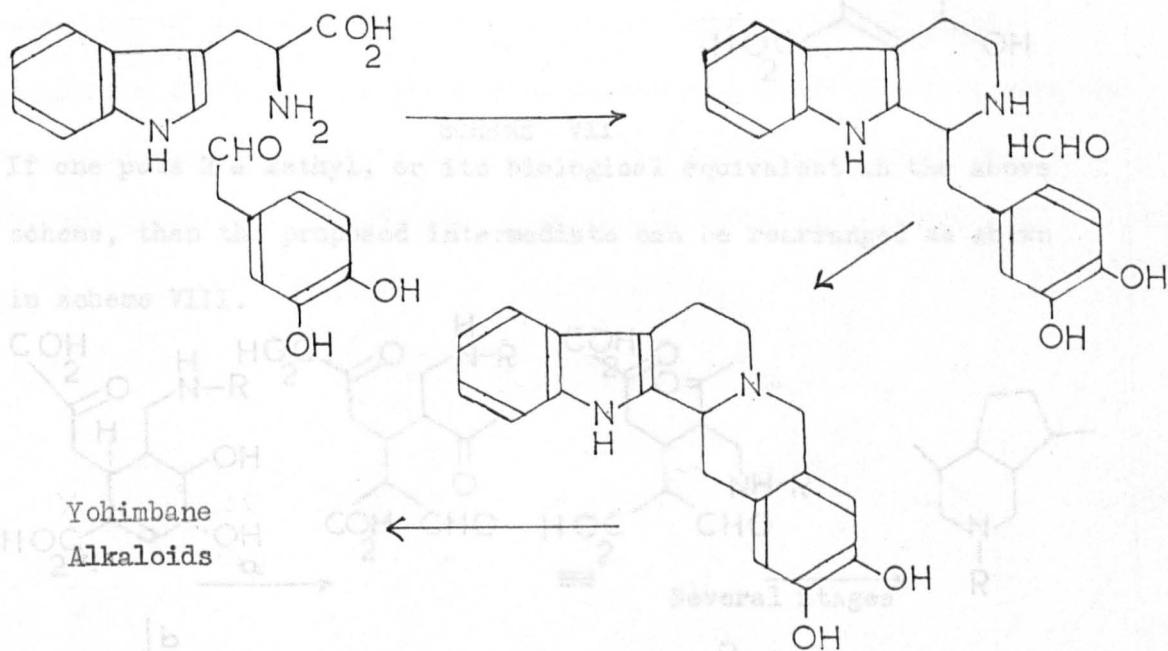
SCHEME VI

The validity of this scheme has been questioned by Wenkert, who found it did not adequately explain all the known facts concerning section (b) of the yohimbane skeleton.[55] Wenkert suggested a shikimic-prephenic acid pathway for the biogenesis of section (b). This pathway may be

summarised by scheme VII.
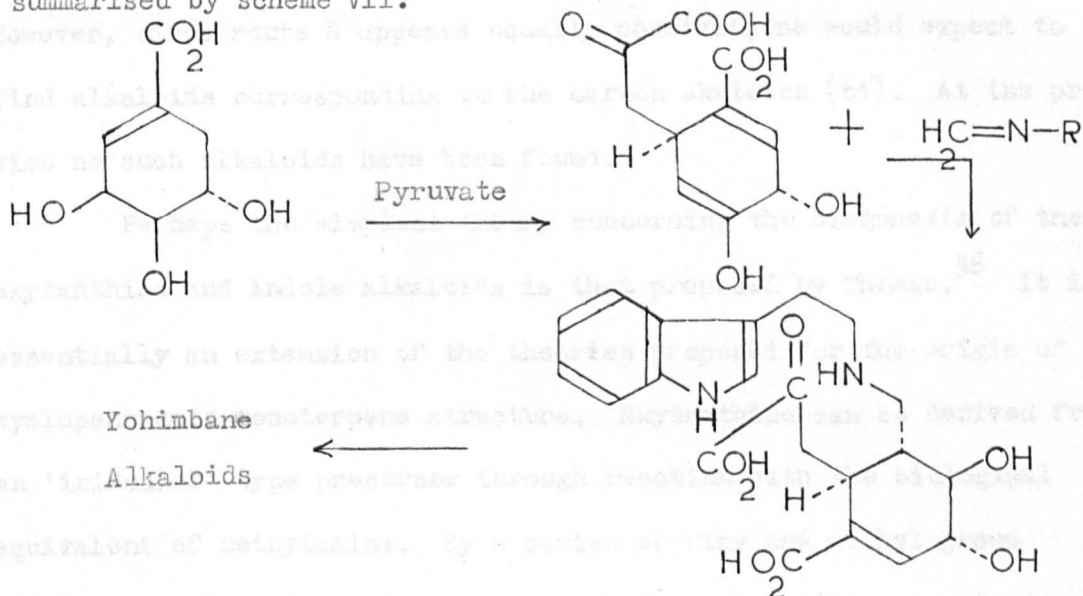
SCHEME VII

If one puts R = Methyl, or its biological equivalent in the above
scheme, then the proposed intermediate can be rearranged as shown

in scheme VIII.

(61)
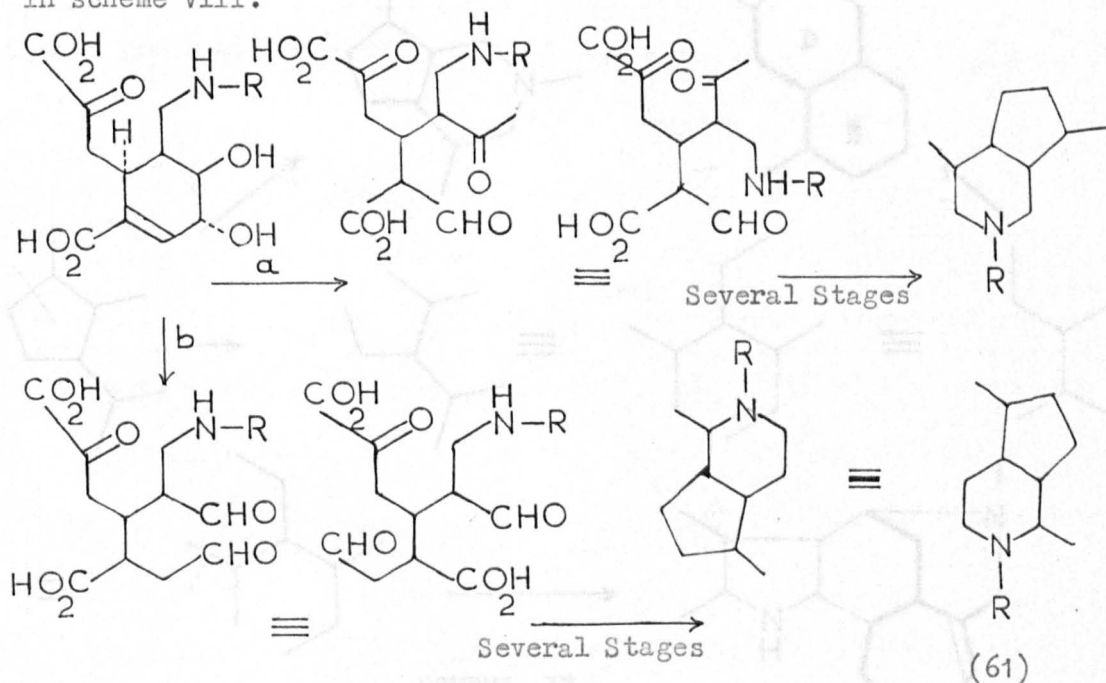
SCHEME VIII

Route A illustrates a possible route to the skytanthine structure.
However, since route B appears equally possible, one would expect to
find alkaloids corresponding to the carbon skeleton (61). At the present
time no such alkaloids have been found.

Perhaps the simplest theory concerning the biogenesis of the
skytanthine and indole alkaloids is that proposed by Thomas.[56] It is
essentially an extension of the theories proposed for the origin of the
cyclopentanoid monoterpene structure. Skytanthine can be derived from
an 'iridodial' type precursor through reaction with the biological
equivalent of methylamine. By a series of ring and methyl group
oxidations, the basic cyclopentanoid monoterpene skeleton could give the
fragments corresponding to those found in the (b) section of the
yohimbane skeleton. These reactions are illustrated in scheme IX.
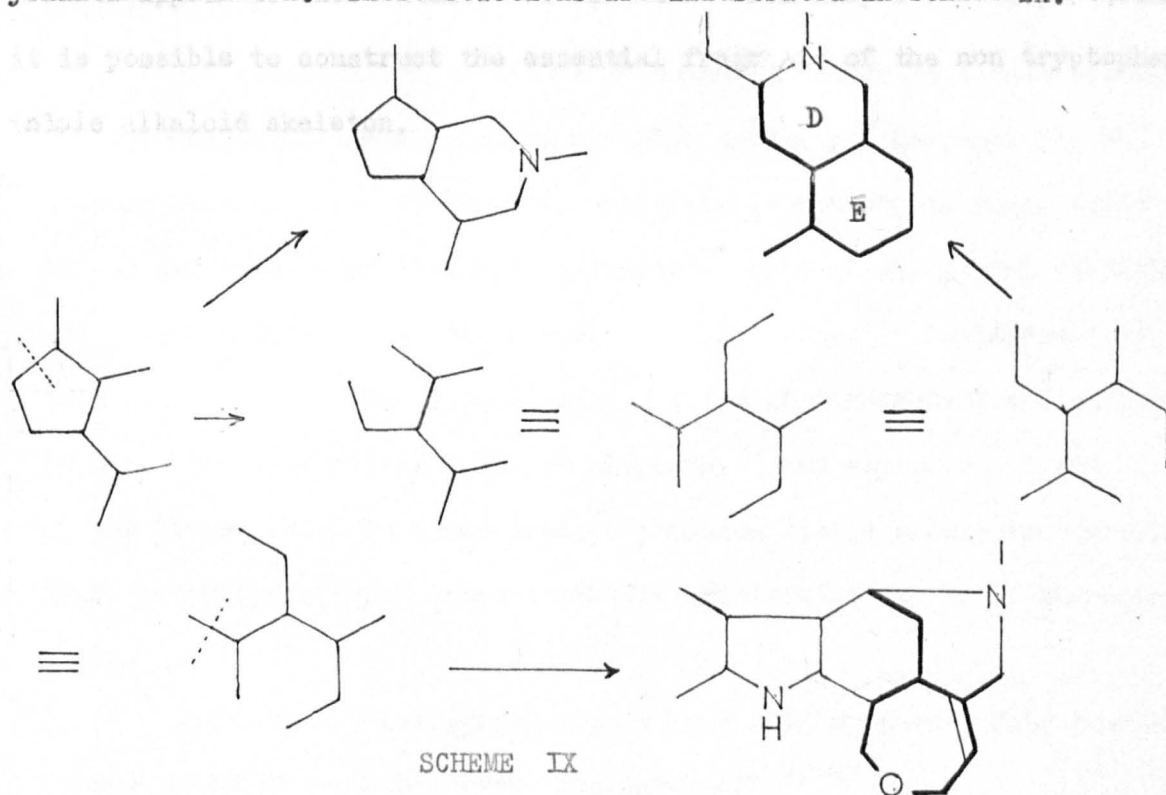
SCHEME IX

The ring fission necessary in this scheme has an analogy in the ring opening reactions of thujone (62).[57] These are shown below.

(62)
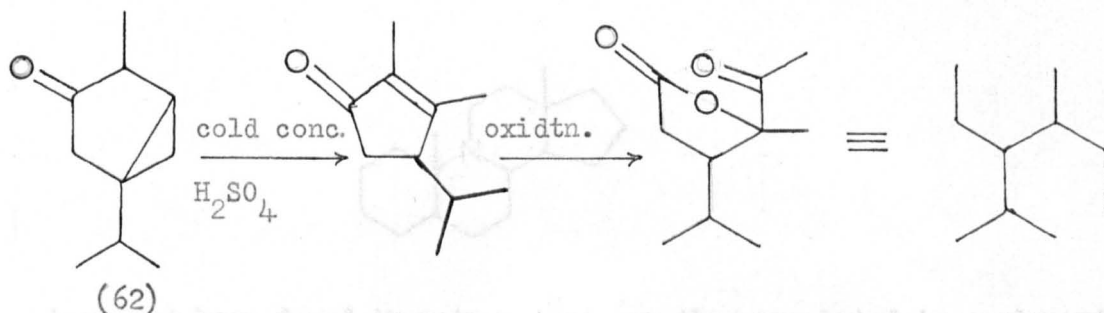
Feeding experiments on **Skytanthus acutus** have established the fact that the incorporation of $2\text{-}C^{14}$ mevalonate is 80 times as great as the incorporation of labelled phenylalanine or acetate. Recently it has been shown, by two groups of workers, that $2\text{-}C^{14}$-mevalonate is incorporated into the indole alkaloid Vindoline (49) and Reserpinine (50).[58] These results appear to substantiate the view that from simple monoterpene precursors, it is possible to construct the essential fragments of the non tryptophan indole alkaloid skeleton.

THE CHEMISTRY OF 9-AZASTEROIDS

The 9-azasteroid skeleton is shown below.   9-Azasteroids
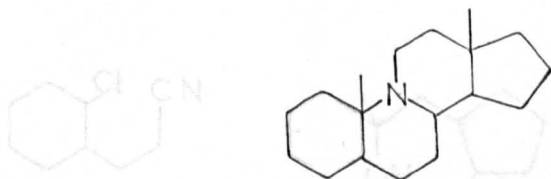
have not been found in nature, and are thus unrelated to cyclopentanoid

monoterpene alkaloids. However, the C/D ring system in a 9-azasteroid

is essentially the same as the carbon skeleton of the monoterpene

alkaloids. Since the work described in this thesis is an attempt to

find synthetic routes to cyclopentanoid monoterpene alkaloids and the C/D

ring system of a 9-azasteroid, the chemistry of 9-azasteroids will be

briefly reviewed.

The modification of naturally occurring steroids causes enhancement
or suppression of certain facets of their activity. The activity of
steroid hormones is, in general, specifically related to their structure,
and it has been found that only a limited number of structural variations
are possible with retention of biological activity.[59]   Replacement of
trigonal sp^2 carbon by trigonal nitrogen, or of tetrahedral sp^3 carbon
by tetrahedral positively charged nitrogen,[60] and expansion of one
of the rings from 6 to 7 membered,[61] produces little change in overall

size or configuration. Hence synthetic azasteroids may be of therapeutic

value.

Although a 9-azasteroid has not yet been prepared, four possible
routes to their synthesis have been published.[62-65]

The first of these syntheses is outlined below.[62]
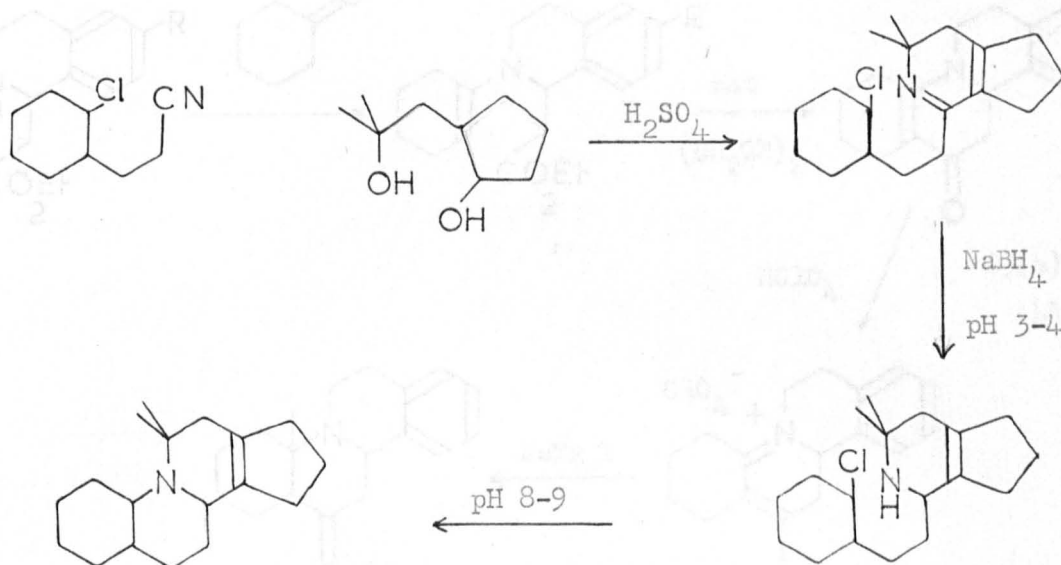
One of the features of the synthesis is that isolation of the dihydro and tetrahydropyridines is unnecessary, suitable conditions for the reduction and cyclisation stage being achieved simply by dilution with water and adjustment of the pH.

D-homo-9-azasteroids have been synthesised by two methods. The compounds (63(a)) and (63(b)) were prepared by condensation of the appropriate 3,4-dihydro-isoquinoline (64) with 2-acetyl-cyclohexanone in ethanol.[63]

(64)

(63(a)) R = OMe
(63(b)) R = H
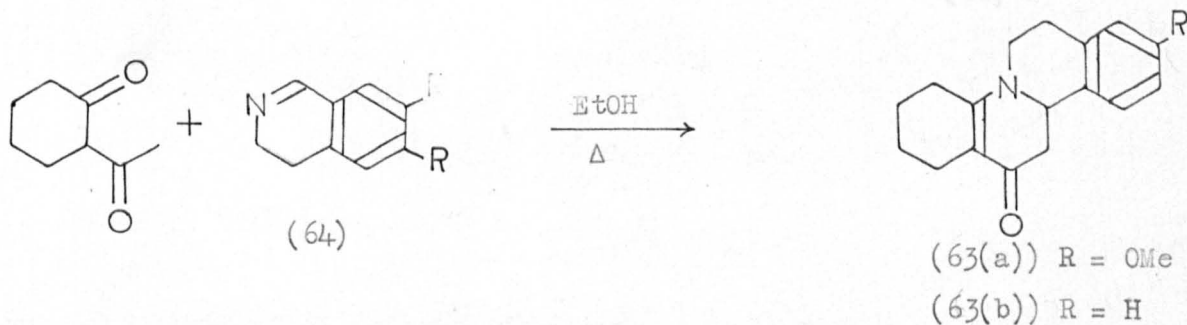
These compounds have also been prepared by a synthesis due to Meyers, and outlined below.[64]

63(a) R = OMe
(b) R = H
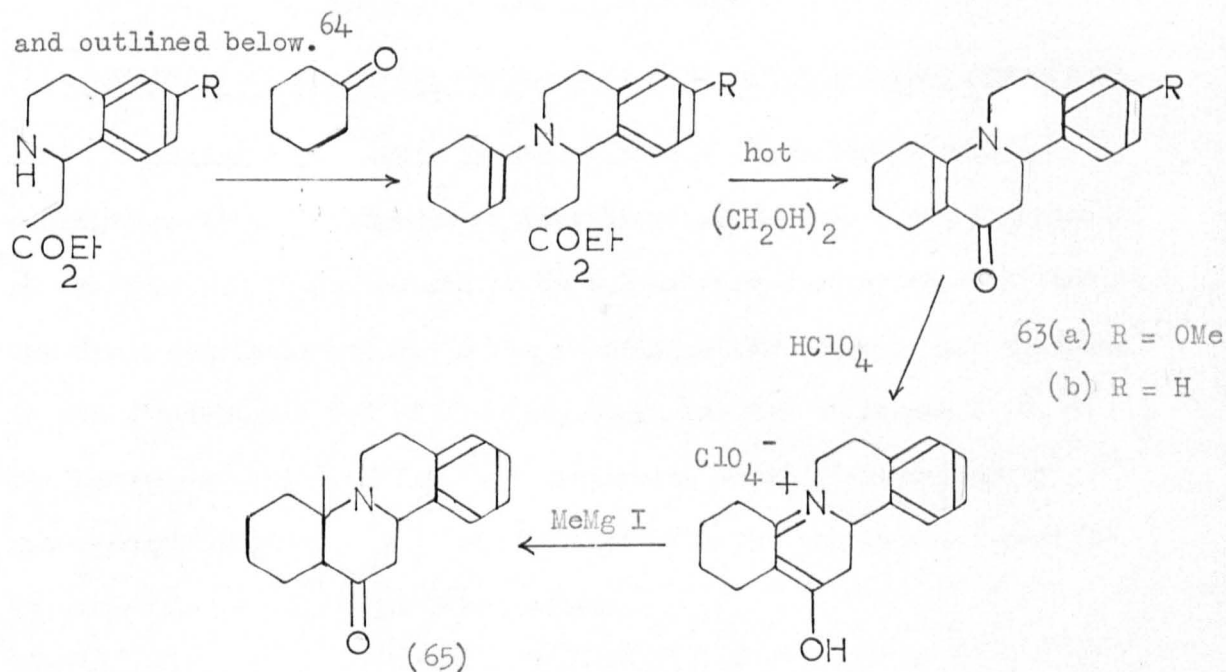
The compound (63(b)) has been converted into the methylated derivative (65) by reaction of its perchlorate salt with methyl magnesium iodide. Finally the compound (66) has been prepared as shown.[65]
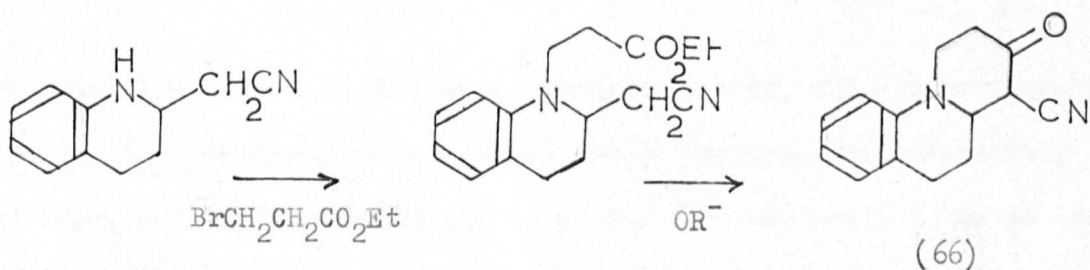
(i) Syntheses of pyridine derivatives from cyclopentanoid precursors.

Initial experiments in the synthesis of cyclopentanoid monoterpene alkaloid structures were directed towards a total synthesis of the compound (38), thought to be 6,7-dihydro-7-methyl-5H-2-pyrindine. The first synthesis attempted was a modification of that used by Sakan in his synthesis of D,L actinidine, shown earlier in Scheme I (p. 5). The keto-ester required for this synthesis, ethyl (2-keto-3-methyl cyclopentyl)acetate (67) was prepared from the enamine of 2-methyl -cyclopentanone and ethyl bromoacetate.

DISCUSSION

(67)

The reaction of (67) with liquid hydrogen cyanide, and dehydration to the unsaturated cyano-esters, could not be performed satisfactorily however, and it was decided not to pursue this synthesis. Instead an attempt was made to prepare 6,7-dihydro-7-methyl-5H-2-pyrindine by another method. A modification of the synthesis used by Sakan to prepare optically active D(+)actinidine. (Scheme II, p. 6), was used. The proposed synthesis is outlined in Scheme XII.

(i) Syntheses of pyrindine derivatives from cyclopentanone precursors.

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(67)

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(68)   (38)

(69(a) R= OH)
(69(b) R= Cl)

(70)

SCHEME XII

An advantage of this preparation was that it would lead to a pyrindine derivative having an optically active 7-methyl group, whose absolute configuration could be used to determine the absolute configuration of the compound (38). Furthermore, from the compound (70), it might be possible to synthesise tecostidine (41).
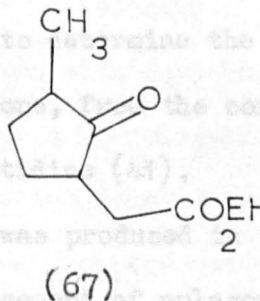
The keto-ester (68) was produced in two stages from D(+)pulegone (26). The Favorskii rearrangement of pulegone dibromide (71) with aqueous base gives both isomers of pulegenic acid (72(a) and (b) R = H).[66] Treatment of the dibromide with sodium methoxide in methanol gives a mixture of the methyl esters (72(a) and (b) R = CH_3). Ozonolysis of these esters gives the keto-ester (68).
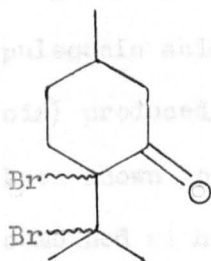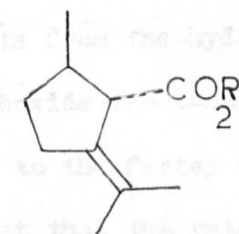
(71)   trans isomer   cis isomer
              (72(a))   (72(b))
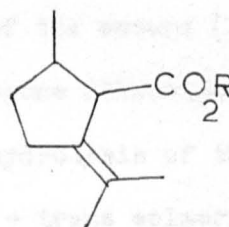
Because pulegenic acid possesses the cyclopentanoid monoterpene skeleton, it has been used as a starting material for the synthesis of several of these compounds.[67] The mechanism and stereochemistry of the Favorskii rearrangement of pulegone dibromide have been recently investigated.[68] While our experiments were performed with the sole purpose of obtaining the keto-ester (68) it is worth mentioning that the results obtained are in complete agreement with those of Wolinsky.[69] It has been found that treatment of pulegone dibromide with aqueous potassium hydroxide gave a mixture of cis and trans isomers of pulegenic acid in the ratio 60% cis/ 40% trans. This result was established through vapour phase chromatography of the methyl esters, prepared from the acids by the action of diazo- methane. When pulegone dibromide was treated with a solution of sodium in methanol, and the product hydrolysed, almost pure trans pulegenic acid was produced. The material produced by the methoxide treatment of pulegone dibromide, when isolated prior to hydrolysis, was shown to contain both isomers of methyl pulegenate, with a composition of approximately 30% of the cis isomer and 70% of the trans methyl pulegenate. These findings have been confirmed and explained by Wolinsky.[69] The rearrangement with aqueous base is kinetically controlled, giving a

- 31 -

slight preponderance of the cis pulegenic acid. Almost pure trans pulegenic acid results from the hydrolysis of the esters (70% trans/ 30% cis) produced by methoxide treatment of pulegone dibromide. This has been shown to be due to the faster rate of hydrolysis of the trans ester, combined with the fact that the rate of cis → trans epimerisation of the non-equilibrium cis/trans ester mixture is faster than the rate of hydrolysis of the cis methyl pulegenate.

Ozonolysis of the trans ester (72(a) R = CH_3) in ethyl acetate proceeded in 90% yield to give the keto-ester (68). Acetone was detected in the effluent gases through formation of its 2,4-dinitrophenyl-hydrazone derivative. The rate of ozonolysis of the equilibrium mixture of cis and trans methyl pulegenate was slower than that of the pure trans ester, presumably due to the steric hindrance involved in forming the ozonide of the cis isomer. The progress of the ozonolysis reactions could be followed by vapour phase chromatography.

The critical reaction in the proposed synthetic scheme was the Knoevenagel condensation of the keto-ester with cyanoacetamide to give 4-cyano-1,3-dihydroxy-6,7-dihydro-7-methyl-5H-2-pyrindine (69(a) R = OH). There appears to be only one example in the literature of a cyclopentanoid β keto-ester reacting with cyanoacetamide under the conditions of the Knoevenagel reaction. This reaction was done by Prelog and Metzler, who condensed ethyl cyclopentanone-2-carboxylate with cyanoacetamide in the presence of a catalytic amount of piperidine and obtained a 38% yield of the compound (73), after heating the reactants in aqueous methanol for three days at 50°.[70]

OH

(73)
C N
OH

When this reaction was performed with methyl 5-methyl-cyclopentanone-2-
-carboxylate, a 36% yield of crude 4-cyano-1,3-dihydroxy-6,7-dihydro-7-
-methyl-5H-2-pyrindine was obtained. The product was a yellow-red solid
which could be recrystallised from an ethanol-water mixture, but
with only a 15% recovery of material.

In an effort to improve the yield of condensation product, several
other reactions which could yield a pyrindine derivative were performed.
By allowing equimolar amounts of ethyl acetoacetate, cyanoacetamide and
piperidine to react in boiling methanol, Bobbit and Scola obtained a
66% yield of the piperidinium salt of 3-cyano-2,6-dihydroxy-4-methyl
pyridine.[71] The salt, which precipitates out during the reaction, can be
converted almost quantitatively to 3-cyano-2,6-dihydroxy-4-methyl pyridine
on acidification. Application of this method to the cyclic keto-ester
(68), resulted in no visible production of a piperidinium salt after
24 hrs. boiling in methanol, and work-up of the reaction gave a lower
yield of the desired compound than that produced by the initial method.

Sakan reported a 68% yield of the ammonium salt of

4-cyano-1,3-dihydroxy-6,7-dihydro-5H-2-pyrindine by allowing equimolar
amounts of ethyl cyclopentanone-2-carboxylate and ethyl cyanoacetate to
react together in 28% ammonium hydroxide for 2 days.[72] Application of
this method to methyl – 5-methyl cyclopentanone -2-carboxylate gave
mainly recovered starting material and only a very low yield of the
desired compound.

     Finally an attempt was made to produce ethyl α-cyano-α-(2-
-carbomethoxy-3-methyl-cyclopent-1-enyl)acetate by reaction of the
keto-ester (68) with ethyl cyanoacetate. Following the procedure of
Ayerst and Schofield, equimolar amounts of the keto-ester and ethyl
cyanoacetate were set aside for 48 hrs., together with a catalytic amount
of piperidine.[73] On working up the reaction, only a low yield of a
compound having nitrile, ester and ketone bands in its infrared spectrum
was produced. The larger part of the residue was unchanged starting
material.

     With the exception of the method due to Sakan, involving the use
of aqueous ammonia, ethyl cyanoacetate and ethyl cyclopentanone-2-
-carboxylate, the syntheses of pyrindine derivatives by these methods do
not proceed in yields greater than 40%. The low yield obtained in the
preparation of 4-cyano-1,3-dihydroxy-6,7-dihydro-7-methyl-5H-2-
-pyrindine prevented the completion of the synthesis of 6,7-dihydro-
-7-methyl-5H-2-pyrindine. The possible reasons for the low yield of
condensation reactions of this type will now be considered.

     The yields of the initial condensation product of a cyclopentanoid
β keto-ester with a nucleophile such as ethyl cyanoacetate are variable,

ranging from 20 - 70% for reactions performed under apparently identical conditions. For example, ethyl cyclopentanone-2-carboxylate has been condensed with ethyl cyanoacetate under various conditions. The conditions of the reaction and yields of ethyl α-cyano-α-(2-carboethoxy-cyclopent-1-enyl)acetate (74) are shown in Table I.
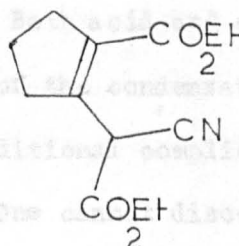
(74)

TABLE I

Reaction Conditions	Yield and Reference	
Approximately equimolar quantities of reactants plus a catalytic amount of piperidine. 2 days at room temperature then 4-5 hrs. on steam bath.	50%	74
	20.8%	73
	72%	75
	72%	70
As above but with no heating.	68%	73
As above but no reaction times or temperatures given.	33%	77
Reactants plus piperidine heated at 100° for 4 hrs.	57%	77
Keto-ester slowly added to the potassium salt of the cyano ester in ethanol. 2 days at room temperature.	59%	74
Reactants plus ammonium acetate in acetic acid. Boiled in benzene following the conditions of Cope.[76]	21.5%	73
	62%	75

While there is some variation in the yields produced by the initial

condensation, there is little variation in the yields of the cyclised

product, 1,3-dihydroxy-6,7-dihydro-5H-2-pyrindine. The cyclisation

of the initial condensation product is performed with acid or alkali.

In this and related cyclisations the yields of pure material are low,

of the order of 10 - 20%. Both acid and alkaline cyclisations are

complicated by hydrolysis of the condensation product to a cyclopentane-

-dicarboxylic acid. An additional complication may be present in cyclic

structures such as (74). One cannot discount the possibility that the

double bond may be exocyclic to the cyclopentane ring, especially if it

is still conjugated with electron withdrawing groups. The position of

the double bond in structures such as (74) has not been determined.

However, there is evidence that in the condensation of 2-indanone with

ethyl cyanoacetate the double bond in the product (75) is entirely

exocyclic.[78]
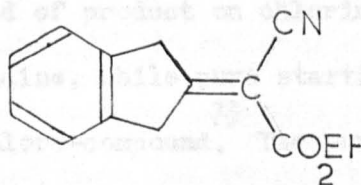
(75)

There is physical evidence to suggest that an exocyclic double bond may

be more stable in ethyl cyclopentanone-2-carboxylate.[79] This compound

is almost entirely ketonic in ethanol and carbon tetrachloride. An

explanation of this could be the ring strain introduced in the formation

of the enol.

If the double bond is exocyclic to the ring system then two structures (76) and (77) are possible for the condensation product between the keto-ester (68) and cyanoacetamide. Under the conditions used in this reaction only compound (77) would be expected to cyclise readily.

(76)   (77)

The next stage in the preparation of 6,7-dihydro-7-methyl-5H-2-pyrindine was the chlorination of crude 4-cyano-1,3-dihydroxy-6,7-dihydro-7-methyl-
-5H-2-pyrindine with phosphorus oxychloride. The reactants were heated in a sealed tube at 180° for 6 hrs., and gave a 31% yield of 4-cyano-
-1,3-dichloro-6,7-dihydro-7-methyl-5H-2-pyrindine (69(b) R = Cl). Schofield reports only a 14% yield of product on chlorination of crude 1,3-dihydroxy-
-6,7-dihydro-5H-2-pyrindine, while pure starting material gave a 76%
                                                    73
yield of the desired chloro-compound. The purification of crude 4-cyano-1,3-dihydroxy-6,7-dihydro-7-methyl-5H-2-pyrindine was found to be time-consuming and to give such a low recovery of material that all chlorinations were performed on the crude compound. Reduction of the chloro-pyrindine derivative with hydrogen and a 5% palladium on charcoal catalyst in the presence of sodium acetate gave 4-cyano-6,7-dihydro-7-
-methyl-5H-2-pyrindine, (70), together with a small quantity of a compound

thought to be a mono-chloro-pyrindine derivative.

The last stage in the synthesis was the removal of the nitrile group. Hydrolysis of this group to a carboxylic acid was attempted, following the procedure used by McElvain for the hydrolysis of 4-methyl-nicotinitrile.[80] This involved heating 4-cyano-6,7-dihydro-7--methyl-5H-2-pyrindine with a solution of sodium hydroxide in 70% alcohol, until the smell of ammonia was no longer apparent. A carboxylic acid was isolated from this reaction and the sodium salt of the acid mixed with soda lime, was pyrolysed in vacuo. Although a pungent pyridine-like odour was apparent it was not possible to isolate any organic material from this reaction. Low yields encountered in the early stages of the preparation of 4-cyano-6,7-dihydro-7-methyl-5H-2-pyrindine indicated that the production of a reasonable amount of this intermediate would be a very lengthy process.

The partial synthesis of 6,7-dihydro-7-methyl-5H-2-pyrindine, from a degradation product of asperuloside, was published during our experiments.[38] Through the courtesy of Professor L. H. Briggs we were able to compare the picrate of his material with the picrate of compound (38). The melting points and infrared spectra of the two picrates were identical. This confirmed the structure (38) for the alkaloid from Tecoma stans.

It was then decided to investigate synthetic routes to the Tecoma alkaloids from 4-piperidone precursors. It was hoped that a method could be found for the synthesis of alkaloids such as Tecomanine (37) and also for the construction of a C/D 9-azasteroid ring system.

(ii) Synthesis of Pyrindine Derivatives from 4-piperidone precursors.

The synthetic problem was the efficient fusion of a 5-membered ring across the 3 and 4 positions of a 4-piperidone ring, to give bicyclic structures which could be converted into a perhydro- pyrindine structure, such as (78), related to the cyclopentanoid mono- terpene alkaloids, and to the C/D ring system of a 9-azasteroid.

(78)

It was hoped that intermediates in the synthesis of (78) could be converted into compounds related to tecomanine (37).

The construction of the 5-membered ring system can in theory be performed in several ways. The ring could be constructed by addition of a three or four carbon chain at position 3 of the 4-piperidone, and subsequent cyclisation of an activated carbon in the chain onto the 4-carbonyl group in the piperidone ring. Typical intermediates in this type of synthesis would be compounds (79) and (80). X is a protecting group attached to nitrogen, e.g. benzoyl.

(79) (80)
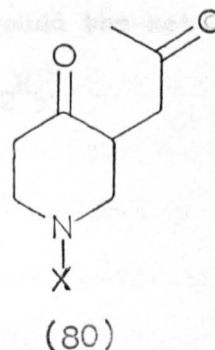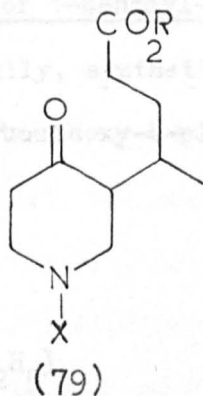
A second solution to this problem could be the synthesis of an

intermediate such as (81), which could then undergo a Dieckmann ring

closure.

(8I) (82) (83)
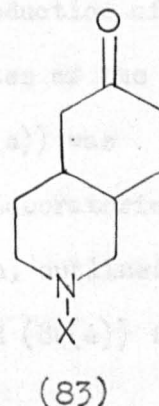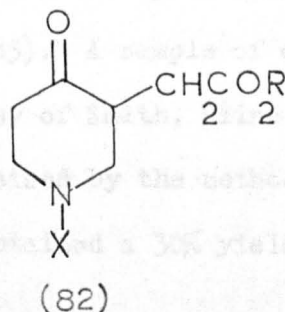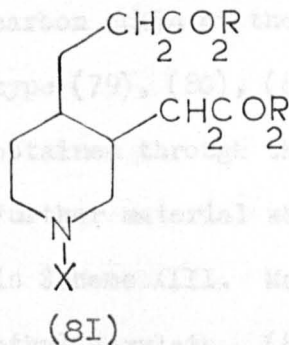
This diester could result from the application of the Reformatsky

reaction to a compound such as (82). The intermediate (81) might also

arise from the application of standard ring contraction techniques to

a compound such as (83).

While these two general methods of solving the problem are not

the only ones, they appeared at first sight to be the most promising.

Syntheses based on both methods of approach have been used, and it is

intended to discuss each attempted synthesis individually, and to

compare them with standard synthetic routes wherever possible.

a)   <u>Syntheses of 1-benzoyl-3-carboethoxy-4-piperidone</u>

     Initially, synthetic work was centred around the keto-ester
1-benzoyl-3-carboethoxy-4-piperidone (84(a) R = C$_2$H$_5$).

(84(a) R = C$_2$H$_5$)

(84(b) R = CH$_3$)
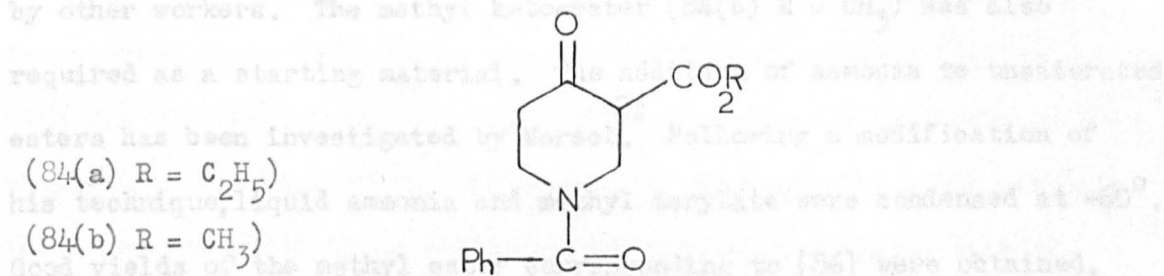
In this compound the nitrogen is relatively inert towards alkylating
agents, while the 3-carboethoxy group will allow the introduction of a
carbon chain at the 3-position, thus producing intermediates of the
type (79), (80), (82) and (83). A sample of compound (84(a)) was
obtained through the courtesy of Smith, Kline and French Laboratories.
Further material was synthesised by the method of McElvain, outlined
in Scheme XIII. McElvain obtained a 30% yield of compound (84(a)) from
ethyl acrylate, (85).[81]

1. NH$_3$ + CH$_2$=CH-CO$_2$Et $\xrightarrow{\text{Autoclave}}$ HN(CH$_2$CH$_2$CO$_2$Et)$_2$ + N(CH$_2$CH$_2$CO$_2$Et)$_3$

(85)   (86)   (87)

PhCOCl

NaH/PhH

(86(a))

SCHEME XIII

This synthesis is extremely tedious, and in our hands gave a yield of approximately 15% from ethyl acrylate. A similar yield has been obtained by other workers.[82] The methyl keto-ester (84(b) R = CH₃) was also required as a starting material. The addition of ammonia to unsaturated esters has been investigated by Morsch.[83] Following a modification of his technique, liquid ammonia and methyl acrylate were condensed at -60°. Good yields of the methyl ester corresponding to (86) were obtained, but it was found that the tertiary ester corresponding to (87) was unstable, undergoing partial decomposition on distillation. This decomposition was most marked in the benzoylation reaction, when no appreciable yield of N,N-di-(β-carbomethoxyethyl) benzamide was produced from the tri-ester. The reaction conditions, which involve boiling the tri-ester in xylene, apparently lead to extensive decomposition at this temperature. Subsequently, other workers reported the synthesis of (84(b)), and they were also unable to benzoylate tri-(β-carbomethoxyethyl)-amine.[82]

In 1964 Carelli and Morlacchi published a different synthesis of compound (84(a)).[84] This synthesis is outlined in Scheme XIV.

$$PhCONHCH_2CH_2CO_2Et \quad + \quad NaH \quad \xrightarrow{PhH} \quad PhCO\overset{\ominus}{N}CH_2CH_2CO_2Et$$

(88)

$$\downarrow CH_2 = CH-CO_2Et$$

(84(a))

(90)

SCHEME XIV

The addition of the sodium salt of ethyl-N-benzoyl-alanine (88) to
a molecule of ethyl acrylate is followed by spontaneous cyclisation of
the intermediate (90) to the desired keto-ester (84(a)). The yield
is reported to be 95%. Since the preparation of compound (88) is
rather a tedious process,[85] it was decided to attempt a synthesis of this
compound by addition of the sodium salt of benzamide to ethyl acrylate.
The ester was added to an equimolar quantity of the sodium salt of
benzamide, prepared from benzamide and sodium hydride in benzene. After
boiling for one hour and working up the reaction, the product was a
mixture of the keto-ester (84(a)) and unchanged benzamide. Further
experiments showed that if a one to three molar ratio of benzamide
to acrylate was used, the keto-esters (84(a)) and (84(b)) could be
prepared in yields of 55 - 65% based on benzamide. The reaction
was complete in three hours, compared with the minimum time of two days
required to complete the synthesis due to McElvain.[81] Both the ethyl and
methyl esters were isolated as yellow-red oils, which could be crystallised
from 40/60 petroleum ether. Both keto-esters appeared to crystallise
in a mixture of the keto and enol forms. The infrared spectrum of the
crystalline material showed a band of medium intensity at 1720 cm.$^{-1}$
with a stronger band at 1670 cm.$^{-1}$ due to the unsaturated ester carbonyl
in the enol form. The amide band appears at 1650 cm.$^{-1}$ and there is
a weak band at 1625 cm.$^{-1}$, possibly due to the carbon-carbon double bond
in the enol form.[79(a)] After standing in carbon tetrachloride, the band at
1720 cm.$^{-1}$ becomes extremely weak. Corelli and Morlacchi observed
frequencies of 1730 cm.$^{-1}$, 1670 cm.$^{-1}$ and 1620 cm.$^{-1}$ in the infrared

spectrum of (84(a)). They assign the 1620 cm.$^{-1}$ band to the amide

carbonyl group. This assignment would appear to be incorrect.

1-Benzoyl-4-piperidone shows two strong bands in the carbonyl stretching

region at 1725 cm.$^{-1}$ and 1650 cm.$^{-1}$. These bands must be due to

the carbonyl group in the ring and to the amide carbonyl group. Neither

the methyl nor ethyl keto-ester (84) showed an enolic OH band in their

infrared spectrum, in solution, or as a mull. This absence of this

band has, however, been observed in other cyclic keto-esters, structurally

related to 4-piperidone.[86]

Both McElvain and Corelli had great difficulty in removing the

ester group from 1-benzoyl-3-carboethoxy-4-piperidone, due

to concomitant hydrolysis of the amide linkage.[81(b), 84] In this laboratory

1-benzoyl-4-piperidone has been produced in 50% yield from this keto-

-ester, by boiling this compound with 100% glacial acetic acid until the

solution gives no colouration with ferric chloride solution. Hydrolysis

of the amide linkage does occur, however, and prolonged boiling reduces

the yield of 1-benzoyl-4-piperidone.

The reaction of the sodium salt of benzamide with ethyl or

methyl acrylate must presumably follow the path shown in Scheme XV.

PhCONH$^{\ominus}$ Na$^{\oplus}$ + CH$_2$=CHCO$_2$Et $\longrightarrow$ PhCONH$_2$-CH$_2$-CHCO$_2$Et$^{\ominus}$

$\downarrow$

(84(a)) $\leftarrow$ [structure] $\overset{CH_2=CH-CO_2Et}{\longleftarrow}$ PhCONH-CH$_2$CH$_2$CO$_2$Et$^{\ominus}$

(89)

SCHEME XV
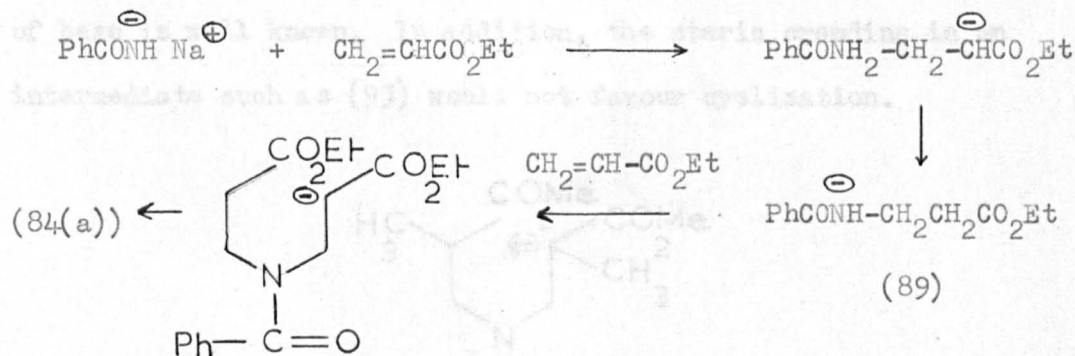
The reaction of the intermediate (89) with a second molecule of ethyl acrylate must be faster than the initial addition reaction of the sodium salt of benzamide, since it was not possible to isolate ethyl-N-benzoyl-alanine. No reaction occurred between the sodium salt of benzamide and ethyl acrylate in the cold, while after heating the reactants, only the keto-ester (84(a)) was isolated. The reaction also works with acetamide and methyl acrylate, although the yields of 1-acetyl-3-carbomethoxy-4-piperidone are much lower than those for the 1-benzoyl compound. Attempts to react the sodium salt of benzamide with ethyl crotonate and methyl methacrylate both failed to give the corresponding keto-esters (91) and (92).

(91)   (92)
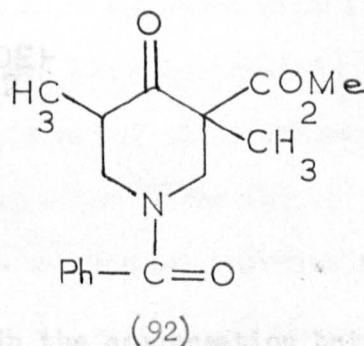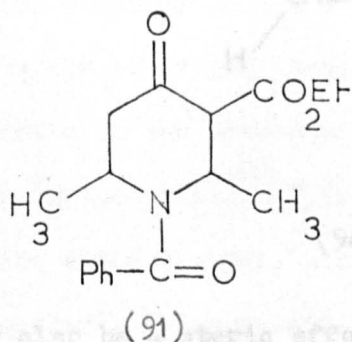
This is perhaps understandable in the case of methyl methacrylate, where polymerisation of the monomer under the influence of base is well known. In addition, the steric crowding in an intermediate such as (93) would not favour cyclisation.

(93)   Ph—C=O

The failure of ethyl crotonate to react is rather more difficult to explain. One reason may be that proton transfer of the type shown below occurs.

$$\text{PhCON}\overset{\ominus}{\text{H}}\ \overset{\oplus}{\text{Na}} + \underset{3}{\text{CH}}-\text{CH}=\text{CH}-\underset{2}{\text{COEt}} \rightarrow \text{PhCON}\underset{2}{\text{H}} + \overset{\oplus}{\text{Na}}\ \underset{2}{\overset{\ominus}{\text{CH}}}-\text{CH}=\text{CH}-\underset{2}{\text{COEt}}$$

It has recently been shown that under the influence of basic catalysts self condensation between two molecules of ethyl crotonate occurs, to give structures such as (94).[87]

(94)

There may also be a steric effect operating in the condensation between the benzamide salt and ethyl crotonate, especially in the reaction required to form the intermediate diester (95).

(95)

These theories do not fully account for the failure of benzamide and ethyl crotonate to react, however, since it is known that the sodium salts of secondary amides, such as (96), will undergo addition and cyclisation with unsaturated esters, including ethyl crotonate, to give high yields of the pyrrolidone keto-esters, (97) and (98).[88]

R = H, CH_3,

C_6H_5, CO_2Et
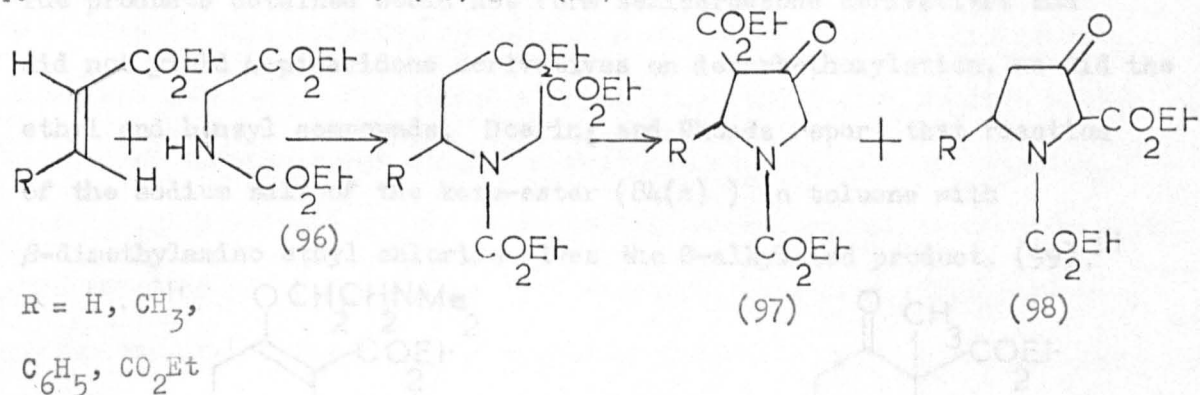
The addition of a primary amide salt to unsaturated esters is, however, a new reaction. Benzamide will add to two molecules of acrylonitrile in the presence of Triton B to give N,N-di-(β-cyanoethyl) benzamide in good yield.[89] This compound is unstable to the action of alkoxide anion however, and undergoes a retro Michael reaction to give the mono-adduct, N-β-cyanoethyl-benzamide.[90] The reaction of benzamide with two moles of ethyl acrylate in the presence of Triton B gave an almost complete recovery of unchanged starting material after 60 hrs. refluxing in dimethoxyethane.

(b) Alkylation reactions of 1-benzoyl-3-carboethoxy-4-piperidone

The first synthesis of the perhydropyrindine system from 1-benzoyl-3-carboethoxy-4-piperidone (84(a)) involved the preparation of intermediates related to compounds (79) and (81). These were prepared by alkylation of the keto ester (84(a)). This compound has

been alkylated with several alkyl halides. McElvain obtained good
yields of the 3-ethyl and 3-benzyl compounds from the corresponding
halides, but found that reaction of the keto-ester with
β and γ phenoxyethyl iodide or bromide did not give C-alkylated products.[81]
The products obtained would not form semicarbazone derivatives and
did not yield 4-piperidone derivatives on decarbethoxylation, as did the
ethyl and benzyl compounds. Doering and Rhoads report that reaction
of the sodium salt of the keto-ester (84(a)) in toluene with
β-dimethylamino ethyl chloride gives the O-alkylated product, (99).[91]

(99)   (100)
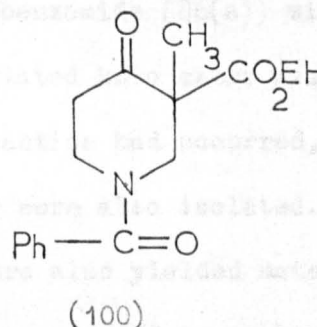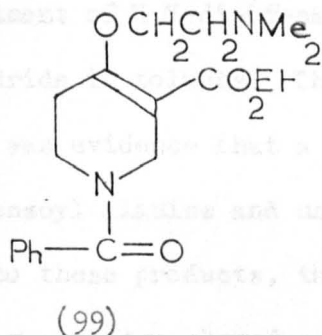
Recently, Spickett and Ganellin have successfully alkylated the keto-ester
(84(a)) with ethyl iodide and isobutyl iodide.[82]

To obtain experience in the preparation of the alkylated
derivatives of 1-benzoyl-3-carboethoxy-4-piperidone, its reaction
with methyl iodide under various conditions was studied. Following
the procedure of McElvain,[81] the sodium salt of the keto-ester,
produced by the action of sodium hydride in toluene, was treated with a
slight molar excess of methyl iodide. Boiling the mixture for 48 hrs.
under reflux gave a 70% yield of 1-benzoyl-3-carboethoxy-3-methyl-4-
-piperidone (100) as a pale yellow oil. Column and vapour phase chroma-
tography indicated that the product was a single compound. The method

of Ritchie and Taylor,[92] involving the use of a dimethyl formamide-benzene

solvent system to dissolve the sodium enolate, did not improve this

yield. The best reaction medium for the alkylations of the keto-ester

(84(a)) was found to be dry dimethoxyethane. When the alkylation was

performed in this solvent, an 84% yield of pure methylated keto-ester

(100) was obtained. The direct alkylation of the sodium enolate of the

keto-ester formed in the Dieckmann reaction is a well-known reaction.[93]

This reaction was attempted, using methyl iodide, on the product resulting

from treatment of N,N-di-(β-carboethoxyethyl) benzamide (86(a)) with

sodium hydride in toluene. The yield of methylated keto ester was low,

and there was evidence that a retro Michael reaction had occurred, since

ethyl N-benzoyl alanine and unchanged di-ester were also isolated. In

addition to these products, the reaction mixture also yielded material

whose n.m.r. spectra showed a H - $\overset{\overset{C}{|}}{\underset{\overset{|}{C}}{C}}$ - CH$_3$ group, as well as a sharp

methyl singlet, and the methyl triplet from the carboethoxy group. This

product was tentatively assigned the structure (101). Another product
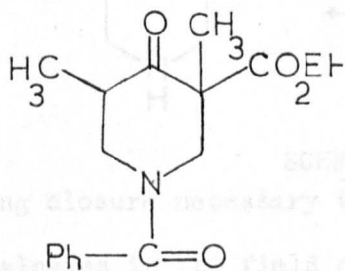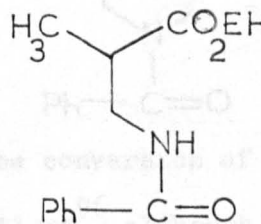
(101)   (102)

was thought to be the compound (102). These compounds were obtained in

low yield, after chromatography on alumina. Their structures are assigned

on the basis of their n.m.r. and infrared spectra.

A complete explanation for the production of these compounds would require
a thorough investigation of this reaction. This was not undertaken, but
the work of Hauser[94], on the dianions derived from acyclic β-keto-esters,
and of Pincock and Rolston,[95] on alkylation at the a carbon of esters, lends
support to the structures proposed for compounds (101) and (102).

Having shown that the keto-ester (84(a)) can be efficiently
alkylated under controlled conditions, the first synthesis of the
perhydropyrindine system was attempted. It is outlined in Scheme XVI.
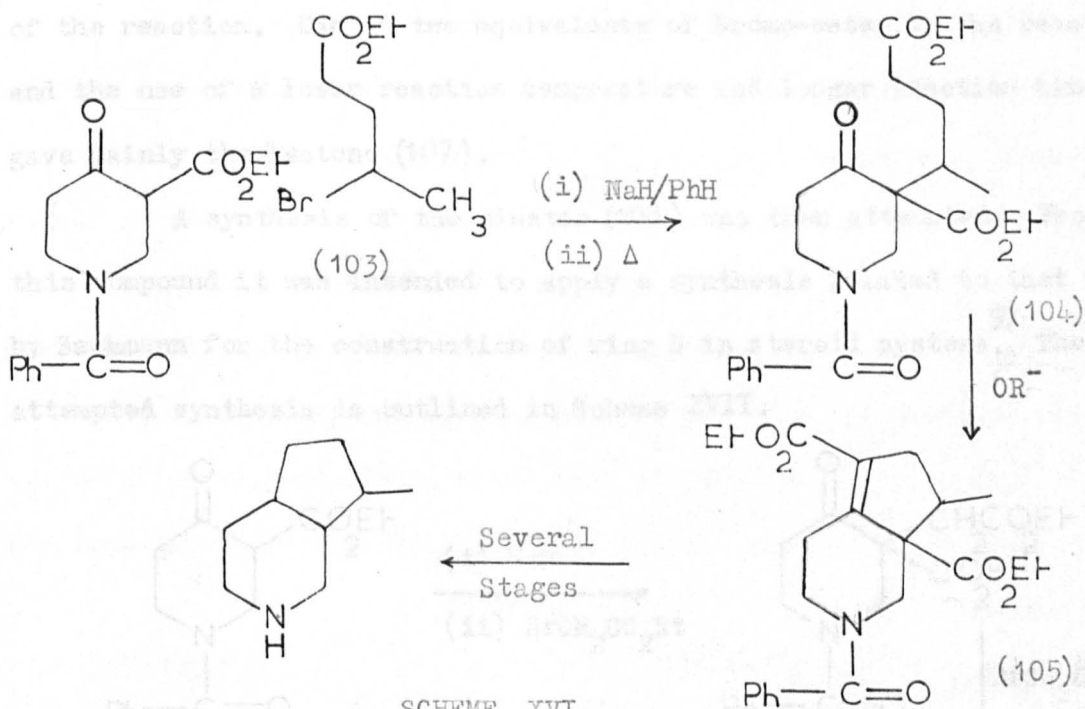
SCHEME XVI

The ring closure necessary to accomplish the conversion of (104) to (105)
has analogies in the field of steroid reactions,[96] although it could also
produce compounds such as (106).

The structures at top:

(106) — bicyclic diketone with CH₃, COOEt, N-C(=O)-Ph substituents

(107) — γ-valerolactone with CH₃
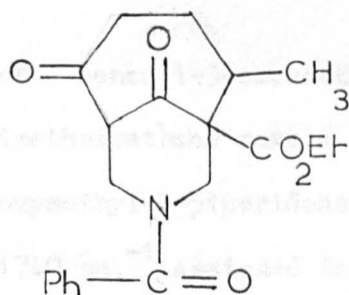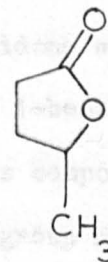
However, a more fundamental obstacle in this synthesis was discovered in
the initial alkylation step. It was found that ethyl γ-bromo valerate
(103) formed almost exclusively γ-valerolactone (107) under the conditions
of the reaction. Use of two equivalents of bromo-ester in the reaction,
and the use of a lower reaction temperature and longer reaction time, still
gave mainly the lactone (107).

A synthesis of the diester (108) was then attempted. From
this compound it was intended to apply a synthesis related to that used
by Bachmann for the construction of ring D in steroid systems.[97] The
attempted synthesis is outlined in Scheme XVII.

Scheme reactions:

Starting piperidinone with COOEt, N-C(=O)-Ph

$\xrightarrow{\text{(i) NaH}}$
$\text{(ii) BrCH}_2\text{CO}_2\text{Et}$

→ (108) with CHCO₂Et / COOEt groups

(108) $\xrightarrow[\text{Reformatsky}]{\text{BrCH}_2\text{CO}_2\text{Et/Zn}}$

→ (109) HO-substituted compound with CHCO₂Et, CHCO₂Et, COOEt

(109) $\xrightarrow[\text{(ii) H}_2]{\text{(i) -H}_2\text{O}}$

→ compound with CHCO₂Et, CHCO₂Et, COOEt, N-C(=O)-Ph

$\xleftarrow[\text{Stages}]{\text{Several}}$

→ octahydro bicyclic amine (NH)
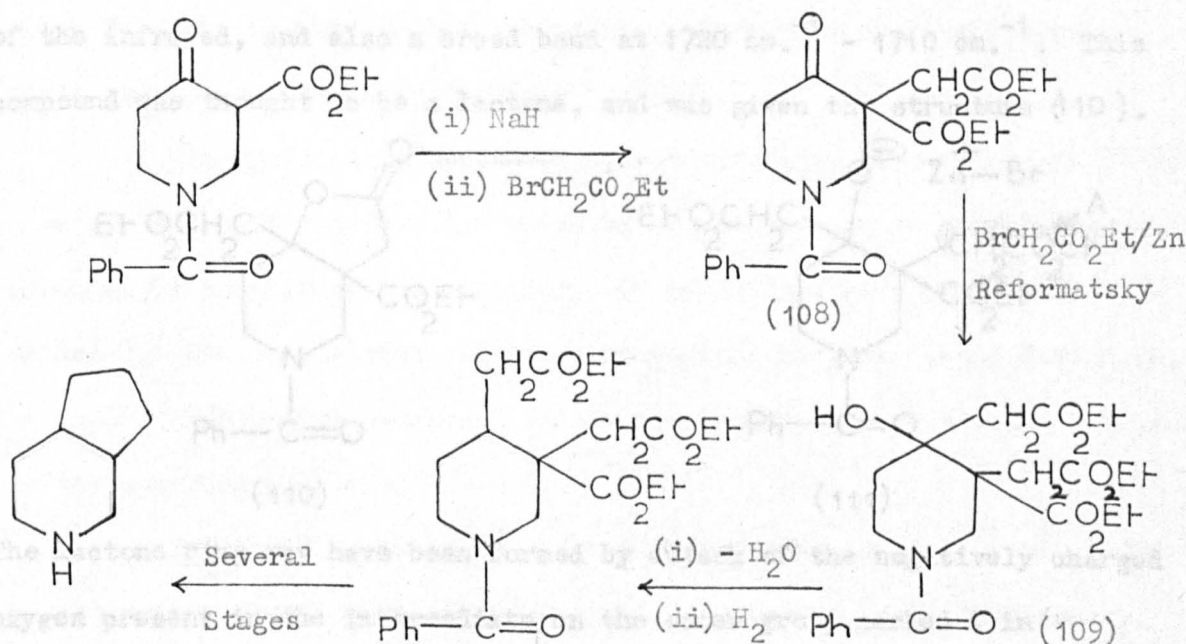
SCHEME XVII

The initial alkylation of 1-benzoyl-3-carboethoxy-4-piperidone with
ethyl bromoacetate in dimethoxyethane gave a 60% yield of 1-benzoyl-3-
-carboethoxy-3-carboethoxymethyl-4-piperidone (108). This compound showed
carbonyl stretching at 1740 cm.$^{-1}$ assigned to the ketone group and two
peaks at 1730 cm.$^{-1}$ and 1725 cm.$^{-1}$ for the ester carbonyls. A similar
alkylation was also performed with ethyl a-bromo propionate to give
1-benzoyl-3-carboethoxy-3-(1'-carboethoxyethyl)-4-piperidone in a yield
lower than that obtained from the straight chain halo-ester.

A Reformatsky reaction was performed on compound (108) using
ethyl bromoacetate in benzene solution. The crude product was isolated
by addition of water and extraction of the organic material. Unreacted
ethyl bromoacetate was removed by briefly heating the crude product
at 100° and 15 mm pressure. The material was then chromatographed on
Spence alumina grade H, and the product obtained was a solid, m.pt. 95-97°.
It showed a medium intensity band at 1785 cm.$^{-1}$ in the carbonyl region
of the infrared, and also a broad band at 1720 cm.$^{-1}$ - 1710 cm.$^{-1}$. This
compound was thought to be a lactone, and was given the structure (110).

(110)   (111)
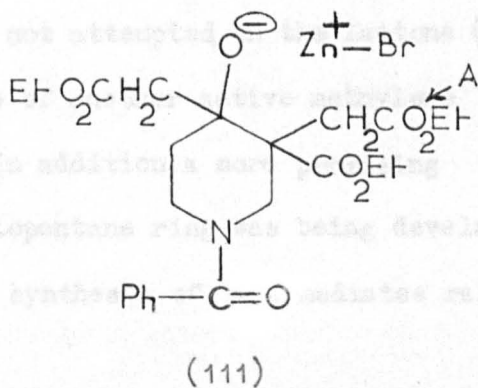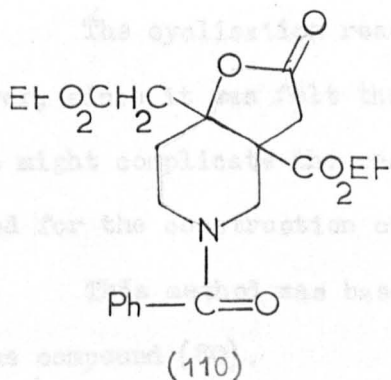
The lactone ring may have been formed by attack of the negatively charged
oxygen present in the intermediate, on the ester group marked A in

figure (111). Alternatively and perhaps more likely, the lactone ring could be produced by the thermal elimination of ethanol from the compound (109), the expected product of the Reformatsky reaction.

The lactone structure (110) might undergo the **Dieckmann** reaction, although it is likely that a strongly basic cyclising agent would be required. In his synthesis of caryophyllene, Corey found that only the methyl sulfinyl carbanion would produce the cyclisation of the lactone (112) to the tricyclic structure (113).[98]

$$CH_3-\overset{\overset{O}{\|}}{S}-\overset{-}{C}H_2$$

(112)   (113)
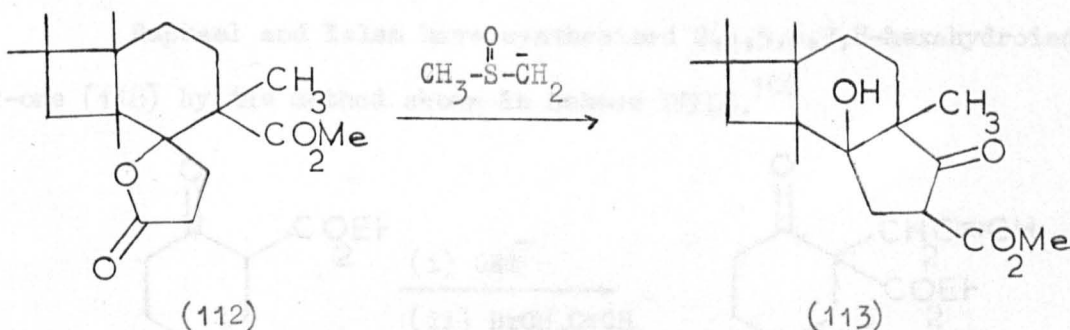
This was found to be due to the high acidity of the α-carbon of the lactone, which leads to proton transfer reactions, rather than cyclisation, with bases such as methoxide or tertiary butoxide.

The cyclisation reaction was not attempted on the lactone (110) however, since it was felt the presence of another active methylene group might complicate the reaction. In addition, a more promising method for the construction of the cyclopentane ring was being developed.

This method was based on the synthesis of intermediates related to the compound (80).

It seemed likely that a 1,4-diketone such as (114) would undergo a cyclisation reaction to give the bicyclic compound (115), 2-benzoyl-

1,2,3,4,7,7a-hexahydro-6H-2-pyrindin-6-one.

(114)   Ph—C=O

(115)   Ph—C=O
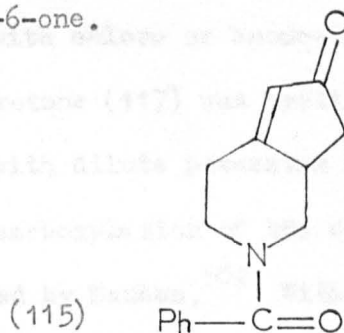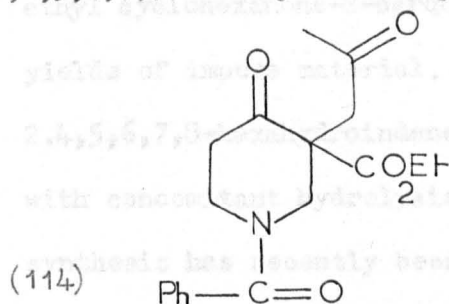
The cyclisation of diketones of this type to cyclopentenone systems is a well known reaction, and has been used as a method for the attachment of ring D onto an ABC ring steroid precursor.[99]

Raphael and Islam have synthesised 2,4,5,6,7,8-hexahydroindene--2-one (118) by the method shown in Scheme XVIII.[100]

$\xrightarrow[\text{(ii) } BrCH_2C\equiv CH]{\text{(i) } OEt^-}$

(116) $\downarrow$ Hg^{2+}, BF_3, MeOH

$\xleftarrow{\text{dil. aq. } OH^-}$

(118)   (117)
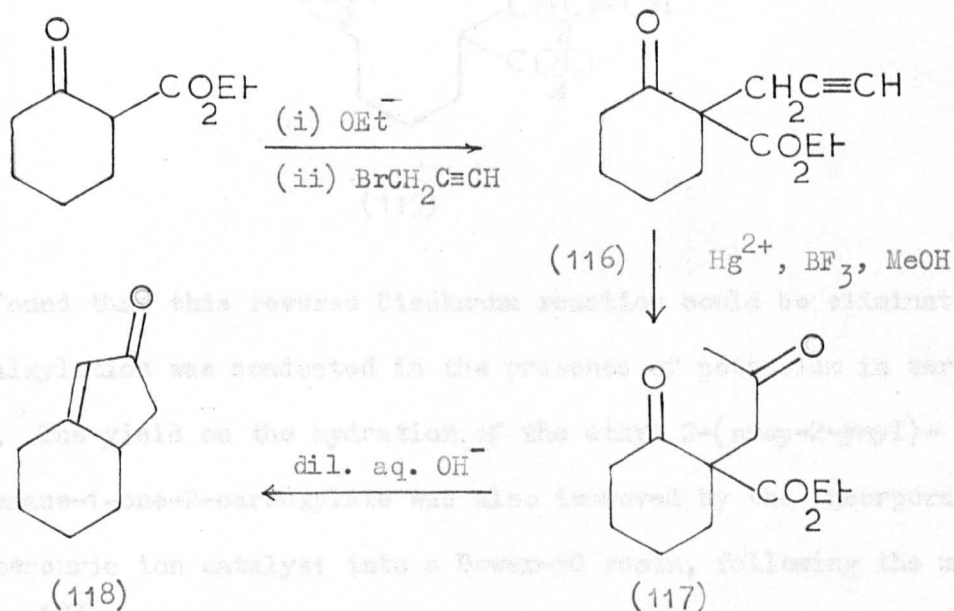
SCHEME XVIII

The sodium salt of ethyl cyclohexanone-2-carboxylate is condensed in ethanol with propargyl bromide. The acetylene is then hydrated by the method of Jones et al.[101] to the diketone (117). The direct alkylation of

ethyl cyclohexanone-2-carboxylate with chloro or bromo-acetone gave low

yields of impure material. The diketone (117) was cyclised to

2,4,5,6,7,8-hexahydroindene-2-one with dilute potassium hydroxide solution,

with concomitant hydrolysis and decarboxylation of the ester group. This

synthesis has recently been repeated by Dauben.[102] With sodium ethoxide

in ethanol, ethyl cyclohexanone-2-carboxylate and propargyl bromide were

found to give approximately equal amounts of ethyl 2-(prop-2-ynyl)-

-cyclohexane-1-one-2-carboxylate (116), and diethyl α prop-2-ynyl pimelate

(119).

$$CO_2Et \qquad CHC\equiv CH$$
$$CO_2Et$$

(119)
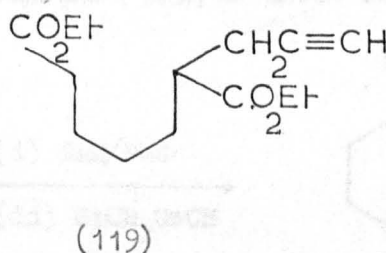
It was found that this reverse Dieckmann reaction could be eliminated

if the alkylation was conducted in the presence of potassium in tertiary

butanol. The yield on the hydration of the ethyl 2-(prop-2-ynyl)-

-cyclohexane-1-one-2-carboxylate was also improved by the incorporation

of the mercuric ion catalyst into a Dowex-50 resin, following the method

of Newman.[103] The attempted cyclisation of the diketone (117) to ethyl

2,4,5,6,7,8-hexahydroindene-2-one-8-carboxylate (120) with sodium

ethoxide in ethanol yielded exclusively the product of a reverse Dieckmann

reaction, diethyl α-acetonyl pimelate (121).
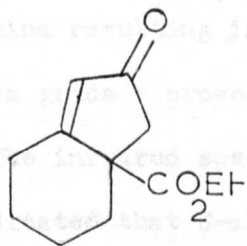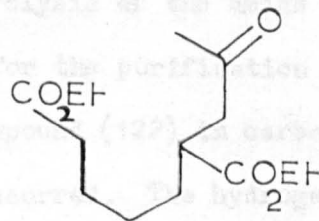
(120)   (121)

This cyclisation was finally accomplished in 39% yield using potassium
in tertiary butanol, but some 2,4,5,6,7,8-hexahydroindene-2-one (118)
was always produced.

It was decided to follow the procedure of Raphael and Islam, in an
attempt to synthesise the compound (115), as shown in Scheme XIX.

(i) NaH/DME
(ii) BrCH₂C≡CH

$$\text{(i) NaH/DME}$$
$$\text{(ii) } BrCH_2C{\equiv}CH$$

(122)

Hg^{2+}, BF_3, MeOH

(115)   (123)
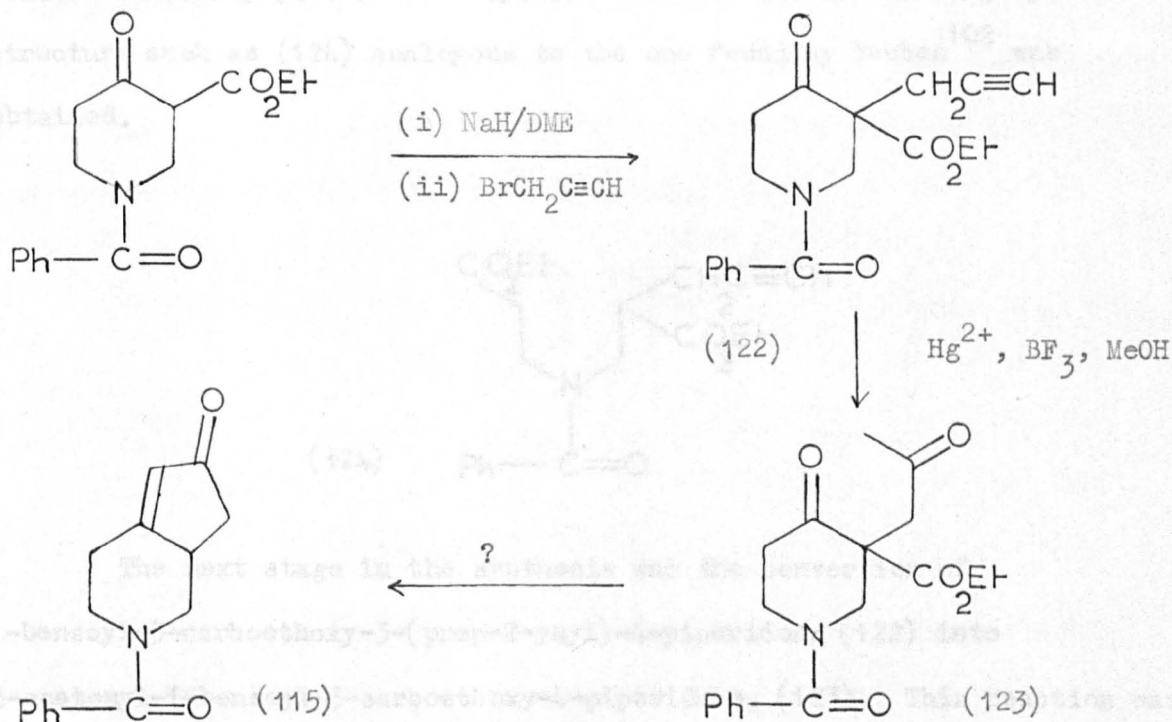
SCHEME XIX

The alkylation of 1-benzoyl-3-carboethoxy-4-piperidone with propargyl
bromide in dimethoxyethane gave a 72% yield of 1-benzoyl-3-carboethoxy-
-3-(prop-2-ynyl)-4-piperidone (122). This compound was difficult to purify,
distillation leading to decomposition, and chromatography on Spence

grade H alumina resulting in extensive hydrolysis of the amide linkage.
Woelm alumina grade V proved satisfactory for the purification of the
compound. The infrared spectrum of the compound (122) in carbon tetra-
chloride indicated that C-alkylation had occurred. The hydrogen attached
to the triple bond was shown as a sharp peak at 3300 cm.$^{-1}$, while the
ester and ketone carbonyl groups appeared in a band at 1725 cm.$^{-1}$
with a shoulder at 1730 cm.$^{-1}$. The n.m.r. spectrum in carbon tetrachloride
confirmed the presence of the propynyl group. The acetylenic hydrogen
was found as a triplet centred at 1.9 p.p.m. (J = 2 c.p.s.). The
methylene group adjacent to the triple bond was shown as a doublet
centred at 2.55 p.p.m. (J = 2 c.p.s.). No evidence of any ring opened
structure such as (124) analogous to the one found by Dauben[102] was
obtained.

(124)
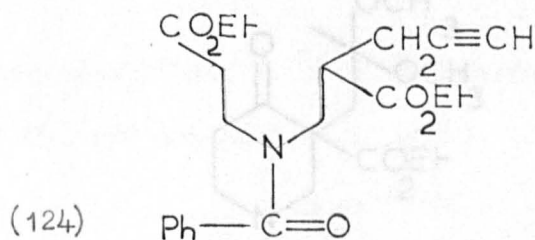
The next stage in the synthesis was the conversion of
1-benzoyl-3-carboethoxy-3-(prop-2-ynyl)-4-piperidone (122) into
3-acetonyl-1-benzoyl-3-carboethoxy-4-piperidone, (123). This reaction was
performed in methanol, using a catalyst prepared from boron trifluoride
etherate, mercuric oxide and tri-chloroacetic acid. The diketone was
isolated by pouring the reaction mixture into dilute sulphuric acid,
followed by ether extraction of the acid solution. Application of this

procedure to the compound (122), and purification of the products by
chromatography, yielded two compounds. One, a pale yellow oil comprising
approximately 70% of the product, was the required diketone (123). Its
infrared spectrum indicated the disappearance of the acetylene band. The
carbonyl region was not resolved, however, and showed only one peak at
1730 cm.$^{-1}$, with a pronounced shoulder at 1720 cm.$^{-1}$. The n.m.r. spectrum
confirmed the presence of an acetonyl group, since it showed a three
proton singlet at 2.05 p.p.m.

The second compound was a crystalline solid, m.pt. 77°.
Its infrared spectrum showed no acetylene band, and the carbonyl region
closely resembled that of the diketone, (123). The n.m.r. spectrum
indicated a three proton singlet at 1.48 p.p.m. and two 3-proton singlets
at 3.2 and 3.3 p.p.m. respectively. This information enabled the
compound to be identified as the methyl ketal (125).

(125)   Ph — C=O
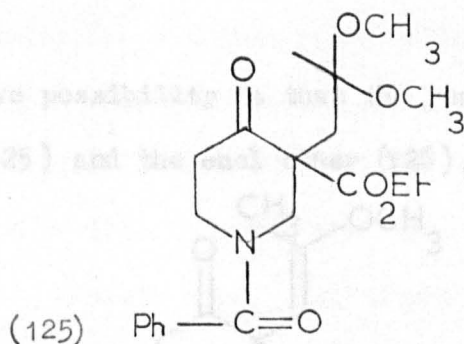
This compound was stable to treatment with cold dilute sulphuric acid.
Cleavage of the ketal group was brought about by boiling a carbon
tetrachloride solution of the ketal with dilute sulphuric acid on a
water bath for approximately twenty minutes. The n.m.r. spectrum of
the carbon tetrachloride solution then indicated the presence of the

- 58 -

diketone (123).

The surprising stability of the ketal (125) can be explained in two ways. Firstly, it is possible that the alkylation of 1-benzoyl-3--carboethoxy-4-piperidone with propargyl bromide may give two epimers, (122a) and (122b), although the infrared and n.m.r. spectra showed no evidence of epimeric products.
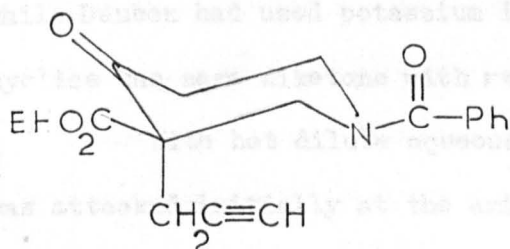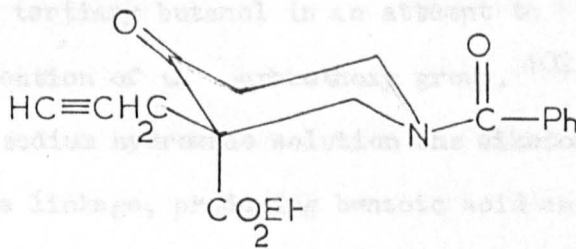
(122(a))   (122(b))

If two epimers were produced, then this would infer that two methyl ketals should then be produced and only one of these may be readily converted to the diketone (123).

An alternative possibility is that the reaction product is a mixture of the ketal (125) and the enol ether (126).
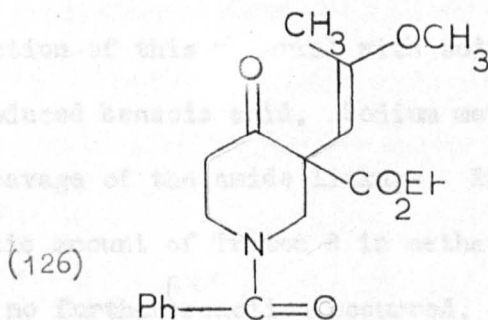
(126)

The reaction of acetylenes with alcohols in the presence of mercuric ion or boron trifluoride is known to give a ketal, and this reaction presumably proceeds through the enol ether.[104] A mercuric complex is an intermediate in these reactions, although the mechanism is not completely understood.

If the enol ether were present at the end of the reaction it would be readily hydrolysed to the diketone (123) by cold dilute acid. Raphael reported only the diketone (117) as the hydration product of the acetylene (116).

The last stage of the synthesis involved ring closure. Raphael and Islam had used aqueous base for the cyclisation of the diketone (117),[100] while Dauben had used potassium in tertiary butanol in an attempt to cyclise the same diketone with retention of the carboethoxy group.[102]

With hot dilute aqueous sodium hydroxide solution the diketone (123) was attacked initially at the amide linkage, producing benzoic acid and a black intractable tar. It was thought that tertiary butoxide would be a sufficiently large anion for the hydrolysis of the amide linkage to be sterically hindered. Brief treatment of the diketone (123) with potassium in tertiary butanol at room temperature gave mainly unchanged starting material. Boiling the solution under reflux for thirty minutes produced a darkening of the reaction mixture, and a black residue was produced. This crude material showed no vinyl hydrogen in its n.m.r. spectrum, and extraction of this material with sodium bicarbonate and re-acidification, produced benzoic acid. Sodium methoxide in methanol also resulted in cleavage of the amide linkage. Reaction of the diketone (123) with a catalytic amount of Triton B in methanol resulted in trans-esterification, and no further reaction occurred. The hydrolysis of the amide linkage complicates any cyclisation that may occur. A cyclised compound such as (115), if hydrolysed at the amide linkage will give a compound structurally related to tecomanine (37). It is known that tecomanine is very unstable to aqueous base.[105]

Attempts at acid catalysed cyclisation, involving the boiling
of the diketone (123) in glacial acetic acid containing varying percentages
of hydrogen chloride were unsuccessful, resulting in cleavage of the amide
grouping, or lack of reaction. While the ease of cleavage of the
benzamide linkage may be the principal reason for the failure of the
cyclisation reaction, there is a possibility of a different type of
cleavage occurring in the diketone (123), especially on treatment with
basic reagents. A base catalysed retro-Michael reaction could occur if
the carbonyl group of the ring were to enolise at a rate comparable with
the rate of enolisation of the carbonyl group of the acetonyl substituent.
This could give rise to structures such as (127).

(127)
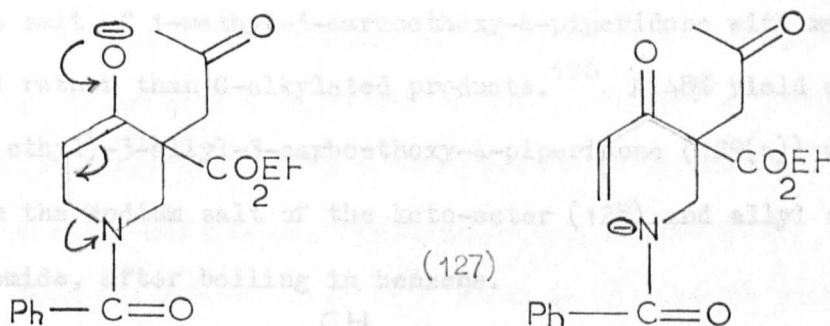
It is conceivable that structures such as (127) could be in tautomeric
equilibrium with the corresponding cyclic structures, especially when
one considers the facile addition of the anions derived from benzamide to
unsaturated esters.

c) Alkylation reactions of 1-benzyl-4-piperidones

One of the major obstacles to the completion of the synthesis

of 2-benzoyl-1,2,3,4,7,7a-hexahydro-6H-2-pyrindin-6-one (115) was the

hydrolysis of the amide group which occurred when attempts were made

to cyclise the diketone (123). Since the yields in all stages of the

synthesis of this diketone were good, it was felt that study of this

synthetic route should be continued. It was decided to attempt an

application of this synthesis to a basic 4-piperidone derivative.

The C-alkylation of basic keto-esters by means of enolate

anions is not a satisfactory reaction. McElvain found that the reaction

of the sodium salt of 1-methyl-3-carboethoxy-4-piperidone with methyl

iodide gave N rather than C-alkylated products.[106] A 48% yield of

1-(2'-phenyl ethyl)-3-allyl-3-carboethoxy-4-piperidone (129(a)) was

obtained from the sodium salt of the keto-ester (128) and allyl dimethyl

anilinium bromide, after boiling in benzene.

(128)
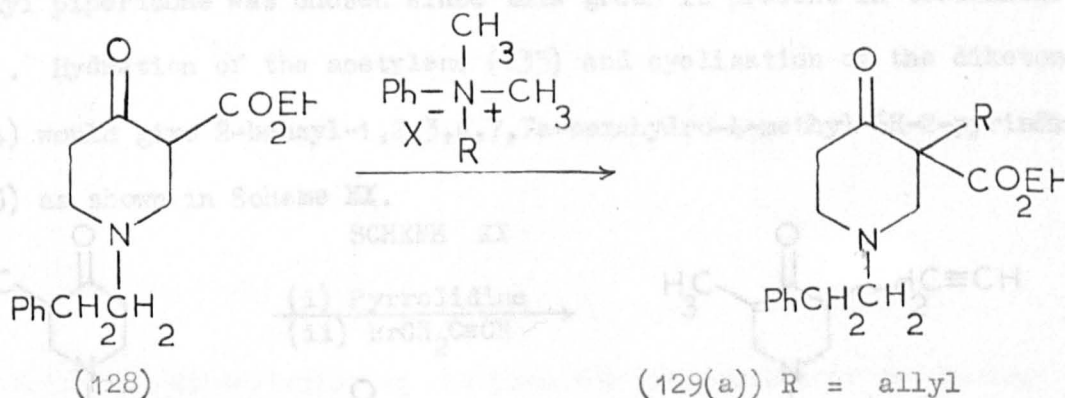
(129(a)) R = allyl
(129(b)) R = benzyl

With benzyl dimethyl anilinium chloride a 72% yield of (129(b)) was

obtained.

Clemo has alkylated the basic keto-ester (130) with methyl

iodide in the presence of potassium ethoxide and obtained a 38% yield

of the methyl ketone (131).[107]
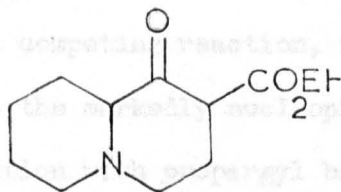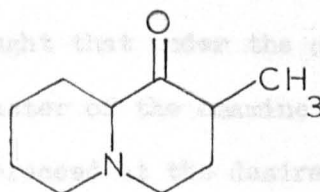
(130)   (131)

The low yields encountered in this type of preparation prompted a
study of other methods of alkylating a basic ketone in the position
adjacent to the carbonyl group. The successful use of enamines as
intermediates in the alkylation of ketones,[108] suggested that they might
be useful in a synthesis of the 1,2,3,4,7,7a-hexahydro-6H-2-pyrindin-6-one
system. It was decided to attempt an enamine alkylation of 1-benzyl-
-3-methyl-4-piperidone (132) with propargyl bromide in the hope of
obtaining 1-benzyl-3-methyl-5-(prop-2-ynyl)-4-piperidone (133). The
methyl piperidone was chosen since this group is present in tecomanine
(37). Hydration of the acetylene (133) and cyclisation of the diketone
(134) would give 2-benzyl-1,2,3,4,7,7a-hexahydro-4-methyl-6H-2-pyrindin-6-one
(135) as shown in Scheme XX.

SCHEME   XX

(i) Pyrrolidine
(ii) BrCH$_2$C≡CH

(132)

(135)

(134)

(133)

Hg^{2+}, BF$_3$, MeOH

- 63 -
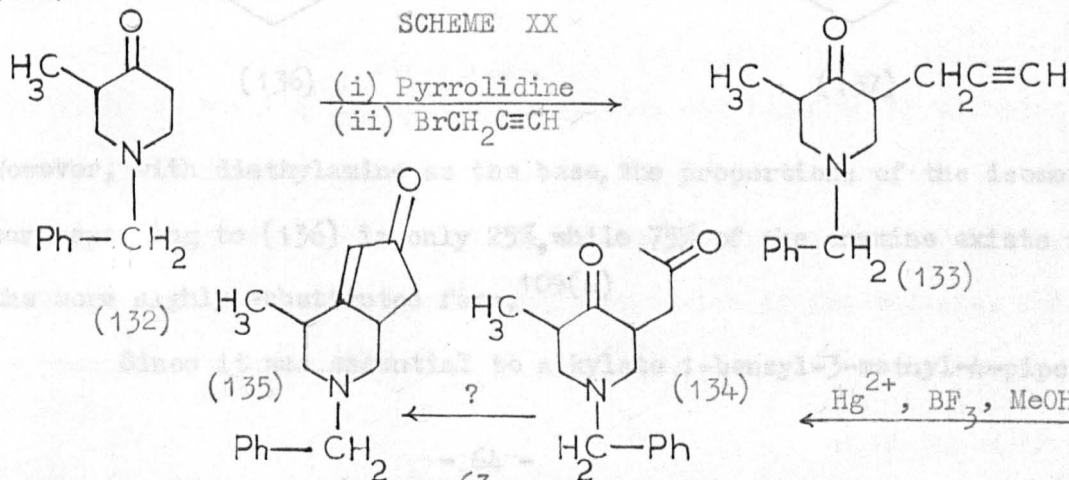
No enamines of basic ketones have been alkylated with reactive halides.
While aware that alkylation on the nitrogen in the piperidone ring
would be a competing reaction, it was thought that under the correct
conditions, the markedly nucleophilic character of the enamine would
allow reaction with propargyl bromide to proceed at the desired position
a to the carbonyl group.

The structure of the enamine from 2-substituted cyclohexanones
has been extensively studied.[109] Experimental results indicated that
alkylation of the enamine derived from a 2-substituted ketone occurred at
the 6-position, implying that the direction of enamine formation was
towards this unsubstituted position in the ketone. A large proportion
of these enamine reactions use pyrrolidine as the basic co-reactant with
the ketone. It has been shown that the pyrrolidine enamine of 2-methyl
cyclohexanone is composed of 90% of the compound (136), and 10% of its
isomer (137).[109(a)]
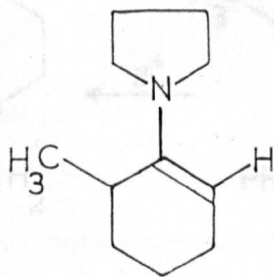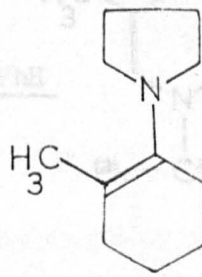
(136)   (137)

However, with diethylamine as the base, the proportions of the isomer
corresponding to (136) is only 25%, while 75% of the enamine exists in
the more highly substituted form.[109(a)]

Since it was essential to alkylate 1-benzyl-3-methyl-4-piperidone

in the 5-position, pyrrolidine was chosen as the base for the reaction. 1-Benzyl-3-methyl-4-piperidone was chosen for the synthesis because its preparation was straightforward, and because the 1-benzyl group provided two sets of characteristic hydrogen atoms, which might be useful in n.m.r. analyses of the reaction products. The benzyl group could possibly be converted, at a later stage, into a N-CH$_3$ group, by hydrogenolysis and methylation. 1-Benzyl-3-methyl-4-piperidone was synthesised by the method of Carabateas and Grumbach[110] outlined in Scheme XXI.

$$PhCH_2NH_2 \ + \ CH_2=\overset{\overset{\displaystyle CH_3}{|}}{C}-CO_2Me \ \xrightarrow{\ MeOH, \ \Delta\ } \ PhCH_2N\overset{\overset{\displaystyle CH_3}{|}}{CH_2CH}-CO_2Me$$

SCHEME XXI

The **yield** on the initial addition reaction was improved by allowing the reactants to stand at room temperature for a week or longer. Carabateas and Grumbach were able to dissolve the sodium enolate of the keto-ester (140) by adding water to the benzene suspension of the enolate, followed by concentrated hydrochloric acid, giving an overall acid strength of

approximately 45%. On following their procedure, the hydrochloride of

the keto-ester was precipitated by the addition of concentrated

hydrochloric acid to the aqueous benzene solution. This hydrochloride was

found to be fairly insoluble in cold 45% hydrochloric acid and boiling

of the solution was required to dissolve the hydrochloride and promote

the decarbomethoxylation reaction. Isolation of the free base gave

1-benzyl-3-methyl-4-piperidone in approximately 40% overall yield from

benzylamine. It showed a rather broad carbonyl band at 1715 cm.$^{-1}$

(liquid film) and strong bands at 2780 cm.$^{-1}$ and 2800 cm.$^{-1}$ These latter

bands are presumably Bohlmann bands,[111] due to the interaction of the

trans-2,6-diaxial hydrogens with the nitrogen lone pair as shown in

fig. (141).
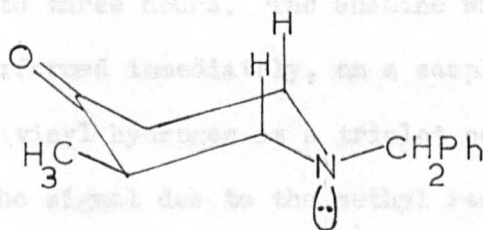
(141)

The n.m.r. spectrum of the ketone in carbon tetrachloride solution

showed a sharp 2-proton peak at 3.65 p.p.m. due to the benzyl group,

and a three proton doublet centred at 0.91 p.p.m. (J = 6 c.p.s.) due

to the methyl group. Each peak of this doublet had a small ill

resolved shoulder on it. Since the ketone has been boiled with acid,

the methyl group would be expected to have the more stable equatorial

position. The shoulders on the n.m.r. signal due to this group may
be due to the presence of a small percentage of the epimer with the
methyl group in the axial position.

The enamine of 1-benzyl-3-methyl-4-piperidone (142) was prepared
in 85% yield by standard procedures.[108]

H$_3$C   N   H

(142)   Ph—CH$_2$
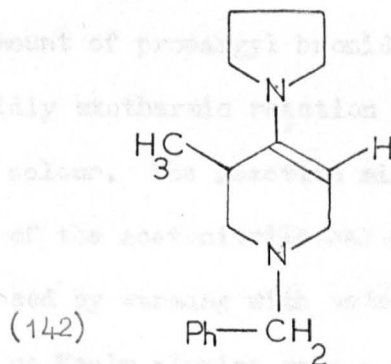
The use of para-toluene sulphonic acid reduced the time required for
complete reaction to three hours. The enamine was distilled, and its
n.m.r. spectrum performed immediately, on a sample of the distillate.
It showed a single vinyl hydrogen as a triplet centred at 4.05 p.p.m.
(J = 2 c.p.s.). The signal due to the methyl resonance appeared as a
doublet centred at 1.16 p.p.m., the shift to a lower field being due
to the effect of the allylic double bond. The signal due to the benzylic
methylene group was composed of two peaks, separated by 0.04 p.p.m. This
rather unusual effect, which is not present in the enamine of 1-benzyl-4-
-piperidone, must be due to the conformation of the enamine, causing the
two hydrogens of the benzyl group to become non-equivalent. Comparison
of the integrated proton signals of the vinyl and benzyl hydrogens con-
firmed that the enamine had formed exclusively in the required direction,
that is, away from the 3-methyl group.

The reaction of the enamine (142) with propargyl bromide was initially performed in acetonitrile solution. This solvent system had been used for the reaction of propargyl bromide with the enamine of the ethylene glycol monoketal of 1,4-cyclohexanedione.[112] The freshly distilled enamine, a pale yellow oil, was dissolved in acetonitrile and an equimolar amount of propargyl bromide was added at room temperature. A mildly exothermic reaction occurred, and the solution became dark red in colour. The reaction mixture was boiled for one hour then the bulk of the acetonitrile was removed under vacuo. The enamine was decomposed by warming with water. Extraction of the product, and chromatography on Woelm alumina gave a 47% yield of 1-benzyl-3-methyl-5-(prop-2-ynyl)-4-piperidone (133) as a pale yellow oil. The infrared spectrum in carbon tetrachloride solution showed a band at 3308 cm.$^{-1}$ with a slight shoulder at 3300 cm.$^{-1}$. Bohlmann bands appeared at 2780 cm.$^{-1}$ and 2800 cm.$^{-1}$. The n.m.r. spectrum showed the acetylenic hydrogen as a poorly defined triplet at 1.8 p.p.m. The methylene group adjacent to the triple bond was not clearly resolved. The doublet due to the methyl group was centred at 0.9 p.p.m.

Two other compounds were also obtained from this alkylation reaction. One was an extremely hygroscopic solid, which formed a tar on brief exposure to the atmosphere. An analytical sample could not be obtained, but the infrared spectrum showed the presence of an acetylene group and a carbonyl group. In addition, weak bands in the region 2700 cm.$^{-1}$ - 2400 cm.$^{-1}$ indicated that the compound was a quaternary salt. The compound is probably produced by the N-alkylation of the piperidone ring

with propargyl bromide.

The first compound to be isolated from the chromatography
of the crude product was a colourless liquid. Its infrared spectrum
showed an acetylene hydrogen at 3300 cm.$^{-1}$. No carbonyl group appeared
to be present in the molecule. The n.m.r. spectrum showed only four
peaks. A 5-proton aromatic signal occurred at 7.38 p.p.m., and a
benzylic methylene group was shown at 3.75 p.p.m. A sharp 4-proton
doublet centred at 3.47 p.p.m. (J = 2 c.p.s.), and a sharp two proton
triplet at 2.25 p.p.m. (J = 2 c.p.s.), were the only remaining peaks.
This information led to the structure (143) for this compound. This
was confirmed by analysis.

$$HC \equiv C \qquad \qquad C \equiv CH$$

(143)
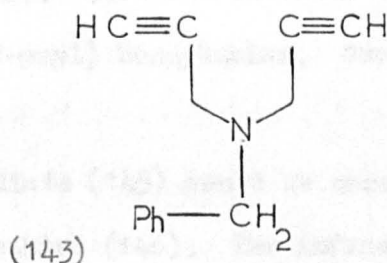
The production of N,N-di(prop-2-ynyl) benzylamine (143) from the
enamine reaction can be explained if initial reaction of the enamine (142)
with propargyl bromide occurs at the nitrogen in the 4-piperidone ring.
This will produce the intermediate (144).

(144)

$$\text{(145)} \longrightarrow \text{(146)} \longrightarrow \text{PhCH}_2\text{NCH}_2\text{C}\equiv\text{CH} \quad (147)$$

$$\text{(148)} \longrightarrow \text{(143)}$$
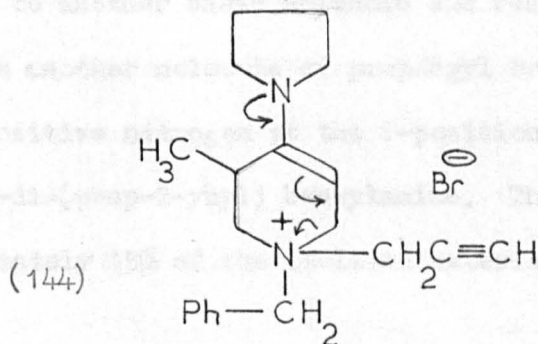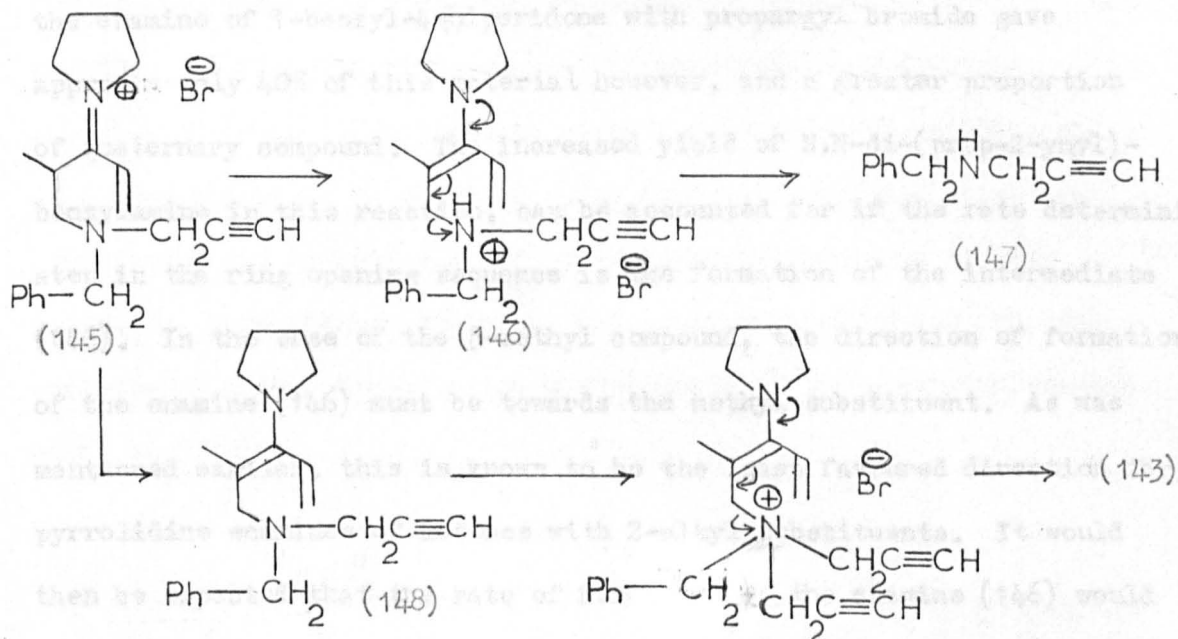
This intermediate can ring open as indicated in fig. (144), to give a structure such as (145). Several reactions of this intermediate could lead to N,N-di(prop-2-ynyl) benzylamine. Two possible paths are shown in the above sequence.

The intermediate (145) could be converted by a proton transfer reaction, into the enamine (146). The influence of the positive charge on the nitrogen adjacent to the benzyl group could then cause a second ring opening reaction, to give the compound (147). This amine would then react with any unreacted propargyl bromide to give N,N-di-(prop-2--ynyl) benzylamine. An alternative reaction of intermediate (145) is a proton transfer to another basic molecule and reaction of the uncharged enamine (148) with another molecule of propargyl bromide. This would again produce a positive nitrogen at the 1-position and ring opening would lead to N,N-di-(prop-2-ynyl) benzylamine. This compound only comprised approximately 15% of the isolated material. The reaction of

the enamine of 1-benzyl-4-piperidone with propargyl bromide gave approximately 40% of this material however, and a greater proportion of quaternary compound. The increased yield of N,N-di-(prop-2-ynyl)-benzylamine in this reaction, can be accounted for if the rate determining step in the ring opening sequence is the formation of the intermediate (146). In the case of the 3-methyl compound, the direction of formation of the enamine (146) must be towards the methyl substituent. As was mentioned earlier, this is known to be the least favoured direction for pyrrolidine enamines of ketones with 2-alkyl substituents. It would then be expected that the rate of formation of the enamine (146) would be slower than the rate of formation of the unsubstituted enamine derived from 1-benzyl-4-piperidone.

In an attempt to reduce the quantity of quaternary material and N,N-di-(prop-2-ynyl)-benzylamine, different reaction conditions were studied. It was felt that a polar solvent, such as acetonitrile, might not be the best solvent for the enamine alkylation, since it would dissolve any quaternary material produced in the reaction, and stabilise any ionic intermediates present in solution. The effect of heat on the reaction was also considered. It was felt that the reactive enamine group would still undergo alkylation at a low temperature, while heating the reaction mixture, although it would enhance the rate of this reaction, might also promote N-alkylation to an even greater extent. Accordingly, the enamine of 1-benzyl-3-methyl-4-piperidone was dissolved in benzene and reacted with propargyl bromide for forty hours at room temperature. An orange oil precipitated from the reaction mixture after three to four hours stirring. A sample of this oil was

warmed with water and extracted to obtain the organic material. This
was found to be 1-benzyl-3-methyl-5-(prop-2-ynyl)-4-piperidone. After
allowing the reaction mixture to stand for forty hours, a 63% yield of
this compound could be obtained. The amounts of N,N-di-(prop-2-ynyl)-
benzylamine and intractable quaternary material produced by this
technique, were greatly reduced. The solid separating out from the
reaction must presumably be the hydrobromide of the alkylated enamine
(149) or (150).

(150) (149)
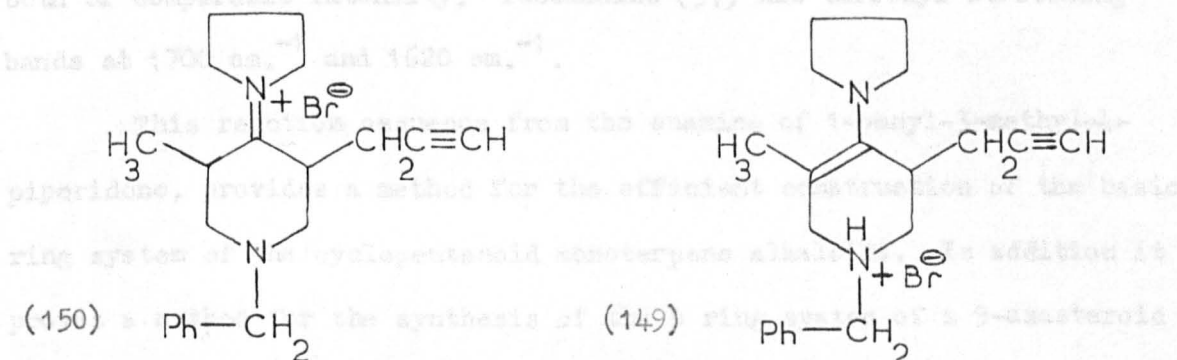
The yield in this alkylation reaction is high, compared with the yield
usually obtained by enamine alkylation of 2-substituted ketones. This
is presumably due to the precipitation of the intermediate (149) or
(150) as it is formed.

The hydration of this compound was performed with the boron
trifluoride - mercuric oxide catalyst in methanol. The methanol
solution was concentrated, filtered from the inorganic material and
heated for twenty minutes at approximately 50° with a 10% aqueous solution
of dilute sulphuric acid. Basification with sodium carbonate, and
ether extraction gave 3-acetonyl-1-benzyl-5-methyl-4-piperidone (134)
in 70% yield. This compound, like the acetylene precursor, was unstable
to distillation, and was purified by chromatography on alumina.

Cyclisation of the diketone (134) was accomplished by treatment with potassium in tertiary butanol at room temperature for thirty minutes. The product, after chromatography on alumina, yielded a compound shown to be 2-benzyl-1,2,3,4,7,7a-hexahydro-4-methyl-6H-2-pyrindin-2-one (135). The n.m.r. spectrum indicated a vinyl hydrogen at 5.76 p.p.m. The centre of the methyl signal was shifted downfield to 1.1 p.p.m. The infrared spectrum of (135) showed carbonyl stretching at 1705 cm.$^{-1}$ and 1620 cm.$^{-1}$, both of comparable intensity. Tecomanine (37) has carbonyl stretching bands at 1700 cm.$^{-1}$ and 1620 cm.$^{-1}$.

This reaction sequence from the enamine of 1-benyl-3-methyl-4-piperidone, provides a method for the efficient construction of the basic ring system of the cyclopentanoid monoterpene alkaloids. In addition it proves a method for the synthesis of the D ring system of a 9-azasteroid from a precursor such as (66).
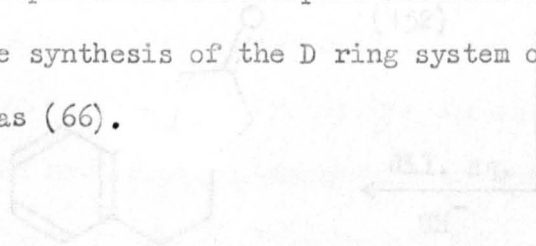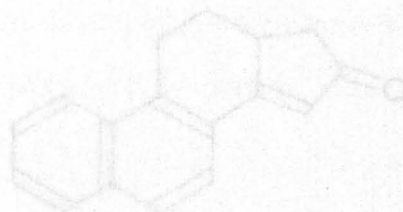
d)   Syntheses of 3-bromo-4-piperidone derivatives.

The reaction of an α-bromo ketone with the sodium salt of a β-keto-ester has been used to produce 1,4-diketones. For example, 2-bromo-1-tetralone (151) will react with ethyl acetoacetate to give the compound (152). This compound can be cyclised with dilute aqueous base to the cyclopentenone derivative (153) as shown below.[113]

$$\text{(151)} \xrightarrow{\text{CH}_3\text{COCH}_2\text{CO}_2\text{Et}} \text{(152)}$$

(153) $\xleftarrow{\text{dil. aq. OH}^-}$ (152)
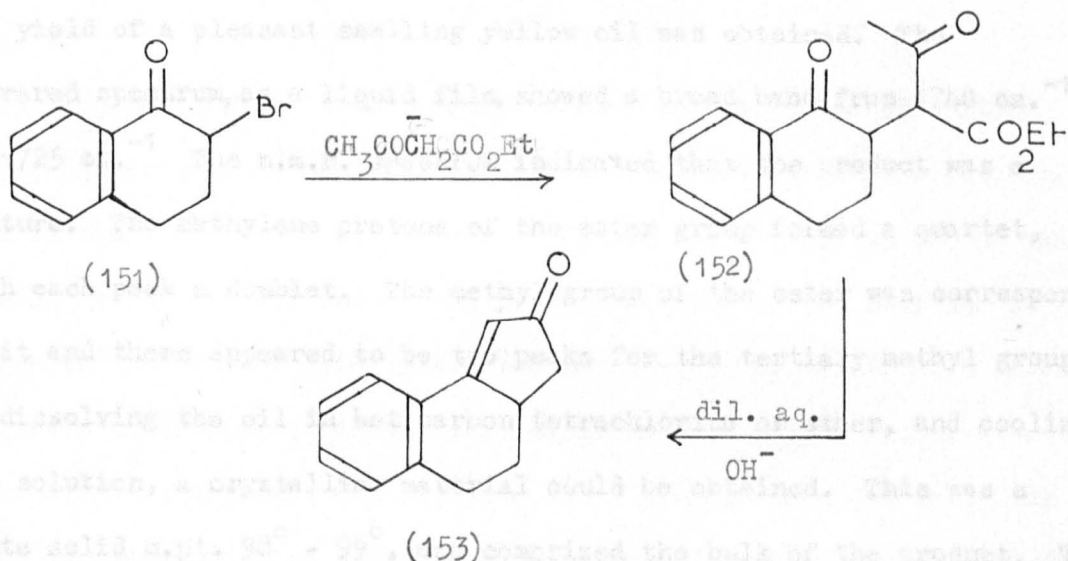
This type of reaction has been applied to the synthesis of steroid analogues, such as (154), from the tricyclic bromo-ketone (155).[114]

(155)   (154)
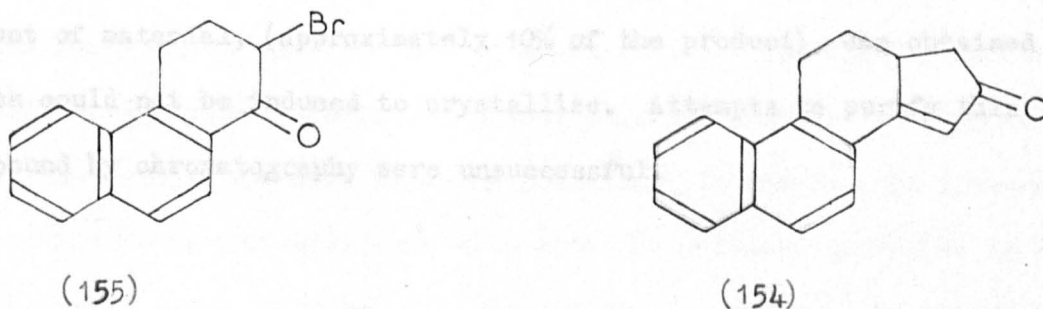
As a preliminary step in the application of this type of synthesis to the production of a 1,2,3,4,7,7a-hexahydro-6H-2-pyrindin-6-one system, the bromination reactions of 1-benzoyl-4-piperidone derivatives were studied.

The bromination of 1-benzoyl-3-carboethoxy-3-methyl-4-piperidone (100) was performed in chloroform, at room temperature, and the solution was allowed to stand overnight before isolation of the product. An 85% yield of a pleasant smelling yellow oil was obtained. The infrared spectrum, as a liquid film, showed a broad band from 1740 cm.$^{-1}$ to 1725 cm.$^{-1}$ The n.m.r. spectrum indicated that the product was a mixture. The methylene protons of the ester group formed a quartet, with each peak a doublet. The methyl group of the ester was correspondingly split and there appeared to be two peaks for the tertiary methyl group. On dissolving the oil in hot carbon tetrachloride or ether, and cooling the solution, a crystalline material could be obtained. This was a white solid m.pt. 98° - 99°, and comprised the bulk of the product. This compound was also produced when the bromination was performed in an ether-acetic acid solution, and the product isolated after allowing the solution to stand for 1/2 hr. Under both types of reaction conditions, a small amount of material, (approximately 10% of the product), was obtained which could not be induced to crystallise. Attempts to purify this compound by chromatography were unsuccessful.

The crystalline material analysed as a mono-bromo compound, and was given the structure (156).

(156)

The stereochemistry of this compound proved of some interest. Its infrared spectrum, in cyclohexane solution, showed carbonyl stretching at 1725 cm.$^{-1}$ and 1720 cm.$^{-1}$, both of comparable intensity, and an amide carbonyl group at 1660 cm.$^{-1}$ The n.m.r. spectrum of the compound in deuterochloroform solution showed the tertiary methyl group as a sharp singlet at 1.37 p.p.m., a downfield shift of 0.16 p.p.m. relative to the unbrominated compound. The proton in the 3 position and the methylene group in the 2 position had also been shifted downfield, and appeared as a complex multiplet around 5.0 p.p.m.

The carbonyl stretching frequency of the α-bromoketone showed no change from that of the starting material, 1-benzoyl-3-carboethoxy-3-methyl-4-piperidone. The work of Jones et al.,[115] and Corey,[116] on the carbonyl frequencies of α-bromoketones, suggests that in the compound (156) the bromine occupies an axial position. In general, the presence of bromine in an equatorial position α to the carbonyl group (as in fig. (157)), leads to an increase of around 10 cm.$^{-1}$ - 20 cm.$^{-1}$ in the carbonyl

stretching frequency.
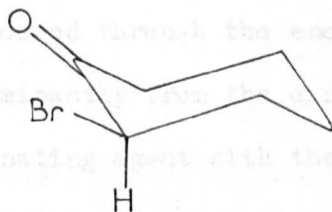
(157)   (158)
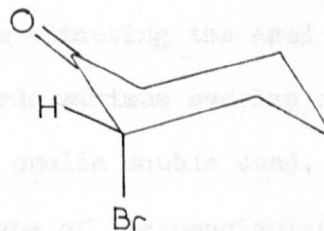
An axial α-bromoketone, such as (158), in which the reduction of dipole
repulsion effects compensates for any steric interaction, shows
essentially no change in its carbonyl stretching frequency.

The downfield shift of the methyl group in (156) is presumably
due to the steric effect of the bromine, since it would alter the
environment of the methyl group, whether the methyl group was in an
axial or an equatorial position.

The unusual feature of this reaction however, is the fact that
the major product is the epimer with the bromine in the axial position.
The reaction in chloroform shows an induction period, but then proceeds
rapidly, and the resulting solution must presumably contain hydrobromic
acid. Leaving this chloroform solution overnight might be expected to
cause equilibration of the axial bromine, (the product of kinetically
controlled bromination), into a conformation with the bromine equatorial.
Corey showed that the equilibrium constant for the reaction axial bromine
equatorial bromine was approximately 2.5, for 2-bromo-6,6-dimethyl-
cyclohexanone in chair conformations. The corresponding equilibrium
constant for 2-bromo-cyclohexanone is more than 50.[117]

The mechanism of the bromination of ketones has been investigated by several workers.[118] Bromination of ketones is thought to proceed through the enol form, the bromine attacking the enol predominantly from the direction which affords maximum overlap of the brominating agent with the π orbital of the enolic double bond. Valls and Toromanoff have pointed out that this type of "perpendicular" attack on the enol may involve either parallel attack, in which the bromine approaches the double bond from the same side as the pseudoaxial bond (see fig. (159)), or anti-parallel attack (see fig. (160)), which results when the bromine approaches from the opposite side.[119]

(159) (162) (163)

(160) (161)
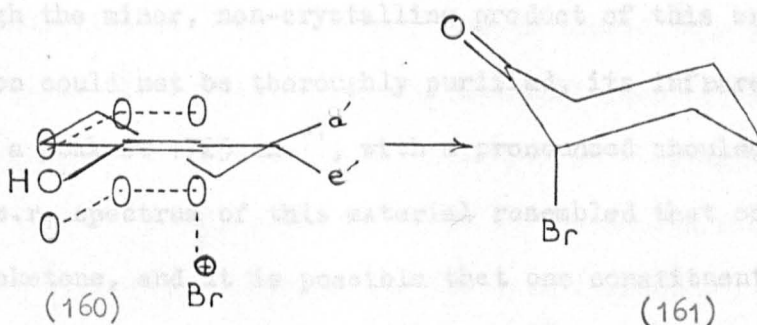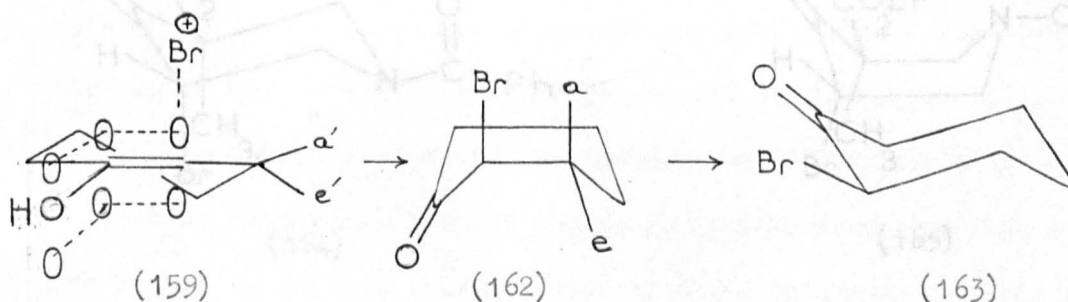
The product in the latter case is an axial α-bromoketone (161), and in the absence of opposing steric effects this is the usual mode of attack.

Steric hindrance can cause parallel addition however, to give the initial boat conformation (162). In general this boat conformation undergoes a ring flip to the chair conformation (163).

The application of this theory to the bromination of 1-benzoyl-3-carboethoxy-3-methyl-4-piperidone suggests that either an axial conformation such as (164) is produced, in which the epimer with the axial bromine atom is the predominant product, or alternatively that the a-bromoketone is in a boat form such as (165).
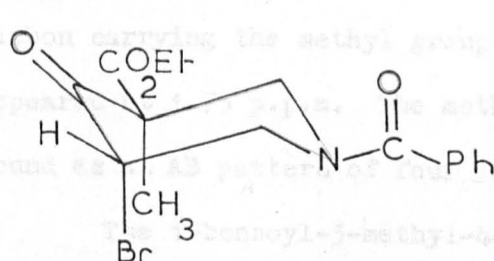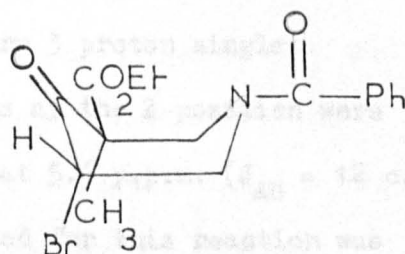
(164)   (165)

Although the minor, non-crystalline product of this bromination reaction could not be thoroughly purified, its infrared spectrum showed a peak at 1725 cm.$^{-1}$, with a pronounced shoulder at 1740 cm.$^{-1}$ The n.m.r. spectrum of this material resembled that of the crystalline a-bromoketone, and it is possible that one constituent of this mixture could be an a-bromo-ketone with an equatorial bromine.

The bromination products of 1-benzoyl-3-methyl-4-piperidone were then investigated. Under the same conditions as those used for

the bromination of 1-benzoyl-3-carboethoxy-3-methyl-4-piperidone, a
yellow oil was obtained, which resisted attempts at crystallisation.
The oil was purified by chromatography, although it was impossible to
obtain consistent analyses on this compound or any of its derivatives.
Analytical figures did indicate that the compound contained only one
bromine atom. The infrared spectrum of the compound, in carbon
tetrachloride solution, showed a strong band at 1740 cm.$^{-1}$ The parent
ketone showed a carbonyl absorption at 1725 cm.$^{-1}$ in the same solvent.
The n.m.r. spectrum indicated that bromination had occurred at the
carbon carrying the methyl group, since a sharp 3 proton singlet
appeared at 1.75 p.p.m. The methylene protons at the 2-position were
found as an AB pattern of four peaks centred at 5.6 p.p.m. (J_{AB} = 12 c.p.s.).

The 1-benzoyl-3-methyl-4-piperidone used for this reaction was
produced by decarboxylation of 1-benzoyl-3-carboethoxy-3-methyl-4-
piperidone, by boiling this compound with 50% hydrochloric acid. This
causes epimerisation of the methyl group, since the n.m.r. spectrum of
the hydrochloride of 3-methyl-4-piperidone showed four peaks in the
methyl region. Benzoylation of this hydrochloride in the presence of
potassium carbonate gave after distillation an oil, which solidified
to a pale yellow solid, m.pt. 57° - 58°. The n.m.r. spectrum of this
compound showed only a doublet for the methyl group. It is most likely
that the more stable conformation of this methyl group would be the one
in which it is equatorial to the 1-benzoyl-4-piperidone ring as in fig. (166).
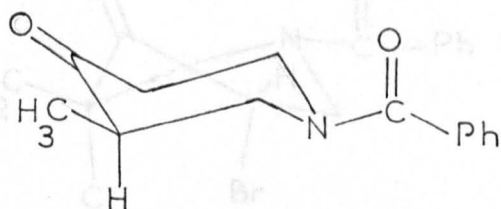
(166)

This would favour axial attack of the bromine, to give initially the epimer with the bromine axial. However, the bromo-ketone isolated from the reaction is the equatorial epimer, judging by the marked increase in the carbonyl stretching frequency. This suggests that the conditions of this reaction are equilibrating, and consequently the bromination of 1-benzoyl-3-carboethoxy-3-methyl-4-piperidone, (which was performed under the same conditions) gives rise to the equilibrium controlled product. The conformation of this bromo-ketone must thus lie somewhere between the extremes of a conformation such as (164) and a boat conformation such as (165), as mentioned earlier. A model of a twist-boat conformation (167) for this compound allows both 5 substituents to be the maximum distance away from the 3-bromo substituent. The 1-benzoyl group is still quasi equatorial, while the bromo substituent can occupy a position whereby the dihedral angle between it and the plane of the carbonyl group is large enough for the bromine sustituent not to have an appreciable effect on the carbonyl group.

(167)

Only one attempt was made to alkylate the bromoketone (156).
It was reacted with the sodium salt of ethyl-1-methyl-acetoacetate
(168) prepared from the β keto-ester by reaction with sodium hydride.
The major product of the reaction was 1-benzoyl-3-carboethoxy-3-methyl-
4-piperidone (100). This must have resulted from attack by hydride
ion on the bromo-ketone. The conversion of (168) to the sodium enolate must
have been incomplete, under the conditions used. A small amount of the
required compound 1-benzoyl-3(1'-carboethoxy-2'-keto-1'-methylpropyl)-
5-carboethoxy-5-methyl-4-piperidone (169) was isolated.

(168)   (169)
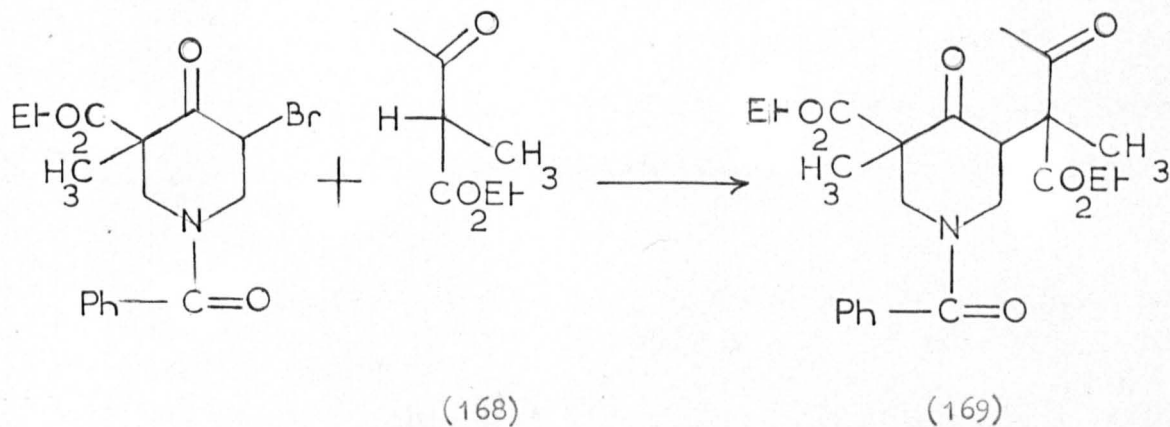
This type of reaction was not repeated however, since, at this

time, all attempts to cyclise the related 1,4 diketone (123) were
proving unsuccessful.

EXPERIMENTAL

Preliminary Notes

Melting points were determined on a Kofler block and are uncorrected.

Infrared absorption spectra were measured with Perkin Elmer Infracord, 221 and 257 spectrometers. The spectra of solids were determined as Nujol mulls, indicated by (Nujol) or in solution (e.g. CCl_4). The spectra of liquids were determined as liquid films (film) or in solution (e.g. CCl_4).

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Ultraviolet absorption spectra were measured on a Unicam SP 700 instrument.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin Elmer 60 megacycle instrument and are quoted in parts per million (p.p.m.) from an internal tetramethyl silane standard (0 p.p.m.).

Analytical gas liquid partition chromatography (v.p.c.) was performed on a 10 ft. spiral glass column packed with Gaschrom P coated with 1% SE-30 silicone grease.

All reactions involving dry solvents were carried out in an inert atmosphere.

Sodium hydride was used as a 50% by weight dispersion in liquid paraffin.

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Microanalyses were carried out by Drs. Weiler and
Strauss of Oxford and by Mr. John Boulton of Keele University.
by the method of Niccle and Berlinguet.

N-(5-methyl-cyclopentenyl)pyrrolidine

Freshly distilled 2-methyl-cyclopentanone [40 gms,(0.41 mole)]
and freshly distilled pyrrolidine [60 gms,(0.84 mole)] were added to
300 mls of dry benzene and the solution boiled under reflux for 16 hrs.
A water separating device was used to remove the water formed in the
reaction. The solvent was removed and the pyrrolidine enamine
distilled under an inert atmosphere. B.pt. 110°/20 mm. Yield 85%.

It was found that the reaction time could be reduced to
2 - 3 hrs by the addition of a trace of para-toluene sulphonic acid
before heating the solution.

The infrared spectrum showed the absence of a carbonyl group
and the formation of a band at 1640 cm., indicating an $\diagdown N - C = C$
group.

Ethyl α(2-keto-3-methyl-cyclopentyl)acetate (67)

The pyrrolidine enamine of 2-methyl-cyclopentanone [48 gms,
(0.32 mole)] was dissolved in 200 mls of dry benzene. Ethyl
α-bromoacetate [53.5 gms,(0.32 mole)] was added, dropwise during one
hour, to the stirred solution of the enamine, which was then boiled
under reflux for 3 hrs. After cooling the flask, a solution of 50 mls

2-Methyl-Cyclopentanone

This was prepared from diethyl adipate and methyl iodide
by the method of Nicole and Berlinguet,[93]

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hour, to the stirred solution of the enamine, which was then boiled
under reflux for 3 hrs. After cooling the flask, a solution of 50 mls

of methanol and 150 mls of water was added, and the solution boiled
under reflux for 1 hr. The benzene layer was then separated, dried
and distilled to give 23 gms (39%) of ethyl a(2-keto-3-methyl-cyclopentyl)-
acetate. B.pt. 134°/25 mm.

ν_{max}(film) 1730 cm.$^{-1}$ - 1740 cm.$^{-1}$(broad)

Found   C, 64.73; H, 8.94%

$C_{10}H_{16}O_3$ req.   C, 65.18; H, 8.75%

The 2,4-dinitrophenylhydrazone was prepared in ethanol and was
crystallised from absolute ethanol. M.pt. 135°.

Found   C, 52.90; H, 5.47; N, 15.23%

$C_{16}H_{20}N_4O_6$ req.   C, 52.74; H, 5.53; N, 15.38%

trans-Pulegenic acid and trans-methyl pulegenate (72)

trans-Pulegenic acid was prepared from D-pulegone by the method
of Wolinsky.[68(a)] It distilled as a yellow oil, b.pt. 106-8°/0.3 mm. The
method of Cavill gave an inferior yield.[68(b)]

trans-Methyl pulegenate was prepared in 90% yield by the
addition of an ethereal solution of diazomethane to an ethereal solution
of the acid. The ester distilled as a colourless liquid, B.pt. 112-115°/
12 mm.

$\nu_{C=O}$(film) 1735 cm.$^{-1}$

The n.m.r. spectrum showed peaks at 1.05 p.p.m. (centre of the
H - C - CH$_3$ doublet) and at 1.65 and 1.55 p.p.m. ((CH$_3$)$_2$C=).

cis and trans-Pulegenic acid

Prepared by the method of Wolinsky,[68(a)] cis and trans pulegenic acid distilled as a yellow-green oil, b.pt. 108°-118°/0.2 mm. V.p.c. analysis of the methyl esters indicated a percentage composition of approximately 60% cis and 40% trans.

cis and trans-Methyl pulegenate

Freshly distilled D(+)pulegone (50 gms, 0.35 mole) was mixed with 75 mls. of glacial acetic acid. Bromine (49 gms, 0.33 mole) was added dropwise to the cooled solution over $1\frac{1}{2}$ hrs, keeping the temperature of the reaction mixture below 5°. The solution was then stirred for 1 hr. The oily dibromide solution was poured onto 50 gms of crushed ice and the aqueous layer separated. After extraction of layer with 40/60 petroleum ether, the petrol extracts were combined with the dibromide, and shaken with a saturated solution of sodium bicarbonate. The colour of the petrol layer changed from red to pale yellow. After drying over Na_2SO_4 the petrol layer was added dropwise, over $1\frac{1}{2}$ hrs, to a solution of 23 gms (1 mole) of sodium in 300 mls of dry methanol. After refluxing for 2 hrs, this solution was cooled and poured into excess of 10% sulphuric acid. The solution was extracted with ether (4 x 200 mls) and the ether layer shaken with bicarbonate solution and then dried over Na_2SO_4. Distillation gave 43 gms of an oil boiling over a range 103 - 120°/0.3 mm. V.p.c. analysis of this oil showed it to be mainly a mixture of pulegone and the cis and trans esters of methyl pulegenate. Approximately 70% of the material was a

mixture of the esters. The esters could be separated from pulegone by careful fractional distillation under reduced pressure. The last traces of pulegone were removed by treatment of the mixture with Girard T. The mixture of cis and trans methyl pulegenate had the approximate composition 30% cis/70% trans.

Methyl- 5-methyl-cyclopentanone -2-carboxylate (68)

A solution of trans methyl pulegenate [9 gms (0.049 mole)] in 100 mls of ethyl acetate was cooled in an ice-salt bath and a steady flow of ozonized oxygen was bubbled through the solution. The progress of the reaction was followed by regular extraction of samples of the solution and v.p.c. analysis of their composition. The reaction was complete in approximately 4 hrs. The solution was then warmed with 100 mls of water to decompose the ozonide. Work-up of the organic layer gave methyl-5-methyl-cyclopentanone -2-carboxylate in 90% yield and essentially 100% purity. Acetone was detected as a product of the reaction by the formation of its 2,4-dinitrophenyl-hydrazone. The initial sample of keto-ester was distilled, b.pt. 94 - 96°/12mm but in subsequent reactions the crude product from the ozonolysis was found to be satisfactory.

$\gamma_{C=O}$(ketone) 1755 cm.$^{-1}$
$\gamma_{C=O}$(ester) 1728 cm.$^{-1}$ (liq. film)

Found   C, 61.68; H, 8.17%

$C_8H_{12}O_3$ req.   C, 61.52; H, 7.75%

4-Cyano-1,3-dihydroxy-6,7-dihydro-7-methyl-5H-2-pyrindine 69(a)

a) This was prepared by a method similar to that used by Prelog and Metzler in their preparation of 4-cyano-1,3-dihydroxy-6,7-dihydro-5H-2-pyrindine.[70]

Methyl-5-methyl-cyclopentanone -2-carboxylate [15 gms (0.096 mole)] was mixed with cyanoacetamide [8.1 gms (0.096 mole)]. A 50% solution of water in methanol was added dropwise, until a homogeneous solution was obtained when warm. Redistilled piperidine [3.0 gms (0.036 mole)] was then added, and the solution stirred for 3 days, while the temperature of the solution was kept at 50°. The solution was then cooled and made acid to Congo Red with 25% hydrochloric acid. A brown oil formed, which on scratching solidified to give 6.5 gms of crude yellow-red material. A further 0.5 gms was obtained by concentration of the filtrate. Total yield 36%. The compound was extremely difficult to recrystallise, from any of the standard solvents. From an ethanol-water mixture a very low recovery (15%) of material was obtained. This could be purified by repeated sublimation in vacuo. The compound thus obtained was in the form of pale yellow plates, m.pt. 217-219° (sublimes 179°-181° on slow heating).

$\nu_{(C\equiv N)}$ 2225 cm.$^{-1}$ (Nujol)

λ_{max} (EtOH) 263 mμ ($\log_{10} \varepsilon$ 3.45) and 333 mμ ($\log_{10} \varepsilon$ 3.80)

Found   C, 63.57; H, 5.76; N, 14.43%

$C_{16}H_{10}N_2O_2$ req.   C, 63.15; H, 5.3; N, 14.73%

b) Methyl-5-methyl-cyclopentanone-2-carboxylate [12 gms,
(0.076 mole)], cyanoacetamide [6.35 gms,(0.076 mole)] and piperidine
[5.5 gms,(0.076 mole)] were allowed to react under the conditions of
Bobbit and Scola.[71] After boiling for 24 hrs in methanol no crystals of
the piperidinium salt of 4-cyano-1,3-dihydroxy-6,7-dihydro-7-methyl-
-5H-2-pyrindine had formed. Working up the reaction as in preparation
a) gave only 0.5 gms of material, plus a large quantity of intractable
material.

c) Equmolar quantities of methyl 5-methyl cyclopentanone-2-
-carboxylate and ethyl cyanoacetate were stirred at room temperature with
28% NH_4OH for 2 days, following the method of Sakan.[72] No pyrindine
derivative could be isolated and the larger part of the reaction mixture
was unchanged starting material.

<u>Attempted preparation of ethyl α-cyano-α-(2-carbomethoxy-5-</u>
<u>-methylcyclopent-1-enyl)acetate</u>

Following the procedure of Ayerst and Schofield[73] an equimolar
mixture of methyl 5-methyl-cyclopentanone-2-carboxylate, ethyl cyano-
acetate and a catalytic amount of piperidine was set aside for 48 hrs.
Ether was then added and the mixture washed with dilute hydrochloric
acid. Distillation of the dried ethereal layer gave only a low
yield of a compound showing a nitrile, ester and ketone bands in its
infrared spectrum. The bulk of the residue was unchanged starting material.
Since only a low yield of condensation product was produced, the reaction
was not pursued.

Attempted preparation of 1,3-dihydroxy-6,7-dihydro-7-methyl--5H-2-pyrindine

Following the procedure of Prelog and Metzler 4-cyano-1,3--dihydroxy-6,7-dihydro-7-methyl-5H-2-pyrindine (5 gms) was heated with 40 mls of 48% constant boiling hydrobromic acid for 7 hrs. [70] On cooling no solid separated out and evaporation of the solution to dryness in vacuo gave only an intractable black tar.

4-Cyano-1,3-dichloro-6,7-dihydro-7-methyl-5H-2-pyrindine 69(b)

Crude 4-cyano-1,3-dihydroxy-6,7-dihydro-7-methyl-5H-2-pyrindine [6.2 gms (0.033 mole)] was heated with 16 mls (excess) phosphorus oxychloride for 6 hrs at 180° in a sealed tube. After cooling, the contents of the tube were poured onto crushed ice, and the black solid which formed was dissolved in chloroform. The aqueous layer was basified with carbonate and extracted with chloroform (3 x 30 mls). The chloroform extracts were combined and dried (Na_2SO_4). Removal of solvent and distillation of the residue in vacuo gave 2.5 gms of the desired product, b.pt. 120°/2.3 x 10^{-3} mm. Yield 31%.

ν C≡N 2220 cm.$^{-1}$

Found: C, 53.10; H, 3.66; N, 11.9%

$C_{10}H_{18}N_2Cl_2$ req. C, 52.88; H, 3.52; N, 12.3%

4-Cyano-6,7-dihydro-7-methyl-5H-2-pyrindine (70)

4-Cyano-1,3-dichloro-6,7-dihydro-7-methyl-5H-2-pyrindine [2.5 gms (0.011 mole)] was dissolved in 40 mls of methanol and sodium

acetate [1.75 gms (0.025 mole)] and 0.5 gms of a 5% palladium on charcoal catalyst were added. The solution was then hydrogenated at 23° and one atmosphere until uptake of hydrogen had ceased (approximately 12 hrs). The solution was filtered and made alkaline with sodium carbonate. It was then concentrated, and after adding water the solution was extracted with chloroform. The chloroform extracts were dried and after removal of solvent the residue was distilled in vacuo to give 1.0 grm. of 4-cyano-6,7-dihydro-7-methyl-5H-2-pyrindine, b.pt. 120°/0.1 mm. Yield 57%. A small amount of a higher boiling compound b.pt. 130°/0.1 mm was also produced.

The lower boiling compound showed infrared bands at 2240 cm.$^{-1}$ ($C\equiv N$) and 1580 cm.$^{-1}$ ($C=N$).

Its n.m.r. showed two aromatic protons at 8.45 p.p.m. and 8.52 p.p.m. with no visible splitting.

Consistent carbon analyses could not be obtained on this reduction product although hydrogen and nitrogen analyses were correct. This could be due to the presence of a trace of the higher boiling material.

This higher boiling material also appeared to be a pyrindine derivative, although it differed from the first fraction in the fingerprint region of its infrared spectra. It showed a strong absorption at 687 cm.$^{-1}$ in its infrared spectrum and was probably a partially reduced dichloro pyrindine derivative.

<u>Attempted preparation of</u> 6,7-<u>dihydro</u>-7-<u>methyl</u>-5H-2-<u>pyrindine</u>(38)

The hydrolysis of the nitrile group was attempted by following a method due to McElvain.[80]

4-Cyano-6,7-dihydro-7-methyl-5H-2-pyrindine [0.55 gms (0.0035 mole)] was added to a solution of sodium hydroxide [0.857 gms (0.021 mole)] in 50 mls of 70% alcohol. The solution was then refluxed until the smell of ammonia was no longer evident (approximately 6 hrs). The solution was then evaporated to dryness under reduced pressure and 5 mls of water were added, followed by enough dilute hydrochloric acid to make the solution just acid to litmus. After drying and removal of the solvent, a residue of 0.22 gms was left. This showed a carboxylic acid peak in the infrared, at 1685 cm.$^{-1}$. The material was taken up in sodium carbonate solution, and this solution evaporated to dryness under reduced pressure. Pyrolysis of this material, which presumably contained the sodium salt of the acid, was attempted. The material was heated in vacuo, but although a pungent odour was observed in the flask after the reaction, no organic material could be isolated.

1-Benzoyl-3-carbomethoxy-4-piperidone (84(b))

This was prepared following a modification of the method of Morsch.[83]

To a mixture of approximately 1 l. of liquid ammonia and 1 l. of absolute ethanol, cooled in a methanol-"Drikold" bath, methyl acrylate, (690 gms, 8 moles), at -60°, was added in one portion. The solution was then left 24 hrs. The ammonia, ethanol and methyl alanate were removed on a steam bath under reduced pressure. The residue was distilled under nitrogen, to give two main fractions. The initial distillate was N,N-di-(β-carbomethoxyethyl)amine, b.pt. 96° - 98° / 0.075 mm. Yield 45 gms. The second fraction boiled over the range 100° - 120° / 0·1 mm. and was a mixture of N,N-di(β-carbomethoxyethyl) amine and tri-(β-carbomethyoxyethyl)amine. Yield 40 gms. This fraction could not be separated by fractional distillation, since decomposition occurred on prolonged heating. Methyl acrylate was detected in the pumping system. The residue (approximately 250 gms.) from the distillation was shown to be essentially pure tri-(β-carbomethoxyethyl)amine. The secondary amino-ester (47 gms, 0.246 mole), and benzoyl chloride (38 gms, 0.27 mole), were heated in dry benzene for 16 hrs. The N,N-di(β-carbomethoxyethyl)benzamide produced was isolated as an oil, b.pt. 196° / 0.6 mm. Yield 48 gms, 65%. Attempts to benzoylate the tri-(β-carbomethoxyethyl)amine were unsuccessful, decomposition occurring and only very low yields of the desired

compound being produced.

The N,N-di-(β-carbomethoxyethyl)benzamide was cyclised with sodium hydride in benzene, following the procedure of McElvain.[81(b)] Yield 75%.

The crude product was an oil. This could be crystallised from 40/60 petroleum ether as white needles, m.pt. 73° - 75° (Ganellin and Spickett subsequently reported the preparation of this compound.[82] Their product had m.pt. 50° - 60° from 40/60 petrol).

ν_{max} (CCl$_4$) = 1720 cm.$^{-1}$ ($\begin{smallmatrix}\text{ketone}\\\text{ester}\end{smallmatrix}$ C=O), 1670 cm.$^{-1}$ (unsaturated ester C=O), 1650 cm.$^{-1}$ (amide C=O) and 1625 cm.$^{-1}$ (enol C=C).

Found   C, 64.03; H, 6.00; N, 5.52%

$C_{14}H_{15}O_4N$ req.   C, 64.36; H, 5.79; N, 5.36%

1-Benzoyl-3-carboethoxy-4-piperidone (84(a))

a) This compound was prepared initially by the method of McElvain.[81] The overall yield from ethyl acrylate was 15%.

b) Benzamide (121 gms., 1 mole) was added to 2 l. of dry toluene. Sodium hydride (24 gms, 1 mole) was added, and the solution boiled under reflux for 1 hr. After cooling this solution to 0°, ethyl acrylate (300 gms, 3 moles) was added in one portion. The solution was gradually heated to boiling, and the ethanol formed in the reaction was distilled out through a 20 cm. Vigreux column, fitted with a take-off head. After all the ethanol was removed, (approximately 2 to 3 hrs.),

the solution was cooled to 0°, and 250 mls of an ice-water solution were added. After filtering off any unreacted benzamide, the aqueous solution was separated, washed once with toluene (50 mls), then acidified with 25% hydrochloric acid to pH 3. The solution was then extracted with chloroform (3 x 100 mls). The combined chloroform extracts were washed with salt water, dried, and evaporated to leave substantially pure 1-benzoyl-3-carboethoxy-4-piperidone as a red syrup. Yield 155 gms, 60%. The syrup could be crystallised from 40/60 petroleum ether to give white needles, m.pt. 65° - 70°. This compound was identical with an authentic sample kindly supplied by Smith, Kline and French Laboratories, and with the material made by the procedure of McElvain.[81]

Under the same conditions, methyl acrylate and benzamide gave a 55% yield of 1-benzoyl-3-carbomethoxy-4-piperidone (84 (b)). This compound was identical with the compound produced by the earlier synthesis.

Preparation of 1-benzoyl-4-piperidone from 1-benzoyl-3-carboethoxy-4-piperidone (84(a)).

The crude keto-ester, (27.5 gms, 0.1 mole), was boiled vigorously in a solution of 100% glacial acetic acid. Extracts from the solution were tested regularly with aqueous ferric chloride solution, and heating was stopped when the solution no longer gave a purple colouration. The solution was boiled to dryness on the steam bath

under reduced pressure, and water was then added. After extraction
with ether, (to remove the benzoic acid), the solution was extracted
with chloroform. The chloroform layer, after washing with salt water
and drying, gave 10 gms of 1-benzoyl-4-piperidone as a red-brown oil.
Yield 50%. The compound was shown to be identical with an authentic
sample, prepared from the keto-ester (84(a)) by the method of McElvain[81(b)].

1-Acetyl-3-carbomethoxy-4-piperidone

Under the conditions described for the preparation of 1-benzoyl-
3-carboethoxy-4-piperidone (84(a)), acetamide and methyl acrylate gave
a 15% yield of 1-acetyl-3-carbomethoxy-4-piperidone as an oil, which
solidified on standing, m.pt. 51° - 55°.

$\nu_{C=0}$ = 1740 cm.$^{-1}$ - 1720 cm.$^{-1}$ (liq. film) and 1710 cm.$^{-1}$ - 1680 cm.$^{-1}$.

Found   C, 53.9; H, 6.20; N, 6.85%

$C_9H_{13}NO_4$ req.   C, 54.26; H, 6.58; N, 7.03%

Attempted preparation of 1-benzoyl-3-carboethoxy-2,6-dimethyl-4-piperidone (91)

Under the conditions used for the preparation of (84(a)), ethyl
crotonate and benzamide gave mainly unchanged starting material. Some
polymeric material was obtained, but it was not investigated.

Attempted preparation of 1-benzoyl-3-carbomethoxy-3,5-dimethyl-4-piperidone (92)

Under the conditions used for the preparation of (84(a)) methyl methacrylate and benzamide produced only a polymeric glass and unchanged benzamide. The glass appeared to have an aromatic group present in the molecule, but its structure was not further investigated.

Attempted preparation of ethyl-N-benzoyl-alanine (88)

An equimolar mixture of the sodium salt of benzamide, (from benzamide and sodium hydride in benzene), and ethyl acrylate was allowed to stand at room temperature for 3 hrs. On acidification of the reaction mixture, almost all of the benzamide was recovered unchanged. The same result was produced after 12 hrs. standing at room temperature. Heating the reaction mixture before isolation of the products, gave mainly unchanged benzamide, and a small amount of the keto-ester (84(a)).

1-Benzoyl-3-carboethoxy-3-methyl-4-piperidone (100)

a) 1-Benzoyl-3-carboethoxy-4-piperidone, (13.75 gms, 0.05 mole), was dissolved in 70 mls of dry toluene, under nitrogen. Sodium hydride, (1.2 gms, 0.05 mole) was then added and the solution boiled under reflux for 2 hrs., with vigorous stirring. The sodium enolate separated as a yellow precipitate. The solution was cooled, and dry methyl iodide

(21.3 gms, 0.15 mole) added. The mixture was boiled under reflux for 40 hrs. It was then cooled, and 50 mls of an ice-water solution were added. The toluene layer was separated and washed with 5% sodium hydroxide, 5% hydrochloric acid and finally bicarbonate solution. Drying, and evaporation of the solvent gave 11.2 gms of a yellow oil. Yield 70%. Chromatography in benzene on Spence alumina grade H showed the material to be substantially pure.

ν_{max} (CCl$_4$) = 1725 cm.$^{-1}$ (ketone and ester C=O), 1660 cm.$^{-1}$ (amide C=O).

The n.m.r. spectrum showed a methyl singlet at 1.24 p.p.m., superimposed on the methyl triplet of the carboethoxy group.

Although the compound could be distilled, b.pt. 110°/ 5.9 x 10^{-4} mm., consistent analyses could not be obtained on the resultant oil. It was analysed as its 2,4-dinitrophenylhydrazone, prepared in ethanol and recrystallised from absolute ethanol, as yellow plates, m.pt. 175.5°.

Found   C, 55.9; H, 4.94; N, 15.4%

$C_{22}H_{23}N_5O_7$ req. C, 56.28; H, 4.94; N, 14.92%

The semicarbazone was prepared in aqueous alcohol and recrystallised from absolute alcohol, m.pt. 195° - 196.5°.

Found   C, 58.9; H, 6.4; N, 16.8%

$C_{17}H_{22}N_4O_4$ req. C, 58.94; H, 6.57; N, 16.18%

b)   This preparation followed the procedure of Ritchie and Taylor.[92] Sodium hydride, (2.4 gms, 0.1 mole) was added to a mixture of 100 mls. of dry benzene and 70 mls. of dimethylformamide. 1-benzoyl-3-carboethoxy-4-piperidone (27.5 gms, 0.1 mole) in 40 mls. of dry benzene was added,

and the solution boiled under reflux for 1 hr. Anhydrous sodium iodide (15 gms, 0.1 mole) was then added, followed by methyl iodide (16 gms, 0.11 mole). Precipitation of sodium iodide occurred immediately. The solution was then boiled for 24 hrs., then poured into ice water. Isolation of the material by the technique used in preparation a) gave, after chromatography on alumina, 8 gms of the desired methylated keto-ester. Yield 28%. This low yield may be due in part to the dimethylformamide being incompletely dried, as some effervescence was observed on addition of the sodium hydride.

c)   A yield of 84% of 1-benzoyl-3-carboethoxy-3-methyl-4-piperidone was obtained by the use of dry dimethoxyethane as the reaction solvent. The experimental technique was the same as that used in experiment a), except that to isolate the product, the dimethoxyethane solution was concentrated to a small volume, and the residue poured into water. The aqueous solution was exhaustively extracted with chloroform. The chloroform extracts were washed with 5% sodium hydroxide solution, 5% hydrochloric acid solution and finally with a bicarbonate solution. Drying, and evaporation of the solvent gave 1-benzoyl-3-carboethoxy-3-methyl-4-piperidone.

        This procedure for the alkylation of 1-benzoyl-3-carboethoxy-4-piperidone was subsequently used with several reactive halides and will be frequently referred to.

<u>Attempted alkylation of the enolate formed by cyclisation</u>

<u>of N,N-di-(β-carboethoxyethyl)benzamide (86)</u>.

N,N-di-(β-carboethoxyethyl)benzamide, (75.7 gms, 0.236 mole),
was cyclised in dry benzene, using sodium hydride, (5.7 gm, 0.236 mole),
and 2 mls of absolute ethanol. After 3 hrs. boiling, the suspension of
the enolate was cooled and methyl iodide, (36 gms, 0.25 mole) was added.
The solution was then refluxed for 48 hrs. Working up the reaction, by
the procedure used in preparation a) of 1-benzoyl-3-carboethoxy-3-methyl-
4-piperidone, (P. 99), gave 67 gms of a yellow oil.

Chromatography of a sample of this oil on Spence grade H
alumina gave five compounds. 1-Benzoyl-3-carboethoxy-3-methyl-4-
piperidone was eluted in benzene, together with a second compound. The
infrared spectrum of this latter compound was almost identical to the
monomethylated product, but its n.m.r. spectrum indicated 9 protons, as
a complex multiplet around 1.1 p.p.m.. Peaks due to a tertiary methyl
group and the methyl of the ester group could be identified, while the
remaining peak appeared as a doublet. The compound was thought to be
1-benzoyl-3-carboethoxy-3,5-dimethyl-4-piperidone (101). Elution with a
benzene-ether solvent produced unchanged N,N-di-(β-carboethoxyethyl)
benzamide as the principal constituent of the mixture. Ethyl-N-benzoyl
alanine (88) was eluted in ether, together with a compound thought to be
β-carboethoxypropyl-benzamide (102). As the principal product of this
reaction appeared to be the unchanged diester (86), the technique of
direct alkylation was not further investigated.

Following the alkylation technique outlined in preparation c),
P.(101), 1-benzoyl-3-carboethoxy-4-piperidone, (20.2 gms, 0.0735 mole),
was treated with sodium hydride (1.76 gms, 0.0735 mole). Ethyl
γ-bromovalerate (31 gms, 0.147 mole) was then added dropwise over 20
mins and the solution boiled for 24 hrs. Working up the reaction gave
unchanged keto-ester, ethyl γ-bromovalerate and γ-valerolactone (detected
by a strong C=O band at 1785 cm.$^{-1}$ in the infrared spectrum). No
material corresponding to the desired product was obtained. Allowing the
sodium enolate to stand with ethyl γ-bromovalerate at room temperature
for 24 hrs. did not result in alkylation.

1-Benzoyl-3-carboethoxy-3-carboethoxymethyl-4-piperidone (108)

Using the alkylation technique described in preparation c),
(P. 101) 1-benzoyl-3-carboethoxy-4-piperidone (27.5 gms, 0.1 mole),
sodium hydride (2.4 gms, 0.1 mole), and ethybromoacetate (18.5 gms,
0.11 mole) gave 21.6 gms of 1-benzoyl-3-carboethoxy-3-carboethoxymethyl-
4-piperidone, as an orange oil. It was distilled for analysis, b.pt.
190°/ 5 x 10^{-3} mm.

Found   C, 63.71; H, 6.75; N, 3.60%

$C_{19}H_{23}NO_6$ req.   C, 63.14; H, 6.42; N, 3.88%

The 2,4-dinitrophenylhydrazone was prepared in ethanol, and recrystallised
from absolute ethanol, m.pt. 167°.

Found   C, 54.56; H, 4.57; N, 12.96%

$C_{25}H_{27}N_5O_9$ req.   C, 55.45; H, 5.03; N, 12.93%

Under the same reaction conditions, ethyl α-bromopropionate gave a 38%

yield of 1-benzoyl-3-carboethoxy-3-(1'carboethoxyethyl)-4-piperidone.

This was distilled for analysis b.pt. $183^{\circ}/ 5.9 \times 10^{-3}$ mm.

Found   C, 63.42; H, 6.50; N, 3.38%

$C_{20}H_{25}NO_6$ req.   C, 63.98; H, 6.71; N, 3.73%

Attempted preparation of 1-benzoyl-3-carboethoxy-3,4-di-

carboethoxymethyl-4-piperidinol (109)

1-Benzoyl-3-carboethoxy-3-carboethoxymethyl-4-piperidone

(2.8 gms, 0.0078 mole) was dissolved in benzene (25 mls). Ethyl

bromoacetate (3.0 gms, 0.018 mole), 3 gms of zinc dust and a crystal

of iodine were then added. The solution was boiled for 4 hrs. The

product was isolated by addition of water, and separation of the

benzene layer. After drying and evaporation of the solvent, the

residue was heated at 100° under reduced pressure, in order to remove

unreacted ethyl bromoacetate. The crude material (3.6 gms) showed a

lactone peak in its infrared spectrum at 1785 cm.$^{-1}$ After chromatogaphy

in benzene on Spence grade H alumina,0.8 gms of the lactone (110)

were isolated, as the only identifiable product. M.pt. $95^{\circ} - 97^{\circ}$

Found   C, 61.7; H, 6.5; N, 3.75%

$C_{21}H_{25}NO_7$ req.   C, 62.5; H, 6·25; N, 3.47%

1-Benzoyl-3-carboethoxy-3-(prop-2-ynyl)-4-piperidone (122)

Following the alkylation technique used in preparation c),

(P. 101) 1-benzoyl-3-carboethoxy-4-piperidone, (55 gms, 0.2 mole),

sodium hydride, (4.8 gms, 0.2 mole) and propargyl bromide (35.7 gms,

0.3 mole) were boiled under reflux for 48 hrs. Isolation of the product

gave crude 1-benzoyl-3-carboethoxy-3-(prop-2-ynyl)-4-piperidone as a

red oil. Yield 45 gms, 72%. The compound was unstable to distillation

and was purified by percolation through Woelm alumina grade V in ether.

$\nu_{max(CCl_4)}$ 3300 cm.$^{-1}$ ($\underline{H}$ – C≡C), 2125 cm.$^{-1}$ (C≡C), 1725 cm.$^{-1}$ and

1730 cm.$^{-1}$ (shoulder)(C=O ketone and ester).

The 2,4-dinitrophenylhydrazone was prepared in ethanol and

crystallised from absolute ethanol, m.pt. 170°.

Found   C, 57.89; H, 4.35; N, 14.59%

$C_{24}H_{23}O_7N_5$ req. C, 58.42; H, 4.70; N, 14.19%

The semicarbazone was prepared in aqueous ethanol and recrystallised

from absolute ethanol, m.pt. 185°.

Found   C, 61.3; H, 6.37; N, 14.7%

$C_{19}H_{22}O_4N_4$ req. C, 61.61; H, 5.99; N, 15.13%

3-Acetonyl-1-benzoyl-3-carboethoxy-4-piperidone (123)

1-Benzoyl-3-carboethoxy-3-(prop-2-ynyl)-4-piperidone (9.6 gms, 0.031 mole) dissolved in 20 mls of dry methanol, was added to a catalyst solution prepared from 2.5 gms of red mercuric oxide, 1 ml of boron trifluoride etherate, 50 mg. of trichloracetic acid and 5 mls of methanol. An orange-yellow precipitate formed, and a mildly exothermic reaction ensued. The solution was stirred at room temperature for 2 hrs., during which time the solution cooled and assumed a dark brown colour. The reaction mixture was then poured into 250 mls of 10% sulphuric acid solution. A brown oil separated, and the solution was extracted with chloroform (6 x 50 mls). The chloroform layer was washed with saturated salt solution and dried over sodium sulphate. Evaporation of the solvent gave a residue of 8 gms. Yield 78%. This material was a red-brown oil. On trituration of this oil with carbon tetrachloride solution, 2.5 gms of a white solid, m.pt. 77° were obtained. The remaining material was chromatographed in benzene on Woelm alumina grade IV. The initial benzene fractions produced a further 0.2 gms of the crystalline material. A 25% ether-benzene solution then eluted 5.0 gms of a yellow oil, which appeared to be the desired diketone (123).

The solid material was thought to be the methyl ketal (125). Consistent carbon analyses could not be obtained on this compound, although the hydrogen and nitrogen figures were correct for structure (125)

Ketal

$$\gamma_{max}(CCl_4) = 1735 \text{ cm.}^{-1} \text{ (C=O ketone and ester).}$$

<u>Diketone</u>

$$\nu_{max}(CCl_4) = 1730 \text{ cm.}^{-1} \text{ with shoulder at } 1720 \text{ cm.}^{-1}$$

The diketone (123) was unstable to distillation, and was analysed as its disemicarbazone derivative, prepared in aqueous methanol and recrystallised from methanol, m.pt. $212^\circ - 215^\circ$.

Found   C, 53.57; H, 6.0; N, 21.7%

$C_{20}H_{27}N_7O_5$ req.C, 53.92; H, 6.11; N, 22.01%.

<u>Attempted preparation of 2-benzoyl-1,2,3,4,7,7a-hexahydro-</u>
<u>-6H-2-pyrindin-6-one (115)</u>

a)   3-Acetonyl-1-benzoyl-3-carboethoxy-4-piperidone (8.3 gms, 0.025 mole) was mixed with 255 mls of boiled water under nitrogen. The solution was boiled under reflux and vigourously stirred, while 45 mls of 2% sodium hydroxide were added over 15 mins. The diketone dissolved to give a yellow solution. This was boiled for six hrs. After cooling, it was extracted with benzene. The benzene extracts, however, contained no appreciable amount of material. The aqueous layer was then made acid, and a black gum was precipitated. This gum resisted all attempts at purification, and did not give a well defined infrared or n.m.r. spectrum. Extraction of the gum with ether produced a small amount of crystalline material, shown to be benzoic acid.

b)   The diketone (2 gms, 0.061 mole) was dissolved in 15 mls of dry tertiary butanol, and added at room temperature to a solution of

potassium (0.25 gms, 0.064 mole) in 15 mls of dry tertiary butanol.
The solution was left for 20 mins., then poured into an ice-water solution.
This solution was extracted with chloroform, then made acid and extracted
once more with chloroform. Both chloroform extracts had very similar
n.m.r. spectra. The acetyl group and the carboethoxy group were present
in both extracts and there was no sign of a vinyl hydrogen. The extracts
contained 1.8 gms of material, which was presumably unchanged diketone.

This material was redissolved in tertiary butanol and added to
a second solution of 0.2 gm of potassium in tertiary butanol. The solution
was boiled under reflux for twenty minutes and the produce isolated as in
the initial experiment. The chloroform extract, on shaking with sodium
bicarbonate solution, produced a vigourous effervescence. Benzoic acid
(0.3 gm) was obtained, while the residue from the chloroform extracts was
a black intractable gum.

c) Benzoic acid was also produced when the diketone (123) was dissolved
in dry methanol and heated with a solution of sodium in methanol. The non-
acidic extract could not be purified. No reaction occurred at room
temperature.

d) The diketone (1 gm, 0.031 mole) was dissolved in methanol and 2 mls
of Triton B were added. The solution was boiled under reflux for 6 hrs.
The product was isolated by pouring the reaction mixture into 10%
hydrochloric acid, and extracting this acid solution with benzene. 1 gm
of material was obtained, the n.m.r. spectrum of which showed the acetyl
group still present, but the absence of the ethyl group, and the
appearance of a singlet at 3.85 p.p.m. The compound appeared to be the

methyl ester of the diketone (123).

This methyl ester was then boiled for 24 hrs. in methanol with 2 mls of Triton B, but was recovered unchanged.

e) The diketone (5 gms, 0.155 mole) was dissolved in a solution of 50 mls of concentrated hydrochloric acid, 100 mls of glacial acetic acid and 4 mls of water. This solution was then refluxed for 36 hrs. The product was isolated by evaporation of the solution to dryness. This produced a mixture of benzoic acid (0.7 gms) and an extremely hygroscopic hydrochloride, as a glass, which could not be crystallised. Basification of this material and extraction with chloroform produced 2.0 gms of a dark-red gum, which decomposed rapidly into a black tar.

f) The diketone (3.9 gms, 0.018 mole) was boiled in 100% glacial acetic acid for 36 hrs., in an attempt to remove the 3-carboethoxy group prior to cyclisation. Working up the reaction indicated that no decarboxylation had occurred.

1-Benzyl-3-methyl-4-piperidone (132)

This was prepared by the method of Carabateas and Grumbach.[110] The overall yield from benzylamine was 37%. Yields on the initial addition reaction were improved by allowing the reactants to stand for a week or longer, following the initial boiling. It was neccessary to isolate and dry the hydrochloride of 1-benzyl-3-carbomethoxy-5-methyl-4-piperidone before proceeding with the decarboxylation reaction.

ν_{max}(film) = 1710 cm.$^{-1}$ - 1720 cm.$^{-1}$ (C=O) and 2780 cm.$^{-1}$ - 2800 cm.$^{-1}$ (Bohlmann bands).

Enamine of 1-benzyl-3-methyl-4-piperidone

A solution of 1-benzyl-3-methyl-4-piperidone (12.34 gms, 0.061 mole) and pyrrolidine (5.2 gms, 0.073 mole) in 50 mls of dry benzene, containing a catalytic amount of para-toluene sulphonic acid, was boiled under a water separating device, until the calculated amount of water had been formed. The benzene and excess pyrrolidine were then removed on a water bath under reduced pressure, and the residual liquid distilled under nitrogen. The enamine distilled as a yellow-green oil, b.pt. 158°/0.02 mm. Yield 13.2 gms, 85%. The n.m.r. spectrum indicated a vinyl hydrogen at 4.05 p.p.m.

1-benzyl-3-methyl-5-(prop-2-ynyl)-4-piperidone (133)

a) The enamine of 1-benzyl-3-methyl-4-piperidone, (13.0 gms, 0.051 mole) was dissolved in 100 mls of dry acetonitrile at room temperature. Propargyl bromide (6.0 gms, 0.051 mole) was then added dropwise over 20 mins. The solution became dark red and an exothermic reaction occurred. The solution was then boiled under reflux for 1 hr. The bulk of the acetonitrile was removed, and 100 mls of water were then added. This solution was then warmed on a steam bath for 30 mins., to decompose the enamine, and then extracted, first with ether, and then chloroform. After drying and evaporation of the ether extract, 6.9 gms of material were obtained as a red mobile oil. Chromatography on Woelm alumina grade IV gave two main fractions. With 5% benzene - 95% petrol, 1.0 gm of a

colourless oil were obtained. Analysis of this oil, b.pt. $60^{\circ}-63^{\circ}/$ 0.1 mm, indicated an empirical formula $C_{13}H_{13}N$. ν_{max} = 3300 cm.$^{-1}$ The n.m.r. spectrum showed the methylene group of the propenyl substituent at 3.47 p.p.m., with the acetylene hydrogens at 2.25 p.p.m. This confirms that the compound was N,N-di-(prop-2-ynyl)benzylamine.

With ether as the eluent, 5.7 gms of 1-benzyl-3-methyl-5-(prop-2-ynyl)-4-piperidone were produced. Yield 47% ν_{max} (CCl$_4$) = 3308 cm.$^{-1}$, 3300 cm.$^{-1}$(shoulder), 1710 cm.$^{-1}$ - 1720 cm.$^{-1}$ The compound could not be distilled without decomposition. A picrate was prepared in an ethanol-ether solution, and was recrystallised from 95% ethanol, m.pt. $137^{\circ}-138^{\circ}$.

Found   C, 56.4; H, 4.31; N, 11.6%

$C_{22}H_{22}O_8N_4$ req. C, 56.17; H, 4.71; N, 11.91%.

b)   The enamine of 1-benzyl-3-methyl-4-piperidone (20.92 gms, 0.082 mole) was stirred in dry benzene with propargyl bromide (9.1 gms, 0.077 mole) for 40 hrs. at room temperature. A yellow-red oil formed as the reaction proceeded. The enamine was decomposed and the product isolated by the technique used in experiment a), to give 12.4 gms of the acetylene compound (133). Yield 63%. Approximately 3 gms of quaternary material were obtained, plus 1.1 gms of N,N-di-(prop-2-ynyl)benzylamine.

Enamine of 1-benzyl-4-piperidone

This was prepared in benzene from 1-benzyl-4-piperidone (20 gms, 0.106 mole) and pyrrolidine (10.8 gms, 0.15 mole). The solution was

boiled for 8 hrs. under a water separating device. The enamine distilled

as a yellow oil, b.pt. $138^{\circ}/2.36 \times 10^{-3}$ mm. Yield 22.2 gms. 87%.

The n.m.r. spectrum showed a vinyl hydrogen as a triplet centred

at 4.05 p.p.m. The benzylic methylene group was a singlet at 3.5 p.p.m.

1-benzyl-3-(prop-2-ynyl)-4-piperidone

a) The enamine of 1-benzyl-4-piperidone (20 gms, 0.083 mole) was

reacted in acetonitrile with propargyl bromide (9.5 gms, 0.083 mole)

under the conditions described in preparation a) of 1-benzyl-3-methyl-

-5-(prop-2-ynyl)-4-piperidone. The solution became appreciably warm,

and assumed a dark red colour. After refluxing for 1 hr., it was

worked up to give a large quantity (approximately 7 gms) of intractable

quaternary material, and 11 gms of ether soluble material. This was

chromatographed on Woelm grade IV alumina to give 4.5 gms of

N,N-di-(prop-2-ynyl)benzylamine and 5.1 gms of 1-benzyl-3-(prop-2-ynyl)-

-4-piperidone as a yellow oil. Yield 21%.

ν_{max}(film) = 3295 cm.$^{-1}$ ($\underline{H}$ - C$\equiv$C), 1715 cm.$^{-1}$ - 1720 cm.$^{-1}$ (C=O).

The compound formed a picrate from an ethanol-ether solution. This was

initially an oil, which solidified on trituration with ether. The solid

was recrystallised from methanol, m.pt. 141°-142°.

Found C, 54.81; H, 4.11; N, 11.95%

$C_{21}H_{20}O_8N_4$ req. C, 55.26; H, 4.42; N, 12.28%.

b) 1-benzyl-4-piperidone (7.42 gms, 0.039 mole) was dissolved in

120 mls of dry dimethoxyethane. Sodium hydride, (0.94 gms, 0.039 mole)

was added and the solution was boiled under reflux for $^1/2$ hr. It

was then cooled to room temperature, and propargyl bromide (4.7 gms,

0.039 mole) was added in one portion. The solution was then boiled for

24 hrs. The initial yellow solution of the enolate assumed a deep red

colour, and sodium bromide formed in the bottom of the flask. The

bulk of the dimethoxyethane solution was removed, and the residue was

poured into water. Extraction with chloroform (6 x 50 mls), drying

and removal of solvent gave 5 gms of crude material. On trituration with

ether, approximately 2 gms of presumably quaternary material were produced.

The ether extract, after evaporation, appeared to contain approximately

equimolar amounts of N,N-di-(prop-2-ynyl)benzylamine and the desired

compound. This was ascertained by comparison of the integrated peaks

in the n.m.r. spectrum, corresponding to the terminal acetylene

hydrogen(s), and the methylene group of the propenyl substituent. The

mixture was not further investigated.

3-Acetonyl-1-benzyl-5-methyl-4-piperidone (134)

1-Benzyl-3-methyl-5-(prop-2-ynyl)-4-piperidone (13.0 gms, 0.054

mole) in 20 mls of dry methanol was added dropwise over 10 mins to a

catalyst solution prepared from 2.0 gms of red mercuric oxide, 1.5 mls

of boron-trifluoride etherate, 10 mgs of trichloracetic acid and 5 mls

of methanol. No change in temperature was detected, and the solution

was stirred at room temperature for 3 hrs.

The solution was then filtered from the grey inorganic salts, and concentrated on the steam bath. It was then added to 100 mls of 10% dilute sulphuric acid and stirred for 20 mins at approximately 50°. The solution was cooled and made alkaline with solid sodium carbonate. The solution was saturated with salt and extracted with ether (6 x 50 mls). After drying and evaporation of solvent, a residue of 9.9 gms was obtained. This compound was a yellow-red oil, unstable to distillation. Chromatography on Woelm alumina grade IV in 20% benzene - 80% ether gave 9.5 gms of a pale yellow oil. Yield 68%. ν_{max}(film) = 1710 cm.$^{-1}$ The n.m.r. spectrum in carbon tetrachloride solution showed a CH_3 - CO group at 2.1 p.p.m. It was found impossible to obtain satisfactory analyses on this compound. Attempts to produce a picrate gave an oil which could not be induced to crystallise. A disemicarbazone derivative was obtained, but melted from 180° - 189° and did not give satisfactory analytical figures.

2-Benzyl-1,2,3,4,7,7a-hexahydro-4-methyl-6H-2-pyrindin-2-one (135)

3-Acetonyl-1-benzyl-5-methyl-4-piperidone (5 gms, 0.0194 mole) in 10 mls of dry tertiary butanol was added dropwise over 10 mins to a solution of potassium (0.76 gms, 0.0194 mole) in 30 mls of dry tertiary butanol, at room temperatur. A mild exothermic reaction occurred and the solution became a dark red colour. After stirring at room temperature for 30 mins, approximately 20 mls of tertiary butanol were removed by heating the solution in an isomantle under reduced pressure. The

residual solution was poured into 150 mls of 5% hydrochloric acid

solution. A black gum formed. The solution was extracted with

chloroform (6 x 50 mls) and washed with sodium bicarbonate solution.

Drying and evaporation of the solvent gave a residue of 4.1 gms, as a

dark red gum. This was extracted with petroleum ether and the petrol

extracts dried. On evaporation they yielded 2.5 gms of a dark red oil.

V.p.c. analysis of this oil showed it to consist of one main fraction.

It was chromatographed in 10% benzene - 90% petroleum ether on Woelm

alumina grade V, and yielded 2.2 gms of a deep red oil, shown to be

approximately 90% pure by v.p.c. analysis. This compound, which

darkened on exposure to air, and was thus stored under nitrogen, appeared

to be 2-benzyl-1,2,3,4,7,7a-hexahydro-4-methyl-6H-2-pyrindin-2-one (135).

Yield 53%. ν_{max}(film) = 1705 cm.$^{-1}$ and 1620 cm.$^{-1}$. The n.m.r.

spectrum indicated a vinyl hydrogen at 5.76 p.p.m. and a methyl group

doublet at 1.1 p.p.m.

The compound was analysed as its picrate, prepared in an ethanol-

ether solution. This picrate was initially an oil, which on trituration

with ether gave a solid. This could be recrystallised from absolute

ethanol, m.pt. 164° - 166°.

Found   C, 55.9; H, 4.5; N, 11.72;

$C_{22}H_{22}O_8N_4$ req. C, 56.17; H, 4.71; N, 11.91%.

The remainder of the crude material, after extraction of the desired

product, was a black gum, from which no identifiable product could be

isolated.

1-Benzoyl-3-bromo-5-carboethoxy-5-methyl-4-piperidone

a)   1-Benzoyl-3-carboethoxy-3-methyl-4-piperidone, (10 gms, 0.0334 mole)
was dissolved in 50 mls of chloroform, and bromine (5.5 gms, 0.0334 mole)
was added dropwise over 2 hrs. at room temperature. A deep red solution
formed, which deposited a yellow solid on the sides of the flask as the
reaction proceeded. The solution was left stirring at room temperature
for 12 hrs. The solution was then a yellow colour. It was poured
into ice-water, whereupon the yellow solid dissolved. The chloroform
layer was separated, and the aqueous layer then extracted with fresh
chloroform, (4 x 50 mls). The chloroform extracts were shaken with
bicarbonate, dried, and the solvent removed to give 11 gms of a

yellow, pleasant smelling oil. This was dissolved in chloroform and
percolated through alumina, to give 10.8 gms of 1-benzoyl-3-bromo-5-
-carboethoxy-5-methyl-4-piperidone. Yield 85%.

The n.m.r. spectrum indicated that the compound was presumably a
mixture of epimers, since two peaks appeared for the tertiary methyl
group and the methyl quartet of the carboethoxy group was also subsplit.

On dissolving the oil in hot carbon tetrachloride, and cooling the
solution, the bulk of the product could be obtained in crystalline form.
A residue of 1.3 gms could not be induced to crystallise from this
solvent. Recrystallisation of the major product produced white needles,
m.pt. 98°-99°, from carbon tetrachloride.

ν max(cyclohexane) = 1725 cm.$^{-1}$ and 1720 cm.$^{-1}$ (both sharp).

Found   C, 52.01; H, 4.80; N, 3.7%

$C_{16}H_{18}O_4NBr$ req. C, 52.20; H, 4.93; N, 3.81%.

b) 1-Benzoyl-3-carboethoxy-3-methyl-4-piperidone (9.6 gms. 0.0332 mole)

was dissolved in 60 mls of dry ether. A solution of bromine (5.31 gms,

0.033 mole) in 30 mls of glacial acetic acid was added dropwise over

45 mins. The solution was then stirred at room temperature for 30 mins.

The ether was evaporated in vacuo, and the residue was poured into 200 mls

of an ice-water solution. It was extracted with chloroform (6 x 50 mls).

The chloroform extracts were washed with water, bicarbonate and finally

water. Drying and evaporation of the solvent gave 10 gms of crude

bromo-ketone. Yield 84%. This could be crystallised from hot carbon

tetrachloride solution by seeding with crystals of the correct material.

8.6 gms. of the bromo-ketone, m.pt. 98°-99°, were produced.

1-Benzoyl-3-methyl-4-piperidone (166)

1-Benzoyl-3-carboethoxy-3-methyl-4-piperidone, (10 gms, 0.0334 mole)

was boiled with 25 mls of concentrated hydrochloric acid and 25 mls of water

for 7 hrs. After cooling the solution, the benzoic acid was filtered off,

and the solution evaporated to dryness in vacuo. To remove the last

traces of hydrochloric acid, ethanol (20 mls) was added, and the

solution again boiled to dryness in vacuo. The hydrochloride of

3-methyl-4-piperidone formed as a glass. Yield 2.5 gms, 40%.

The above hydrochloride (2.5 gms, 0.016 mole) was dissolved in the

minimum amount of water ($^1/2$ ml), and potassium carbonate (1.75 gms,

0.009 mole) was added, followed by 20 mls of chloroform. The solution was

stirred while benzoyl chloride, (2.5 gms, 0.0184 mole) was added

dropwise, at a rate sufficient to maintain gentle boiling. The solution

was boiled under reflux for 4 hrs. Ethanol (5 mls) was then added and boiling continued for 30 mins. The solution was cooled and water (100 mls) was added to dissolve the precipitated salts. The chloroform layer was separated, washed with 5% potassium carbonate solution (2 x 50 mls), water, 5% hydrochloric acid (2 x 50 mls) and finally with water. Drying and evaporation of the solvent gave a pale brown oil. This was distilled under nitrogen, b.pt. $154^{\circ}/0.5$ mm. and on standing formed a pale yellow solid, m.pt. $57^{\circ} - 58^{\circ}$ (Lit.[120] $56^{\circ}-58^{\circ}$) Yield 2.4 gms, 65% from the hydrochloride. $\nu_{max}(CCl_4) = 1725$ cm.$^{-1}$.

Found   C, 71.49; H, 6.55; N, 6.21%

$C_{13}H_{15}O_2N$ req.   C, 71.86; H, 6.96; N, 6.45%.

1-benzoyl-3-bromo-3-methyl-4-piperidone

1-Benzoyl-3-methyl-4-piperidone (2.17 gms, 0.01 mole) was dissolved in 30 mls of dry ether. A solution of bromine (1.6 gms, 0.01 mole) in 20 mls acetic acid was added over 45 mins, and the solution was left 30 mins. after the addition was complete. Working up the reaction as for the bromination of 1-benzoyl-3-bromo-5-carboethoxy-5-methyl-4--piperidone, (P. 117), gave 2.8 gms crude material. This was purified by chromatography on Woelm alumina grade IV. Elution with ether gave 1.9 gms of a yellow oil. Yield 64%. $\nu_{max}(CCl_4) = 1740$ cm.$^{-1}$

The bromo ketone darkened on prolonged standing, and all attempts to obtain analytical samples were unsuccessful. Analysis of a chromatography fraction indicated that only one bromine appeared to be present in the

molecule.

1-Benzoyl-3(1'-carboethoxy-2'-keto-1'-methylpropyl)-5-
-carboethoxy-5-methyl-4-piperidone (169)

Ethyl-1-methyl acetoacetate (1.44 gms, 0.01 mole) was dissolved

in 30 mls of dry thiophen-free benzene and sodium hydride (0.24 gm,

0.01 mole) was added. After boiling the solution for 15 mins., it was

cooled to 0°. A solution of 1-benzoyl-3-methyl-5-carboethoxy-5-methyl-4-

-piperidone in 40 mls of benzene was then added. The solution was

boiled for 3 hrs., during which time the colour of the solution changed

from yellow to deep red. The solution was cooled and poured into an

ice-water mixture. The benzene layer, after separation, was washed with

2.5% potassium hydroxide solution (2 x 50 mls), dilute hydrochloric acid

(2 x 50 mls), bicarbonate, and finally water. Drying and evaporation

of the solvent gave 2.25 gms of crude product. Chromatography on

Woelm alumina grade V in benzene gave 1.6 gms of a compound, whose infrared

and n.m.r. spectra were identical with those of 1-benzoyl-3-carboethoxy-

-3-methyl-4-piperidone. Elution with 20% benzene - 80% ether gave 0.3

gms of a single compound.

ν_{max} (CCl$_4$) = 1725 cm.$^{-1}$ - 1710 cm.$^{-1}$, 1660 cm.$^{-1}$ (amide)

The n.m.r. spectrum showed an acetonyl group at 2.15 p.p.m., and a broad

12 proton peak centred at 1.3 p.p.m.

Attempts to characterise the compound as a 2,4-dinitrophenyl-

-hydrazone or semicarbazone derivative were unsuccessful and an analysis

could not be obtained on the compound.

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