AN APPROACH TO THE SYNTHESIS OF LYCOPODIUM ALKALOIDS.

by

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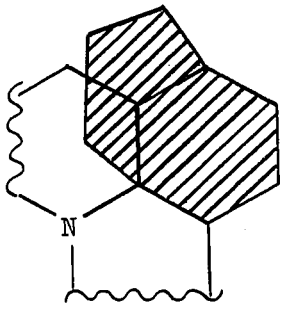
PREFACE

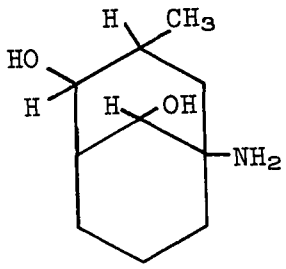
Lycopodium alkaloids attracted the attention of organic chemists as early as 1881[1]. During recent years this earlier work was actively pursued by a number of independent investigators, culminating in the improvement of isolation techniques, the elucidation of the structure of several Lycopodium alkaloids, as well as the stereochemistry and structural relationship of some of these compounds. Finally, a theory for the biogenetic origin of these alkaloids was proposed[2]. However, there seems to be no account in the literature of any work related to a partial or a total synthesis of any of these alkaloids.* This prompted us to study a few approaches which could lead to the synthesis of some of these alkaloids.

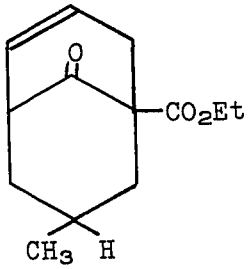
Previous studies have shown that many of the known Lycopodium alkaloids contain a (3.3.1)bicyclononane system, as indicated by the partial structure below:

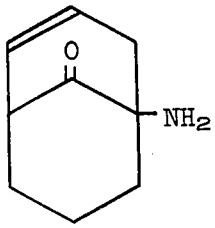


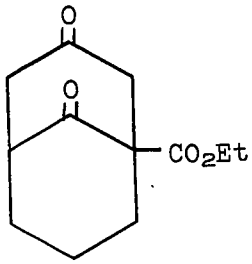
* Note: A conversion of β-obscurine into lycodine was achieved by Ayer and Iverach, while Anet and Rao succeeded in converting lycopodine into lycodine (vida infra).

Therefore, it appeared to us that suitably substituted (3.3.1)bicyclononane derivatives, such as the following compounds:









might serve as possible intermediates for a partial or total synthesis of some of these alkaloids.

The preparation of these and similar compounds and their derivatives is described in this thesis.

Acknowledgments

I wish to thank Dr. F.A.L. Anet for his guidance during the course of this research and for many helpful discussions.

I would like to thank Canadian Industries Limited and the Ontario Research Foundation for financial help in the form of scholarships.

Finally, I thank my wife for her understanding.

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ABSTRACT

The syntheses of a number of new [3.3.1] bicyclononane derivatives are described. Representative compounds include 1-cyano-3-methyl-4-hydroxybicyclo [3.3.1] nonan-9-one, 1-amino-3-methyl-4,9-dihydroxy-bicyclo [3.3.1] nonane, ethyl-7-methylbicyclo [3.3.1] non-3-en-9-one-1-carboxylate, as well as the following derivatives of ethyl-bicyclo [3.3.1] non-3-en-9-one-1-carboxylate: 1-aminobicyclo [3.3.1] non-3-en-9-one, ethyl-3-hydroxy-4-bromobicyclo [3.3.1] nonan-1-carboxylate, ethyl-4-bromobicyclo [3.3.1] nonan-3,9-dione-1-carboxylate and ethyl-bicyclo [3.3.1] nonan-3,9-dione-1-carboxylate.

A Michael condensation of 2-cyanocyclohexanone with α -methyl acrolein afforded 1-cyano-3-methyl-4-hydroxybicyclo [3.3.1] nonan-9-one as a 1:1 complex. Acetylation furnished a mixture of the epimeric acetates, which were separated by fractional crystallization. Oxidation of 1-cyano-3-methyl-4-hydroxybicyclo [3.3.1] nonan-9-one converted it into 1-cyano-3-methylbicyclo [3.3.1] nonan-4,9-dione. Reduction of 1-cyano-3-methyl-4-hydroxybicyclo [3.3.1] nonan-9-one, then saponification of the nitrile group, followed by a Hofmann rearrangement of the amide gave 1-amino-3-methyl-4,9-dihydroxybicyclo [3.3.1] nonane. Several attempts were made to effect cyclization between α -methyl acrolein and 2-carbomethoxy-4-ethylenedioxy cyclohexanone. However, the desired bicyclononane compound was not obtained. An alternative approach was also studied; alkylation using 1-chloro-2-methyl-3-bromopropane and 2-carboethoxy-cyclohexanone or 2-carbomethoxy-4-ethylenedioxy-cyclohexanone gave in both cases the C-alkylated product. Attempts to cyclize these compounds

using a variety of methods gave predominantly O-alkylated products. The base-catalyzed reaction between 2-carboethoxy-4-methylcyclohexanone and acrolein yielded β -(1-ethoxycarbonyl-2-keto-5-methylcyclohexyl) propionaldehyde. Treatment of the latter with acid effected cyclization yielding ethyl-7-methylbicyclo[3.3.1]non-3-en-9-one-1-carboxylate. Ethyl-bicyclo [3.3.1]non-3-en-9-one-1-carboxylate was converted by the following steps: saponification of the ester, conversion of the acid into the acid azide, followed by rearrangement of the latter to the amine hydrochloride; addition of base liberated 1-aminobicyclo[3.3.1]non-3-en-9-one. Treatment of ethyl-bicyclo[3.3.1]non-3-en-9-one-1-carboxylate with N-bromosuccinimide in acid solution gave ethyl-3-hydroxy-4-bromobicyclo[3.3.1]nonan-1-carboxylate, which on oxidation furnished ethyl-4-bromobicyclo[3.3.1]nonan-3,9-dione-1-carboxylate. Reductive removal of the bromine with zinc-acetic acid gave ethyl-bicyclo[3.3.1]nonan-3,9-dione-1-carboxylate. Hydrolysis of the ester in the last compound gave the corresponding acid. Attempts to prepare 1-aminobicyclo[3.3.1]nonan-3,9-dione failed.

Infrared and n.m.r. spectra were used extensively in the structure determination of these compounds as well as their by-products. The identity of all key-compounds was further corroborated by analytical data and ultraviolet spectra.

INTRODUCTION

PART I

A. GENERAL INTRODUCTION

The family Lycopodiaceae includes the monotypic Australian genus Phyloglossum and the ubiquitous genus Lycopodium comprising some 180 species. The various species of Lycopodium are known as ground pine, club moss, creeping pine and ground cedar because of the resemblance of the sporophyte with its small evergreen leaves to many species of coniferous trees. These plants, often inconspicuous in appearance, belong to the great class of vascular cryptogams. In the evolutionary history of plants they form a link between the algae and fungi and the highly evolved flowering plants.

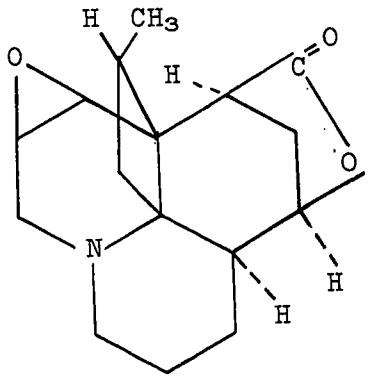
Bödeker[1] first reported the occurrence of an alkaloid in Lycopodium complanatum L., which he called lycopodine. More recently Achmatowicz and Uzieblo[3] obtained lycopodine and two other alkaloids, clavatine and clavatoxine, which they isolated from L. clavatum L. They assigned the correct formula $C_{16}H_{25}ON$ to lycopodine. Following this, Manske and Marion published a series of papers recording the isolation of a large number of new alkaloids from about a dozen species; this work has been reviewed by Manske[4]. Lycopodine was found to be present in all species native to the Northern Hemisphere; l-nicotine, a rather widespread alkaloid, was reported[5] to occur in very small quantities amongst others in Lycopodium flabelliforme L., Lycopodium tristachyum Pursh., Lycopodium clavatum L., Lycopodium lucidulum Michx., and Lycopodium sabinaefolium Willd.

B. STRUCTURAL STUDIES AND REACTIONS

In the following section a brief description of the structural studies and reactions of some of the Lycopodium alkaloids is given. Annotinine, an important alkaloid, has a carbon skeleton different from the others. Only the structure of annotinine is included in this discussion. The chemistry of annotinine has been reviewed in detail by Wiesner and co-workers[6, 7].

a) Annotinine

Annotinine, $C_{16}H_{21}O_3N$, the principal alkaloid of Lycopodium annotinum L. was isolated by Manske and Marion[8]. Structure 1* was shown by Wiesner, Ayer, Fowler and Valenta[9] to be the correct representation of the alkaloid. This was corroborated by X-ray crystallography on annotinine bromohydrin[10]. X-ray analysis also established the relative stereochemistry implied in 1[11]. The absolute configuration of 1 was recently deduced by Wiesner and co-workers[12].



1

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* "Structures enantiomeric with those of all previous publications are used in view of the now known absolute configuration", (6) p. 561 footnote.

(b) Lycopodine

Considerable attention was centered on lycopodine ($C_{16}H_{25}ON$) which is the major alkaloid of several Lycopodium species. It was first isolated by Bödeker[1]. The correct assignment for its molecular formula was made by Achmatowicz and Uzieblo[3] who isolated it from Lycopodium clavatum C.

Lycopodine contains a tertiary nitrogen atom belonging to two rings and a keto group[13]. Many reactions of the compound may be explained by the partial structure 2.[14] The formation of 6-methyl- and 5,7-dimethylquinoline on selenium dehydrogenation of lycopodine indicated that a hydrogenated quinoline system must be present[15].

Reduction of lycopodine with lithium aluminum hydride gave dihydrolycopodine, which could be converted into anhydrodihydrolycopodine.

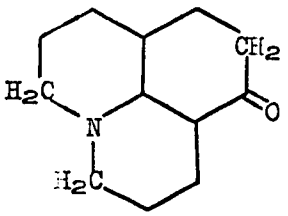
The reaction of lycopodine with cyanogen bromide[13] gave rise to the two isomeric cyanobromolycopodines, α and β, shown in structures 3 and 4. These isomers could be converted into acids with the same number of carbon atoms by exchange of the bromine for an acetoxy group, saponification of the latter to a primary alcohol, and oxidation of this last compound to a carboxylic acid. Both compounds behaved differently on $NaBH_4$ reduction. When the keto group in the acid corresponding to the α-isomer was reduced with sodium borohydride, the hydroxyacid failed to lactonize. Reduction of the β-isomer with sodium borohydride yielded a lactone which was probably 5- or 6-membered as inferred from its infrared spectrum (ν_{max} 1743 cm^{-1}), i.e. the nitrogen and the carbonyl group are separated by three or four carbon atoms in the direction of the β-cleavage.[14]

A modified Kuhn-Roth oxidation of α - and β -cyanodihydrolycopodine, 5 and 6, yielded a mixture of acetic, propionic and butyric acid, while lycopodine itself gave only acetic acid. This indicated that both α - and β -cyanodihydrolycopodine contained a propyl group[16].

A suitable compound for the definition of the environment of the keto group was α -cyanolycopodine (7). Bromination followed by alkaline hydrolysis gave an enolized diketone (8)[17]. Treatment of the benzylidene derivative of α -cyanolycopodine with selenium dioxide gave a mixture of two products, the hydroxy compound 9 and the unsaturated compound 10[16]. Ozonolysis of 9 gave the diketoalcohol 11, which unlike the diketone 8 had no enolic properties. Hydrogenolysis with platinum oxide readily converted the non-enolic compound into the fully enolized derivative 8.[16] These results permit to draw further inferences regarding the environment of the keto group: the only hydrogen available for enolization in the benzylidene ketone is replaced by a hydroxyl group. Consequently, there must be a quarternary center or a bridgehead on the methylene side of the keto group where enolization would be in violation of Bredt's rule. The partial structure 12 accounts well for these observations. This is further substantiated by the fact that deuterium exchange of lycopodine and α -cyanolycopodine established the presence of three enolizable hydrogen atoms in each [16, 18].

Harrison and MacLean[16] proposed the complete structure 13 for lycopodine, which explains all of the discussed information.

Lycopodine has since then been related to annofoline[19], another Lycopodium alkaloid. This provided additional confirmation of structure 13. The relative configuration of the asymmetric centers in lycopodine has been discussed by Anet[20].



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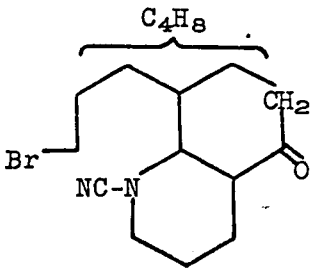

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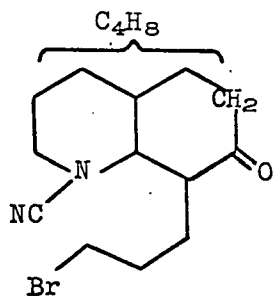
∝-isomer



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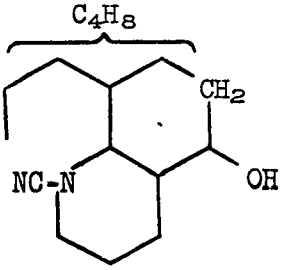
β-isomer



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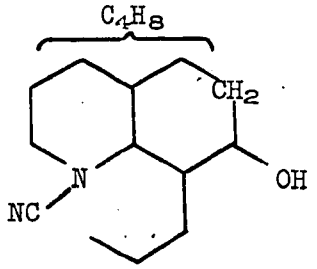

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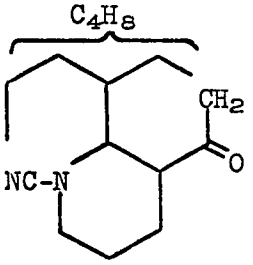

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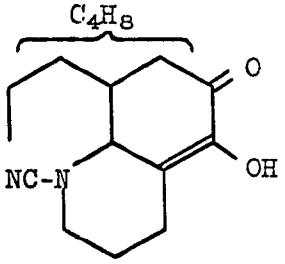

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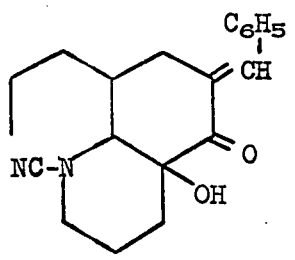

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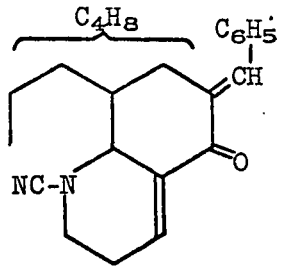

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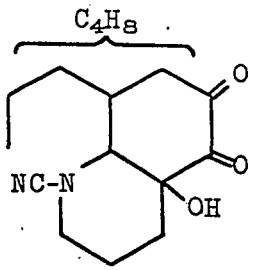

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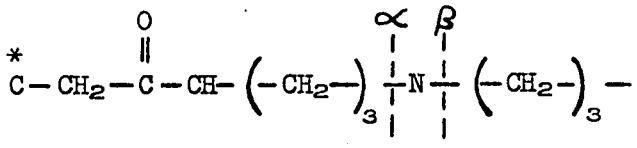
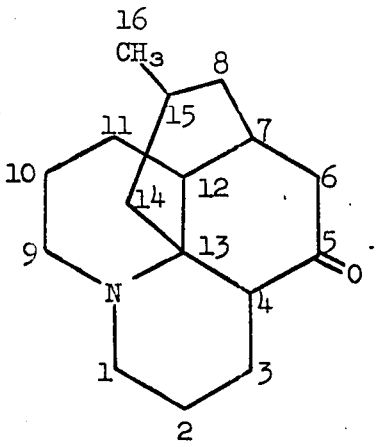


*≡ quarternary center or bridgehead >CH-group

12



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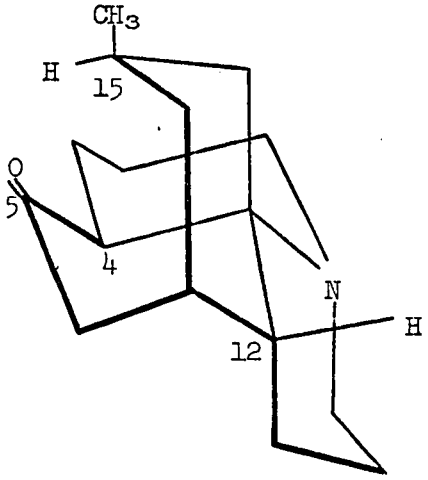


14

Lycopodine

The rotatory dispersion curve of lycopodine has a maximum at 307 mμ ($[\alpha]$ = + 2300)[12]. The application of the octant rule[21] to this result leads to the absolute configuration of lycopodine shown in formula 14.

(c) Acrifoline

Acrifoline ($C_{16}H_{23}O_2N$) is a minor alkaloid of Lycopodium annotinum; it was isolated from the plant Lycopodium annotinum var. acrifolium Fern[22].

From infrared spectral studies of acrifoline, its acetyl derivative and of dihydroacrifolinol, Perry and MacLean[23] confirmed the presence of a hydroxyl group (ν_{max} 3310 cm^{-1}), a double bond (ν_{max} 1670 cm^{-1}) and a carbonyl group (ν_{max} 1700 cm^{-1}) as well as a tertiary nitrogen. They concluded, therefore, that it was tetracyclic.

The carbonyl absorption in the infrared spectrum is of interest: the spectrum of crystalline acrifoline in nujol showed only a weak band at 1700 cm^{-1} while in chloroform it exhibited a strong peak. The difference in behaviour in the solid state and in solution suggested that the hydroxyl group in acrifoline is disposed in such a manner that it can form a hemiketal in the solid state. This indicated that the keto group and the hydroxy group are separated by two or three atoms[24].

The n.m.r. spectrum of acrifoline[25] showed absorption of area 1 at displacements of 2.04 and 3.35 p.p.m. (relative to chloroform), attributed to $>C=C<^{H}$ and $>CHO-$ groups, respectively. A doublet of area 3, occurring at a displacement of 6.20 p.p.m. established the presence of a $>CHCH_3$ group. An examination of the n.m.r. spectrum of acetylacrifoline confirmed the above results. The absence of absorption

at low field in both of the above n.m.r. spectra rules out the presence of an aldehyde group; therefore, the carbonyl group in acrifoline must be ketonic. The hydroxyl group is secondary since the signal area of the CHO- group corresponded to one proton.

Oppenauer oxidation of dihydroacrifolinol[23] - formed by hydrogenation of acrifoline to dihydroacrifoline, followed by reduction of the carbonyl group with lithium aluminum hydride - gave a diketone[24]. Its infrared spectrum had bands at 1700 cm^{-1} and 1420 cm^{-1}. The latter was absent in acrifoline, i.e. the $-CH_2CO-$ group in the oxidation product must have been derived from a $-CH_2CH.OH-$ group in acrifoline.

Catalytic hydrogenation of acrifoline saturated the double bond and yielded two dihydro derivatives, stereo-isomeric at C_{12}. Of these two isomers, one proved to be identical with the alkaloid annofoline which in turn had been directly correlated with lycopodine (vide infra).

The structure 15 proposed by French and MacLean[24] explains all of these reactions.

(d) Annofoline

Annofoline, $C_{16}H_{25}O_2N$, was isolated by Anet and Khan from Lycopodium annotinum L.[26]. It was shown to contain a tertiary nitrogen atom and a C-methyl group. In the infrared spectrum it exhibited a hydroxyl group (3400 cm^{-1}) and a carbonyl group (1700 cm^{-1}). The carbonyl band was much weaker when the spectrum was determined in carbontetrachloride solution (cf. acrifoline), i.e. in solution there exists an equilibrium between the hydroxy ketone and the hemiketal form.[19] The n.m.r. spectrum of annofoline showed a doublet at 8.93 τ indicating that the C-methyl group is present as $CH_3CH<$.

Evidence for the presence of a hexahydrojulolidine system in annofoline was obtained as follows:[19] when annofoline was treated with t-butyl nitrite an oximino acid (16) was obtained. This compound underwent smooth dehydrogenation to yield julolidine.

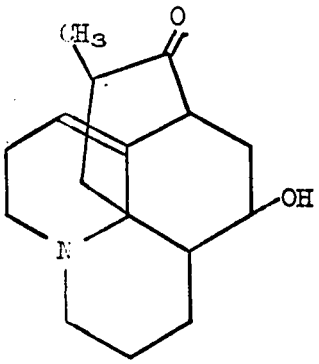
Annofoline gave an α,β -unsaturated ketone when reacted with selenium dioxide. The n.m.r. spectrum of this compound showed an unsplit band at 2.74 τ which was attributed to an olefinic hydrogen atom β to the keto group. The fact that the peak was unsplit suggested that there was a quarternary center adjacent to the -CH= group. Furthermore, the signal for the methyl group (8.18 τ) was unsplit. Thus, the chromophore is -COC(Me)=CH-C*, where C* is a quarternary center.[19]

Anet and Khan[19] proposed structure 17 for annofoline which is in full agreement with all of the observed reactions.

(e) Fawcettiine

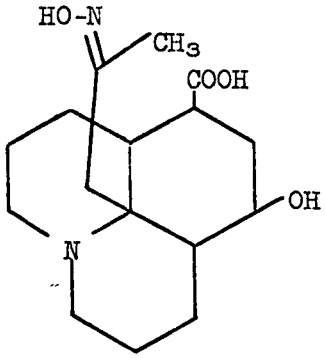
Fawcettiine (β -lofoline), $C_{18}H_{29}O_3N$, was isolated from Lycopodium annotinum[26] and from Lycopodium fawcettii[27]. It contains a hydroxyl group, an O-acetyl group, a tertiary nitrogen atom and a C-methyl group apart from the one in the acetoxyl group.

Fawcettiine on oxidation with Sarett's reagent gave dehydrofawcettiine, $C_{18}H_{27}O_3N$, which was hydrolyzed by base to yield annofoline.[28] It was shown by Anet[20] that the deacetylation of dehydrofawcettiine was accompanied by isomerization to annofoline. On hydrolysis, fawcettiine gave a diol (deacetylfawcettiine); dehydration of the diol led to anhydrodeacetylfawcettiine[27]. The remaining hydroxyl group in this compound was resistant to further dehydration[28a]. The n.m.r. spectrum of anhydrodeacetylfawcettiine showed only one olefinic proton and a $-CHCH_3$ grouping.



15

Acrifoline



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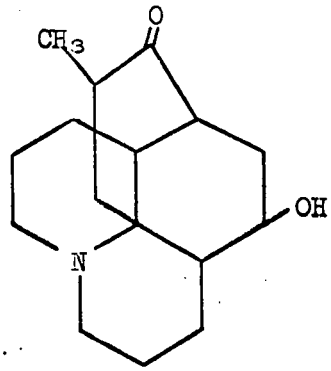
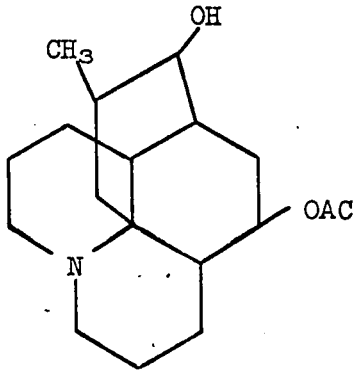


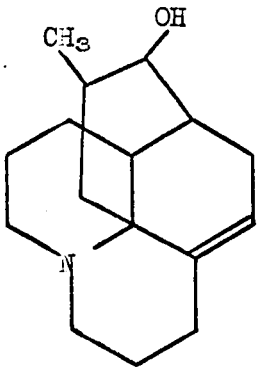
17

Annofoline



18

Fawcettiine



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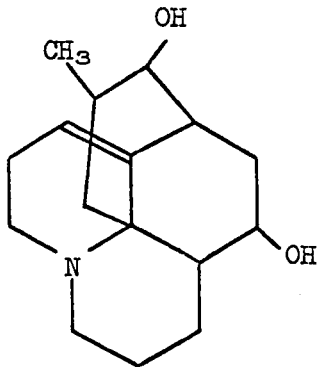


20

Lycofoline

The structure 18 for fawcettiine was assigned by simple correlation with annofoline.[28] Therefore, anhydrodeacetylfawcettiine may be represented by 19.

(f) Lycofoline

This alkaloid, $C_{16}H_{25}O_2N$, was isolated by Anet and Khan[26] from L. annotinum and more recently from L. fawcettii by Burnell and co-workers.[29]

A C-methyl group was found by Kuhn-Roth determination and the tertiary nature of the nitrogen was shown by the formation of a quarternary methiodide, $C_{16}H_{25}NO_2.CH_3I$. The infrared spectrum of lycofoline shows hydroxyl absorption and a weak band at 1675 cm^{-1}, suggesting an ethylenic double bond, probably tri-substituted.[26] Since the base formed a mono- and a diacetate it was unlikely that there was a tertiary hydroxyl group present.[30]

The n.m.r. spectrum of lycofoline[30] and the two acetates provided further information on their structure determination. The band at 9.02 τ (splitting 6 c.p.s.) confirmed the presence of a C-methyl group and indicated that the carbon bearing the methyl group had only one proton. A triplet at 4.71 τ, corresponding to one ethylenic proton, supported the suggestion that the double bond was trisubstituted. Bands at 6.14 τ and 6.82 τ, each corresponding to one proton, were assigned to CHO- groups from their chemical shifts and from the effect of acetylation on the position of these bands.

Formula 20 was arrived at as being consistent with the above facts. The structure for lycofoline was confirmed by reducing acrifoline with sodium borohydride in the presence of sodium hydroxide to give

acrifolinol and a small amount of lycofoline.[30] More recently, Burnell and Taylor[31] have confirmed the findings of Anet and co-workers.

(g) Selagine

Selagine, $C_{15}H_{18}ON_2$, was isolated by Valenta et al[32]. It contained an α-pyridone ring, a primary amino group and two C-methyl groups. Hydrogenation with Adams catalyst in acetic acid yielded tetrahydroselagine; if the hydrogenation was done in ethanol dihydroselagine resulted. Since selagine and the two hydrogenation products had identical ultraviolet spectra it was concluded, that selagine contained two isolated double bonds in addition to the α-pyridone grouping; it must therefore be bicyclic.

From the n.m.r. spectrum, it was inferred that selagine contained a disubstituted pyridone ring attached to the rest of the molecule by the 5- and 6-position; also, each of the double bonds in selagine had to be substituted by one hydrogen and one C-methyl group. This followed from the shift of one or both C-methyl peaks in dihydro- and tetrahydroselagine to higher field relative to their position in the n.m.r. spectrum of selagine. Further proof for this was derived from the Kuhn-Roth oxidation of selagine, di- and tetrahydroselagine, respectively. While selagine gave only acetic acid, dihydro- and tetrahydroselagine gave a mixture of acetic and propionic acid. These findings together with the n.m.r. spectrum of dihydroselagine showed that selagine contained an ethylidene grouping and an endocyclic double bond.

Dehydrogenation of selagine with palladium on charcoal gave 6-methyl-α-pyridone. Dehydrogenation with selenium gave azaanthracene.

All the data presented can be explained by the structure 21 for selagine.

(h) The Obscurines

The two obscurines (α and β) are minor alkaloids and occur in several species of Lycopodium. These alkaloids were first isolated by Manske and Marion[33] from Lycopodium obscurum L.

Ayer and Iverach[34] found that both α - and β -obscurine contained a N-methyl and a C-methyl group as revealed by their n.m.r. spectra. The ultraviolet spectrum indicated that β -obscurine contained an α -pyridone chromophore, while the spectrum of α -obscurine was consistent with a dihydro-α-pyridone. The double bond in α -obscurine was shown to be located in the 4.5- rather than the 2.3-position since the n.m.r. spectrum of this compound did not show the presence of a vinylic hydrogen. Hence it seemed probable that α -obscurine was simply dihydro-β -obscurine. This was confirmed by converting α -obscurine into β-obscurine by treatment with N-bromosuccinimide followed by chromatography on basic alumina.

Both obscurines showed a band characteristic for NH in the infrared spectrum; however, attempted acetylation failed.[35] This further proved that the basic nitrogen is tertiary. α -obscurine on dehydrogenation gave two products: 7-methylquinoline and 6-methyl-2-pyridone.[36]

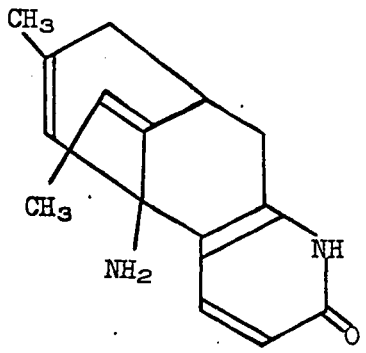
On the above evidence, Ayer and Iverach[34] assigned the structures 22 and 23 to α - and β -obscurine, respectively.

(i) Lycodine

Lycodine, a minor alkaloid of Lycopodium annotinum L. occurs only in minute quantities in the plant. It was isolated by Anet and Eves[35] who assigned to it a molecular formula $C_{17}H_{24}N_2$. This was later revised by Ayer and Iverach[37] to $C_{16}H_{22}N_2$.

Lycodine was shown to be a tetracyclic diacidic base. Ultraviolet spectral studies of the alkaloid in neutral and acid solution indicated the presence of an unconjugated pyridine chromophore. These findings were substantiated by a comparison with various substituted pyridine compounds. It showed the greatest similarity with 5,6,7,8-tetrahydroquinoline. The infrared spectrum of lycodine indicated the presence of NH (3270 cm^{-1}) and a pyridine ring (1580 cm^{-1}).[35]

Its n.m.r. spectrum at 40 Mc showed a broad peak at highest field indicating the presence of a methyl group in lycodine.[35] The presence of this group was further confirmed by a Kuhn-Roth determination and from infrared studies ($\nu_{max}^{CCl_4}$ 1382 cm^{-1}). Unlike the results at 40 Mc, it was found by Anet and Rao[38] that at 60 Mc the methyl group of lycodine was a doublet, although poorly resolved. Consistent with the findings that lycodine contains a 2,3-substituted pyridine ring, the n.m.r. spectrum showed three peaks at low field, which were assigned from low to high field as α, β, γ respectively. In fact, the spectrum of lycodine is very similar to that of 2,3-lutidine, except for a difference in the relative chemical shift of the γ-proton. The reason for the abnormal chemical shift of the γ-proton of lycodine is undoubtedly due to its proximity to the secondary nitrogen atom.[35] This is also in agreement with the large (0.34 p.p.m.) shift in the position (only) of the γ-proton on acetylation.[38]



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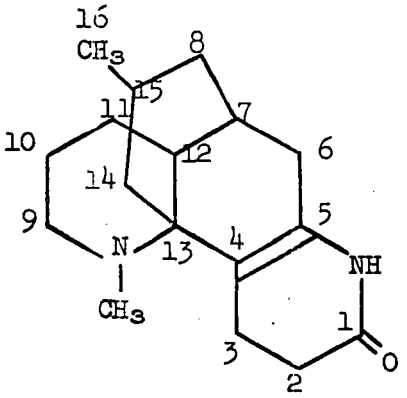
Selagine



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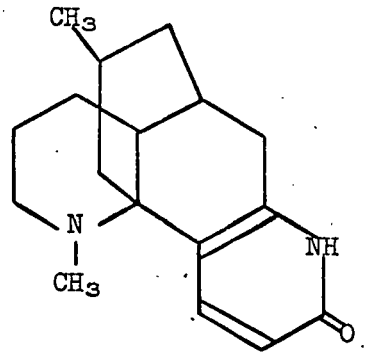
∝-obscurine



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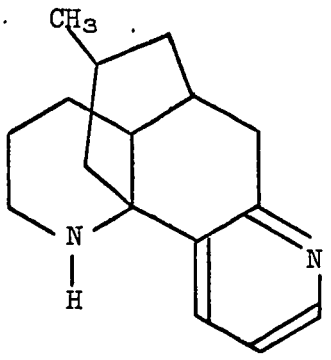
β-obscurine



24

Lycodine

A direct correlation of lycodine with lycopodine was achieved by Anet and Rao;[38] this involved an application of the von Braun degradation. β-cyanobromolycopodine[13] was treated with sodium azide, and the reaction product was hydrogenated with a palladium charcoal catalyst in the presence of acidic ethanol. The resulting base, which was partly cyclized, was dehydrogenated with palladium charcoal in boiling p-cymene. After heating with hydrochloric acid to remove the cyano group, the base obtained was identified as lycopodine.

A close similarity between lycodine and β-obscurine was suggested by Anet and Eves.[35] Ayer and Iverach[34] proposed the structure 24 as a representation of lycodine. They have succeeded in proving their proposal by a direct conversion of β-obscurine into lycodine.[37]

The chemistry and the structure of lycodine was also investigated by Anet and Rao[39] contemporaneous with the work of Ayer and Iverach.[37]

C. ASPECTS ON THE STEREOCHEMISTRY AND INTERRELATION OF SOME LYCOPODIUM ALKALOIDS

An inspection of structures 13, 15, 17 and 18 for lycopodine, acrifoline, annofoline and fawcettiine, respectively, suggests that there must be a close relationship between these alkaloids. Interrelation of these alkaloids and the elucidation of their relative stereochemistry has been done by Anet.[20]

Catalytic hydrogenation of acrifoline gave a mixture of the previously known dihydroacrifoline and about 10% of annofoline, i.e. annofoline and the known dihydroacrifoline are diastereoisomeric at C_{12} (see 13, page 6, for numbering used).

Wolff-Kishner reduction of annofoline followed by chromic acid oxidation[19, 40] gave a compound $C_{16}H_{25}ON$, m.p. 88-92°, which had structure 13; this compound was not identical with lycopodine. It was shown by Anet[20] that these two compounds differ in the configuration of the carbon atom bearing the methyl group (C_{15}).

The reduction of annofoline with sodium borohydride gave a mixture of two isomeric diols (α - and β -dihydroannofoline)[19]. The β -isomer was identical with deacetyl fawcettiine.[27] These two isomers are not merely epimeric alcohols but they are different in the configuration of the C-methyl group. Under neutral conditions the reduction of annofoline with borohydride yielded only the α -isomer. In the presence of alkali, however, up to 50% of the β -isomer was obtained.[20] That β -dihydroannofoline (deacetylfawcettiine) is not a reduction product of annofoline but a C_{15} epimer of annofoline could be shown as follows: 8-ketofawcettiine (25) and O-acetylannofoline are not identical even though both yield annofoline on alkaline hydrolysis. They must, therefore, be different in the configuration of C_{15} which is adjacent to a keto group and may epimerize under the basic conditions. It is evident from these experiments that annofoline is the more stable of the two possible C_{15} epimers. The formation of deacetylfawcettiine on borohydride reduction of annofoline under alkaline conditions may be explained as follows: a base catalyzed equilibrium is very rapidly established between annofoline and its C_{15} epimer. The hydride reduction of this last compound proceeds at a much faster rate than the reduction of annofoline.

Since annofoline and acrifoline exist as mixtures of hemiketal and internally hydrogen-bonded hydroxyketone forms, ring D must exist

predominantly in the boat form. In the chair form there is a very strong repulsion between C_{15} and the axial hydroxyl group on C_5. Furthermore, since annofoline was shown to be the stable isomer at C_{15}, it may be deduced that the methyl group is equatorial on ring D.(see Fig. 1).

In derivatives which do not possess a C_5 axial substituent or if there is a 4,5- or 5,6-double bond, then ring D will be more stable in the chair form.[20] In this conformation the stable isomer at C_{15} has the opposite configuration to that in 17, i.e. equatorial methyl as in 27.

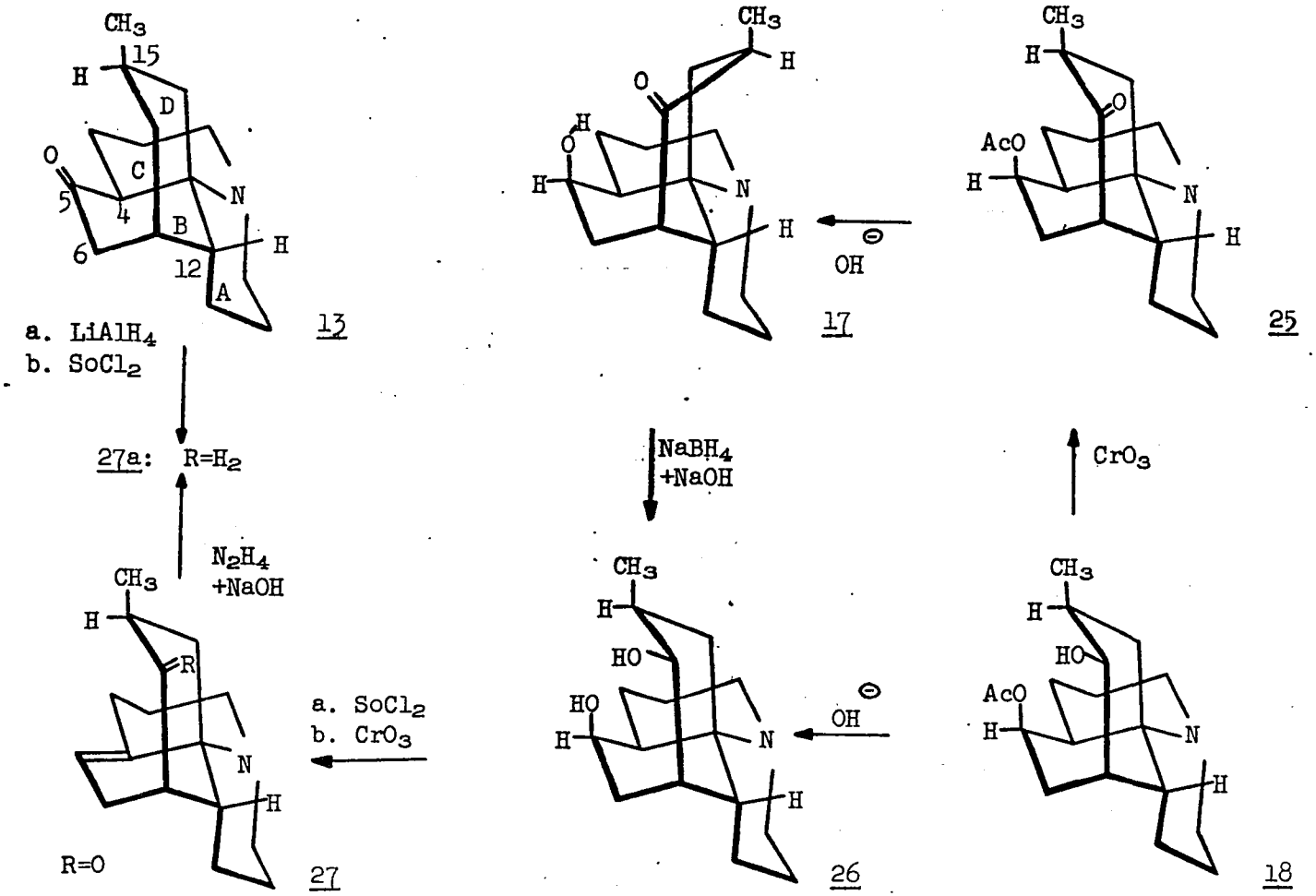
Compound 27 was obtained by oxidation of anhydrodeacetyl-fawcettiine[27], previously prepared by Burnell from deacetylfawcettiine(26). Wolff-Kishner reduction of the ketone gave an oily base, identified as anhydrodihydrolycopodine (27a). The latter compound was also prepared from lycopodine by reduction with lithium aluminum hydride followed by dehydration.[41]

The stability of lycopodine to base shows that ring B and C are trans-fused. The ready dehydration of dihydrolycopodine confirmed this conclusion. Rings A and B are cis-fused which could be shown as follows: α -cyanobromolycopodine was known to be cyclized by base by internal alkylation in a position α to the keto group (i.e. C_4 or C_6). This would be feasible if the ring residue in α -cyanobromolycopodine were axial on ring B.

In deacetylfawcettiine (26) the chair form for ring D should be favored, since the methyl group would be in the extremely unfavorable flagpole position if ring D existed as a boat. The C_8 hydroxyl is equatorial and trans to the methyl group. This is consistent with the stability of the C_8 hydroxyl group to dehydration. The interrelation of fawcettiine, annofoline and lycopodine is shown graphically in Fig. 1.

FIGURE 1

STEREOCHEMISTRY AND INTERRELATION OF SOME LYCOPODIUM ALKALOIDS



PART II

A. GENERAL INTRODUCTION

Bridged rings have long been known in considerable variety. They are associated for instance with terpene derivatives in the camphor series and with the Lycopodium alkaloids; many other systems are recorded in the literature[42]. The atoms for the ring system may include hetero-atoms such as nitrogen, sulfur etc.[43].

B. NOMENCLATURE

In bridged systems the rings are linked through non-adjacent atoms and there are at least three atoms common to the two rings. The bridge is indicated by placing numerals in brackets. The numerals indicate the number of atoms in the chains between the bridgeheads; the bridge is the last of the bracketed numerals.

C. THE [3.3.1] BICYCLONONANE SYSTEM

(a) Compounds Containing No Hetero Atoms

The prototype of this ring system, bicyclo[3.3.1] nonane (28)*, was first synthesized by Meerwein and his co-workers[44a,b]. This compound shows the remarkable high melting point of 145°C.

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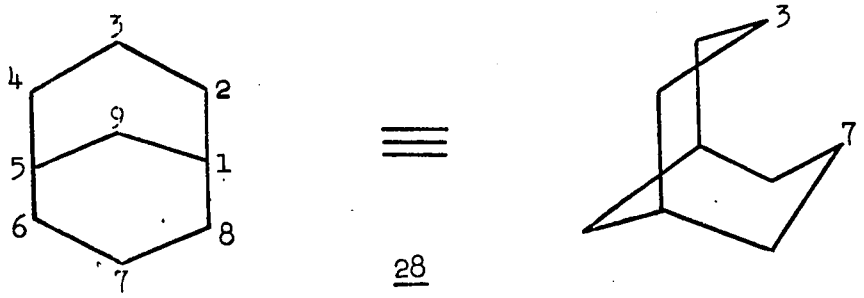
* M.J.T. Robinson showed by a combination of infrared, n.m.r. kinetic and dipole moment evidence that the two-chair conformation for 28 is favored. This conclusion was confirmed by spectroscopic work of J. Martin and W. Parker. 19th International Congress of Pure and Applied Chemistry, London, 1963. Chemistry and Industry, 1345 (1963).



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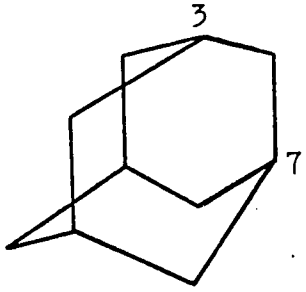

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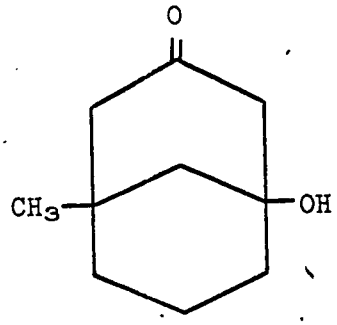

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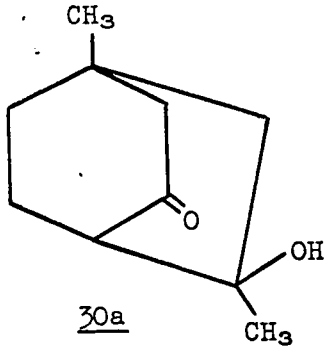

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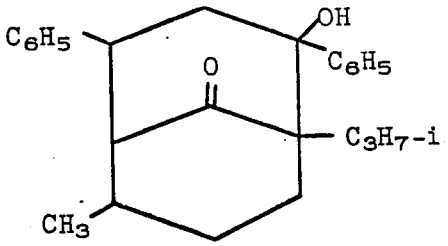


31

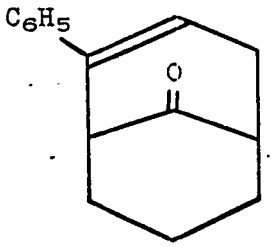
A hydrocarbon which contains this bicyclic system is adamantane (29). In this compound the methylene groups C_3 and C_7 in the chair-chair form of bicyclo[3.3.1]nonane are bridged by another methylene group. It was first prepared by Prelog and Seiwerth[45]; the molecule is now readily accessible by the elegant method of Schleyer[46].

The reaction of 3-acetonyl-3-methylcyclohexanone with base was shown to yield the bicyclo-ketone 30 and not 30a[47]. The product and its xanthate resisted dehydration and the corresponding chloride, prepared by the action of phosphorous pentachloride, could not be dehydrochlorinated, both in accordance with the bridged structure 30.

Stobbe[48] reported the synthesis of a cyclic ketoalcohol (31) which was obtained when menthone was added to benzalacetophenone and the intermediate ketone was cyclized by the action of hydrogen chloride in warm alcohol.

The bicyclic ketones 32-34 having one double bond β,γ to the carbonyl bridge were prepared by Cope and co-workers[49a,b,c]. Starting from 34 Cope and Graham[50] prepared 1-bromo-bicyclo[3.3.1] nonan-9-one (35); when this compound was treated with an aqueous silver nitrate solution no substituted ketone could be obtained. Instead, it was converted to bicyclo[3.3.0]octan-1-carboxylic acid by ring contraction.

A ring system similar to that of 32 was described by Prelog[51] who prepared 4-methylbicyclo[3.3.1]non-3-en-1-carboxylic acid by treating γ-(1-ethoxycarbonyl-2-keto-cyclohexyl) crotyl chloride with sulfuric acid.



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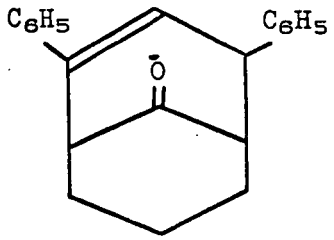

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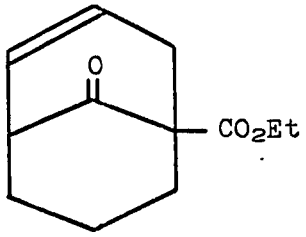

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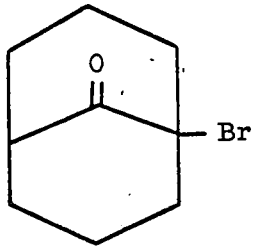

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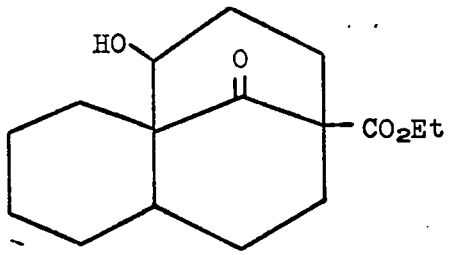

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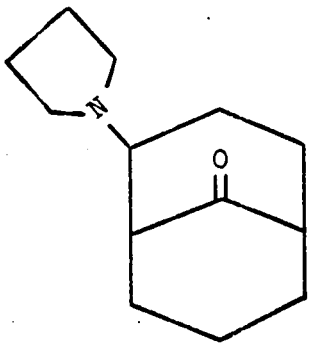

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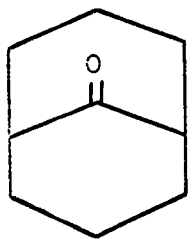

38

Haworth and his co-workers[52] prepared the compound 36 by treating ethyl-1-oxo-2-3'-oxopropyldecalin-2-carboxylate with acid in a manner similar to that employed by Cope and Synerholm[49c]. The structural assignment was based entirely on spectroscopic evidence in the infrared region; the product showed a hydroxyl peak at 3670 cm^{-1}.

The reaction of α,β -unsaturated aldehydes with enamines leads to bicyclic amino-ketones[53] which are formally the product of an internal Mannich reaction of the expected aldehydoketone and the secondary amine used to form the enamine. The condensation of the pyrrolidine enamine of cyclohexanone and acrolein in benzene gave 37.

Gutsche and co-workers[54] studied the reactions of cyclo-alkanones carrying two-carbon and four-carbon side chains with potential diazoalkyl moieties. When N-nitroso-N-acetyl-4-(2'-ketocyclopentyl)-butylamine was decomposed in alcoholic base, an almost quantitative yield of a mixture containing two materials in a ratio of ca. 2 to 1 was obtained. The major fraction was identified as 2-keto-bicyclo[4.3.0] nonane. The other constituent was shown to be 9-ketobicyclo[3.3.1] nonane (38) by its analysis, by a carbonyl absorption at 1715 cm^{-1} and by its chemical properties*.

The preparation of bicyclo[3.3.1]nonane derivatives was studied in some detail by Murray, Parker and Raphael[55] in an effort to find suitably substituted intermediates for the synthesis of clovene. High dilution Dieckmann cyclization of dimethyl-1-methoxycarbonyl-3-

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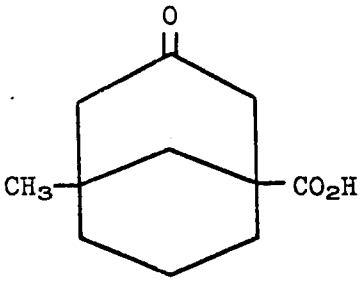
* The preparation of 38 is described in the Ph.D. thesis of C. Foote, Harvard University, 1961. Quoted by Gutsche and co-workers[54].

methylcyclohexane-1:3-diacetate followed by acid hydrolysis and decarboxylation furnished a mixture of the two bicyclo ketoacids 39 and 40. From this mixture, 39 was separated by solvent trituration. A more convenient approach[56] was the acid-catalyzed cyclization of β-(1-ethoxycarbonyl-2-keto-3-methyl cyclohexyl) propionaldehyde. By analogy with previously described examples[49c], ethyl-5-methylbicyclo [3.3.1] non-3-en-9-one-1-carboxylate (41) was obtained in an acceptable yield; it constituted the main component of the reaction mixture. The structure was confirmed by its light absorption and by its general chemical properties.

In several instances when the Robinson annelation method was being used - typified in its simplest form by the condensation of methyl vinylketone with cyclohexanone to produce the octalone 42 - intermediary ketols have been isolated. These substances have invariably been formulated as the ketol which is the direct precursor of the unsaturated ketone formed by a β-elimination process, e.g. 43 → 42. Johnson and his co-workers[57] demonstrated that these ketols may be, on the contrary, correctly represented by a bridged-ring expression like that shown in formula 44.

The methoxide - catalyzed reaction of the tricyclic ketone 45 with methyl vinylketone gave a mixture of isomeric ketols. These ketols were formulated as the two epimeric racemic ketols 46a and 46b. However, chemical evidence provided unequivocal proof that these ketols are bridged-ring epimers with the structure 47[57]. Further confirmation for this structure was provided by the nuclear magnetic resonance spectrum of the mono-acetates.



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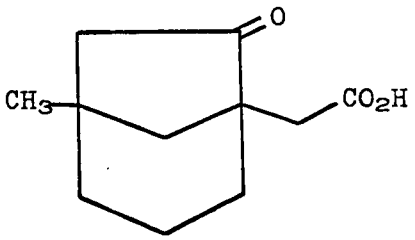

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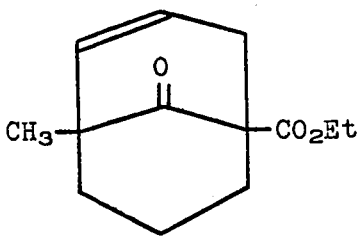

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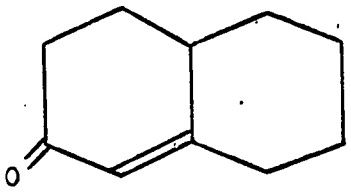

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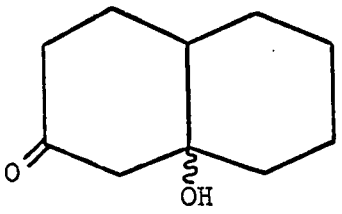

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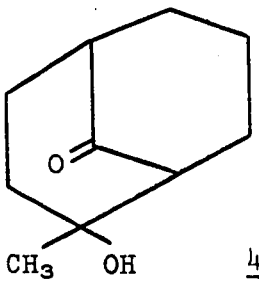

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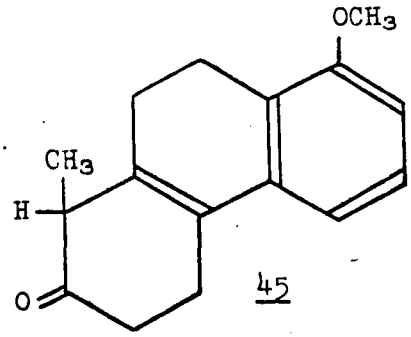

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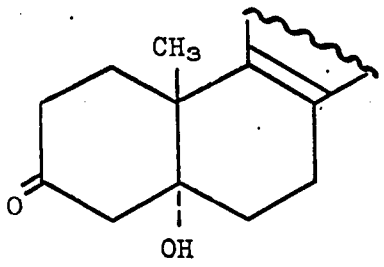

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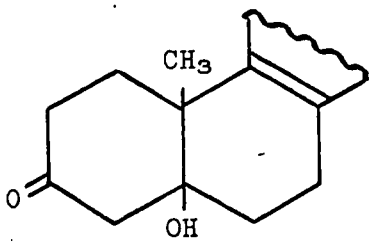
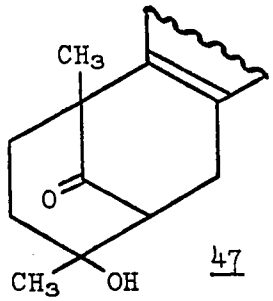


46b



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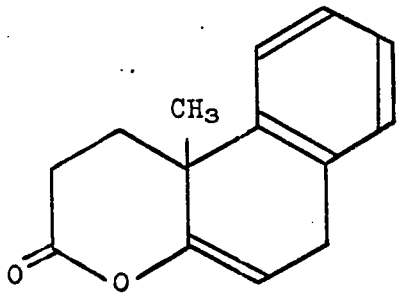

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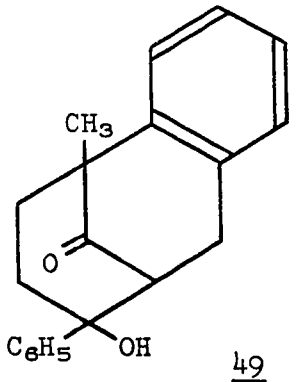
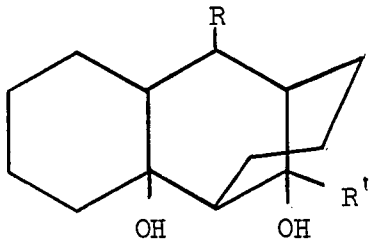


49

Formation of this type of ketol was shown by Zwahlen, Horton and Fujimoto[58] to arise also from the reaction of phenyl magnesium bromide with an enol lactone, (48 → 49). The same ketol (49) was produced by the condensation of 1-methyl-2-tetralone with β-dimethyl-aminopropiophenone.

Julia and co-workers[59a,b] described the preparation of a number of 2,3-cyclohexanobicyclo[3.3.1]nonan-diols-(2,9) (50); see Table 1.



50

(b) Compounds Containing One Nitrogen Hetero Atom

A considerable number of derivatives of the bicyclo[3.3.1]nonane type containing hetero atoms, have been described. Perhaps the most frequently encountered compounds in this category are the aza-analogues. For example, the product obtained from the Dieckmann cyclization of 51 was the bicyclic compound 52[60]. Similarly, 1-aza-bicyclo[3.3.1]nonan-4-one and its 2-methyl homologue were prepared in a 25% yield by this reaction[62].

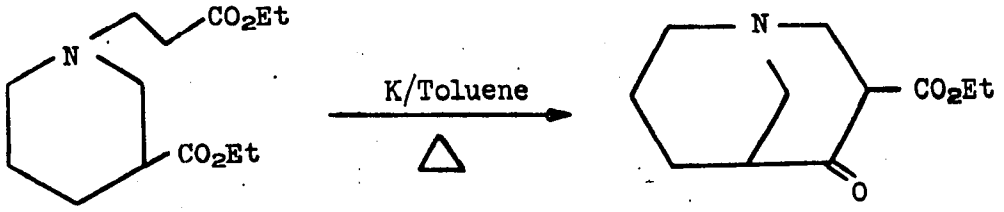
The prototype of this ring system, 1-azabicyclo[3.3.1]nonane (53) was prepared by Prelog, Heimbach and Seiwerth[62]. A 5-substituted (R = C_6H_5) analogue of 53 was obtained[63] inter alia in a 20% yield by

TABLE 1

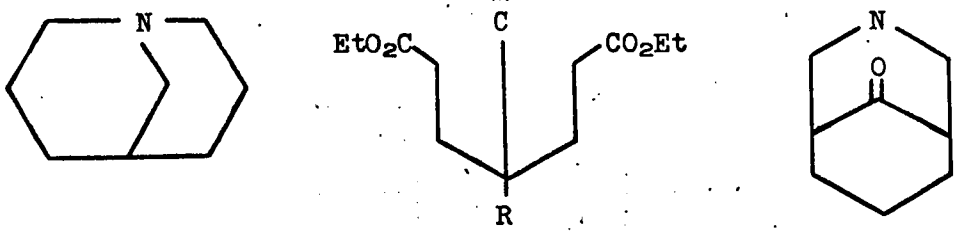
4-(R) and/or 9-(R') substituted

2,3-cyclohexanobicyclo[3.3.1]nonane-diols-(2,9)

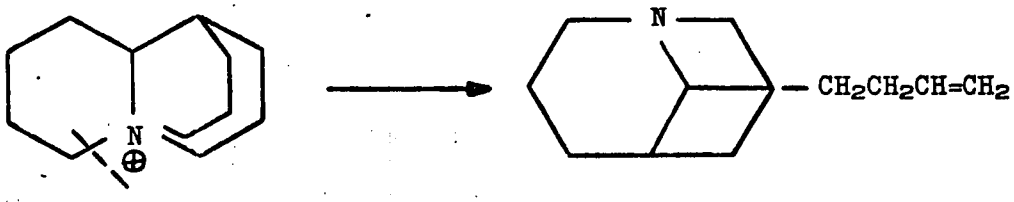
R	R'	R	R'
H	H	H	CH_3
CH_3	H	CH_3	CH_3
C_6H_5	H	C_6H_5	CH_3
CH_3OCH_2	H	CH_3OCH_2	CH_3
$CH_3CH_2OCH_2$	H	$CH_3CH_2OCH_2$	CH_3



51 52



53 54 55



56 57

the hydrogenation of 54 in dioxane solution using a copper chromite catalyst. House and co-workers[64] prepared 3-methyl-3-azabicyclo[3.3.1] non-9-one (55) from the reaction of cyclohexanone with formaldehyde and methylamine in acetic acid.

When 56 was subjected to a Hofmann degradation three products were isolated[65], one of which was thought to be 57, formed by scission of 56 at the dotted line.

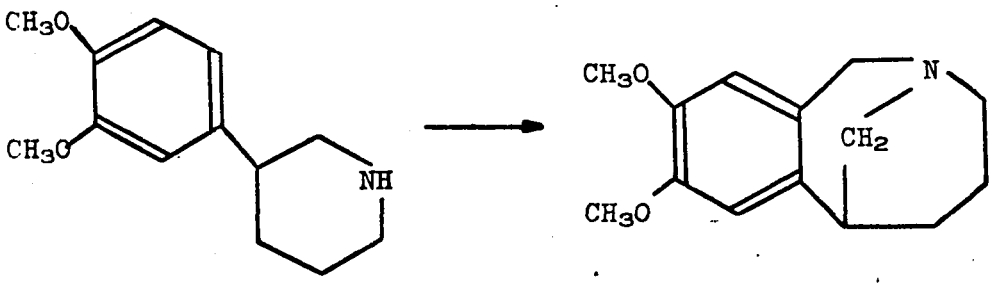
Treatment of 58 with aqueous formaldehyde yielded 1-aza-3,4:1', 2'-(4',5'-dimethoxybenzo)bicyclo[3.3.1]nonane (59)[66].

Ferris and Miller[67] have recently reported the synthesis of 1-carboxy-2-oxo-3-ethylazabicyclo[3.3.1]nonane (60) as a model for the heterocyclic ring system of lycoctonamic acid.

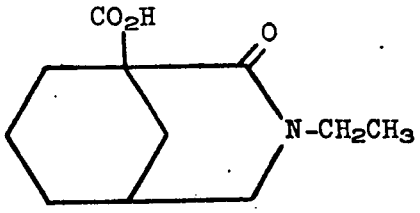
(c) Compounds Containing Two Nitrogen Hetero Atoms

Compounds of the bicyclo[3.3.1]nonane type containing two nitrogen atoms are also known. Bäumler and his co-workers[68] reported that 62 resulted from cyclodehydrohalogenation of 61. Similarly, the Prévost oxidation of 63 yielded a product thought to be 64[69]. Einhorn and Mauermayer[70] reacted methylenediamine with diethylmalonyl chloride to give the 1,5-diazabicyclo[3.3.1]nonane 65. These products would seem to be examples of the "forbidden" bridgehead amide type[71]. The 1,5-diazabicyclo system is also contained in Tröger's base (66).

Recently, Billman and Dorman[72] showed, that 1,5-diazacyclo-öctane undergoes an intramolecular condensation reaction with aromatic aldehydes to form exclusively 9-substituted 1,5-diazabicyclo[3.3.1] nonanes (67). The absense of any N-H absorption in the infrared spectrum clearly demonstrated that both NH groups of 1,5-diazacycloöctane participated in the condensation reaction.



58 59



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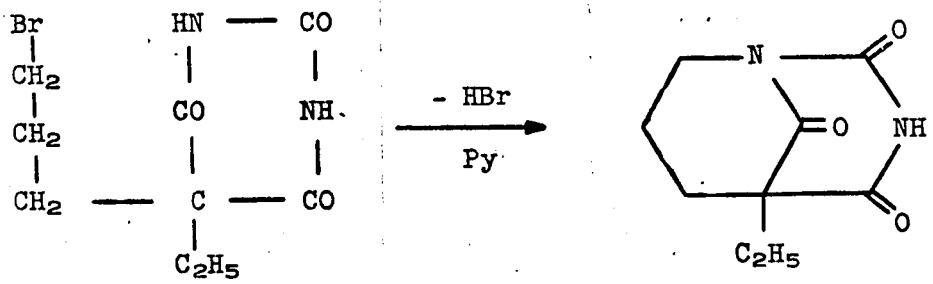
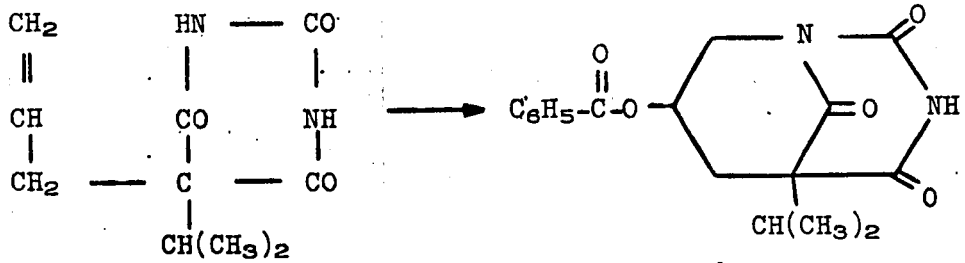


61 62



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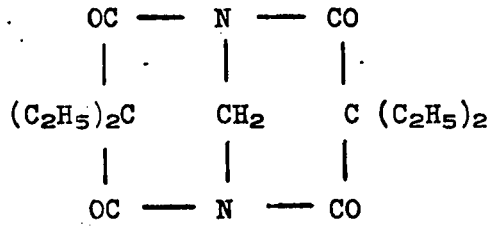

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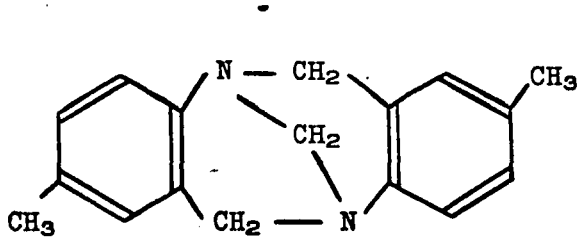

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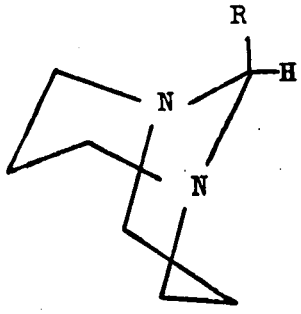

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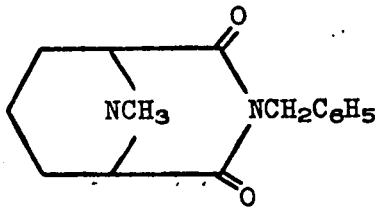

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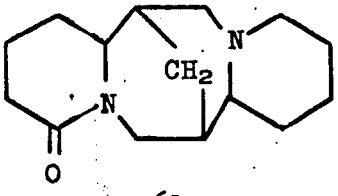

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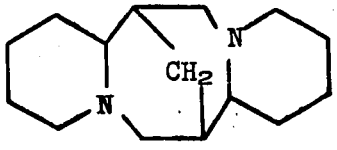

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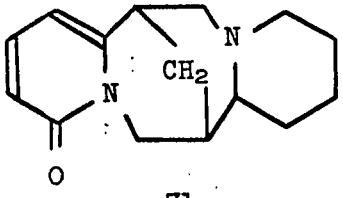


71

Robinson and Blount[73] synthesized some analogues of pseudopelletierine; one of these compounds, containing the 3,9-diazabicyclo[3.3.1]nonane system, was N-methyl-aztropinone.

Barnes and Fales[74] described the condensation of dimethylscopolinate with benzylamine to yield the bicyclic imide 68.

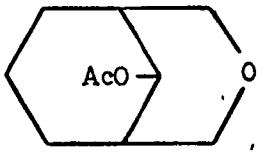
Certain of the lupine alkaloids[75], e.g. lupanine (69), sparteine (70) and anagyrine (71) are representatives of the 3,7-diazabicyclo[3.3.1] nonane system.

(d) Miscellaneous Compounds

(i) Oxygen as Hetero Atom: The acetate of 3-oxabicyclo [3.3.1]nonan-9-ol (72) was obtained in 22% yield from 3-hydroxymethylcyclohexene under the conditions of the Prins reaction[76].

(ii) Nitrogen and Sulfur as Hetero Atoms: The reaction of ammonium sulfide solutions with formaldehyde yields a product with two different hetero atoms. It was first obtained by Delépine[77] who assigned the structure 73. Lefèvre and Lefèvre[78] assigned the more probable structure 74 to this product.

(iii) Boron as Hetero Atom: Köster and co-workers[79a,b] have shown that organoboranes derived from dienes are frequently bridged structures. In searching for a convenient synthetic route to 4-cyclooctene-1-ol, Sharma, Shoulders and Gardner[80] have examined the reaction between 1,5-cyclooctadiene, sodium borohydride and boron-fluoride. This reaction gave after thermal equilibration essentially a single reaction product; its constitution was formulated as 75, based on chemical and n.m.r. evidence.



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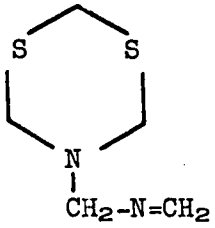

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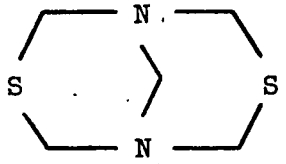

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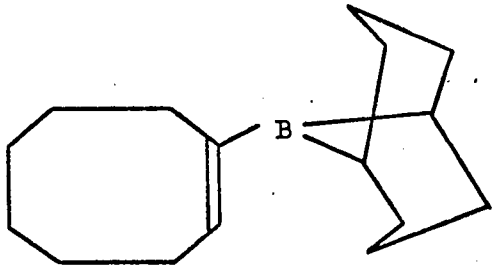

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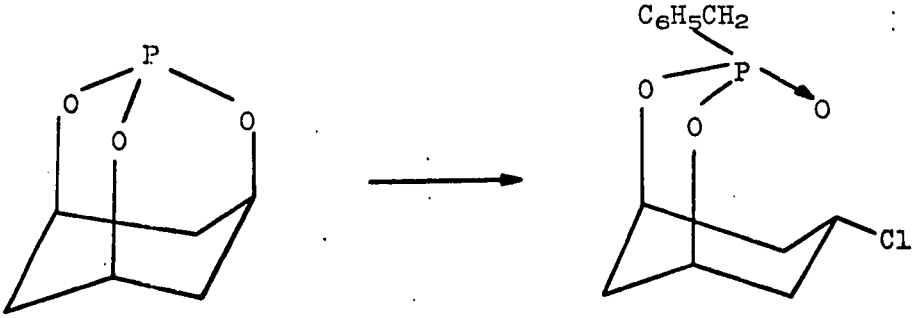

76 77

(iv) Phosphorous and Oxygen as Hetero Atoms: Berlin and co-workers[81] have recently isolated a novel type of [3.3.1] bicyclononane system. When 1-phospha-2,8,9-trioxaadamantane (76) was heated under nitrogen with a slight excess of benzylchloride a bicyclic phosphonate (77) - conformation as yet not confirmed - was isolated in 66% yield.

EXPERIMENTAL

A. DESCRIPTION OF GENERAL METHODS

The melting points (uncorrected) were determined on an electrically heated copper block using glass capillaries. The infrared spectra were measured as films or nujol mulls on a Perkin Elmer "Infracord" double beam instrument. The ultraviolet spectra were recorded using a Beckmann DK-2 spectrophotometer in ethanol solution in 1 cm cells. The nuclear magnetic resonance (n.m.r.) spectra were obtained on a Varian V-4302 high-resolution spectrometer operating at a frequency of 60 Mc/s. All compounds were studied as approximately 10-15% solutions containing a few drops of tetramethylsilane as internal reference. The spectra were calibrated by the use of audiofrequency side bands measured with a frequency counter. The chemical shifts are reported on Tier's scale[82]:

$$\tau \text{ (ppm)} = 10.0 - 10^6 \frac{(H_{ref} - H)}{H_{ref}}$$

where H = magnetic field at resonance. In the case of multiplets, τ values refer to the origin[83]. The "apparent" coupling constants or "splittings"[84] are reported in cycles per second (cps). In all cases the spectra were taken with increasing as well as with decreasing magnetic fields.

B. SYNTHETIC PROCEDURES

2-Chlorocyclohexanone.

It was prepared according to the method of Newman et al.[85].

Infrared: ν_{max}^{film} 1725 cm^{-1} (C=O), shoulder at 1745 cm^{-1}; 700 cm^{-1} and 715 cm^{-1} (C-Cl stretch)[86].

N.m.r.: see Table 2a.

2-Cyanocyclohexanone.

Method a.

200 gms of pure potassium cyanide were added to 600 ml of water in a 3-necked flask equipped with a reflux condenser, stirrer and dropping funnel. The solution was heated to 80°C. 217 gms of freshly distilled 2-chlorocyclohexanone were added with stirring over a fifty minute period[87]. The mixture was stirred for an additional 10-15 minutes at 80-90°C; it was then poured on 1500 ml of crushed ice, acidified to congo and extracted with several portions of ether. The combined ether extracts were washed with water, saturated sodium chloride solution and dried (Na_2SO_4). After filtration and evaporation of the ether, the dark brown oil was distilled through a Vigreux column to give 80 gms (39%) of a clear oil, b.p 122-123° C/5 mm. The yields in separate experiments varied between 35 and 40%. The dark brown acidic residue was not further investigated.

Infrared: ν_{max}^{film} 3450 cm^{-1} broad (O-H); 2275 cm^{-1} (-C≡N), 2220 cm^{-1} (conj. -C≡N); 1730 cm^{-1} (C=O), shoulder at 1750 cm^{-1}; 1675 cm^{-1} (tetrasubst. C=C); 1640 cm^{-1} (conj. C=C).

N.m.r.: see Table 2a.

Calculated for C_7H_9NO: C, 68.27 H, 7.37 N, 11.38

Found: C, 68.38 H, 7.09 N, 11.53

Method b.

15 gms of sodium cyanide (dried at 110°C overnight) were added to 80 ml of dry dimethylsulfoxide[88] (distilled over calcium hydride) in a 3-necked flask equipped with stirrer, thermometer, dropping funnel and reflux condenser. The slurry was subsequently heated to 90°C. 33.4 gms of freshly distilled 2-chlorocyclohexanone were added slowly to the stirred mixture. The rate of addition was adjusted so that the temperature did not rise above 160°. After completion of addition, the mixture was stirred for another 10 minutes and was then poured into 200 ml of ice-water; the mixture was extracted with ether. After removal of the solvent the residue was distilled to give 3.4 gms of an oil; its infrared spectrum was identical with that obtained above. This reaction was not further investigated.

Method c.

Nitrogen was passed through a solution of 9.8 gms of cyclohexanone, 7.5 gms of pyrrolidine and 38 ml of benzene; the solution contained a few crystals of p-toluenesulfonic acid. The mixture was refluxed under nitrogen using a water trap, until the separation of the water had stopped. 1.8 ml of water were collected. The benzene was distilled slowly and the residue was distilled under reduced pressure to give 13.2 gms of the enamine (74-75° C/.11 to .12 mm)[89].

The distilled enamine (6 gms) and 4.1 gms of triethylamine were dissolved in 50 ml of dioxane, distilled from sodium, and 2.5 gms of cyanogenbromide in 10 ml of dioxane were added in a slow stream with stirring, keeping the temperature between 5-10°C. The reaction was kept at 5-10°C for another two hours and then overnight at room temperature.

It was poured into 300 ml of ice-water; the mixture was acidified to Congo with 10% HCl. Ether was added and the acidity was maintained during shaking by adding a little acid periodically.

The ether solution was washed with water, saturated salt solution and dried. The oily residue, 5.3 gms, after evaporation of the ether, was not identical with the cyanocyclohexanone obtained above. This reaction was not further investigated.

1-Cyano-3-methyl-4-hydroxybicyclo[3.3.1]nonan-9-one, (78).

A mixture of 81.5 gms of 2-cyanocyclohexanone and 56 gms of freshly distilled α-methylacrolein was cooled to 10°C in a 2-necked flask equipped with a reflux condenser and a dropping funnel. 10 ml of 37% Triton-B-methoxide was added dropwise to the stirred mixture; the temperature rose sharply to 160°C after the addition of the first few drops of the base. The mixture was stirred for 1 hour; it was then allowed to stand at room temperature for 2 days. The material partially crystallized on standing. 200 ml of ether was added to the reaction mixture and the crystalline material was filtered off; the ether solution was washed with a buffer solution (pH~6), water, saturated sodium chloride solution and dried (Na_2SO_4). Recrystallization from ethanol-petroleum ether (80/100)* gave the pure ketol (64 gms, 54%), m.p. 125-127°C. The viscous residue was not further investigated.

Infrared: ν_{max}^{Nujol} 3460 cm^{-1} (O-H); 2255 cm^{-1} (-C≡N); 1720 cm^{-1} (C=O); 1050 cm^{-1} (C-OH).

N.m.r.: see Table 2a.

Calculated for $C_{11}H_{15}O_2N$: C, 68.37 H, 7.82 N, 7.25

Found: C, 68.29 H, 7.74 N, 7.37

* b.p. 80-100°C

1-Cyano-3-methyl-4-acetoxybicyclo[3.3.1]nonan-9-one, (79).

60 ml of acetic anhydride were added to a solution of 3.6 gms of the ketol 78 in 120 ml of dry pyridine, and the mixture was allowed to stand for 18 hours at room temperature. The solution was diluted with 250 ml of cold benzene, then washed with a 10% HCl solution followed by a cold 10% sodium carbonate solution. After drying ($MgSO_4$) and evaporation of the solvent the crude crystalline residue was recrystallized from chloroform-petroleum ether (80/100). Two crystalline fractions were obtained; a "low" melting acetate (79a) with a m.p. of 119-120°C (fine needles: 1.56 gms) and a "high" melting acetate (79b) with a m.p. of 156-158°C (hexagonal prism; 1.61 gms). The total yield of pure acetate mixture ($\sim$ 1:1) was 3.17 gms (72%).

Infrared: (i) "high" melting acetate: ν_{max}^{Nujol} 2240 cm^{-1} (-C≡N); 1730 cm^{-1} (C=O, ester); 1720 cm^{-1} (C=O, ketone); multiplet centered at 1240 cm^{-1} (C-O-C stretch, ester).

(ii) "low" melting acetate: ν_{max}^{Nujol} 2250 cm^{-1} (C≡N); 1730 cm^{-1} (C=O, not resolved); 1230 cm^{-1} (C-O-C stretch, ester).

N.m.r.: see Table 2b.

Calculated for $C_{13}H_{17}O_3N$: C, 66.36 H, 7.28 N, 5.95

Found: (i) "high" melting acetate: C, 66.33 H, 7.0 N, 5.81

(ii) "low" melting acetate: C, 66.39 H, 7.06 N, 5.92

Attempted dehydration of 1-cyano-3-methyl-4-hydroxybicyclo[3.3.1] nonan-9-one.

Method a.

A solution of 1 gm of 78 in 50 ml of dry pyridine was treated with 3 gms of $POCl_3$. After heating at 90° for 3.5 hours the mixture was poured into 200 ml of benzene. The benzene solution was washed successively with dilute hydrochloric acid, dilute sodium hydroxide and water. Evaporation of the benzene gave a crystalline compound. The infrared and the n.m.r. spectrum did not show any absorption for C=C-H. The compound failed to give a Br_2/CCl_4 test.

Method b.

To a cold solution of 0.97 gms of 78 in 19 ml of pyridine 1 ml of freshly distilled thionylchloride was added. The mixture was kept in the cold for 17 hours. It was decomposed in ice-water and extracted with ether. The ethereal extract was washed with dilute sodium-bicarbonate solution, water and saturated salt solution. Evaporation of the solvent gave 1.1 gms of an oil. The compound gave a negative Br_2/CCl_4 test.

Infrared: ν_{max}^{film} 1190 cm^{-1} strong (sulfite ester)

N.m.r.: No signal for C=C-H.

Method c.

The tosylate of 78 (prepared from 1.93 gms of 78 and 2.9 gms of pure toluenesulfonylchloride in 11.5 ml of dry pyridine) was refluxed with 2,6-dimethylpyridine for three hours. The material which was isolated after the usual work-up failed to show any sign of unsaturation. Its infrared spectrum was identical with that of the starting material.

Infrared: ν_{max}^{Nujol} 2240 cm^{-1} (-C≡N); 1720 cm^{-1} (C=O); 1600 cm^{-1} (C=C aromatic); 1300 cm^{-1} (-S$\leqslant^{O}_{O}$ asymm. stretch); 1170 cm^{-1} (-S$\leqslant^{O}_{O}$ symm. stretch).

1-Cyano-3-methylbicyclo[3.3.1]nonan-4,9-dione, (80).

A solution of 1.5 gms of the ketol in 15 ml of dry pyridine was added to a slurry of 1.5 gms of CrO_3 in 15 ml of dry pyridine[90]. It was kept 20 hours at room temperature and was then poured into 50 ml of water. After filtration through a glass wool mat, it was extracted with ether-benzene (1:1), washed with water and dried (Na_2SO_4). Evaporation of the solvent gave essentially pure diketone (1.3 gms, 87%). It was recrystallized from ethylacetate-petroleum ether (80/100), m.p. 118-120°C.

Infrared: ν_{max}^{Nujol} 2260 cm^{-1} (-C≡N); 1740 cm^{-1} and 1690 cm^{-1} (C=O).

Ultraviolet: λ_{max}^{EtOH} 291.5 mμ (ε 72).

N.m.r.: see Table 2b.

Calculated for $C_{11}H_{13}O_2N$: C, 69.09 H, 6.85

Found: C, 69.30 H, 7.06

1-Cyano-3-methyl-4,9-dihydroxybicyclo[3.3.1]nonane, (81).

5.8 gms of the ketol 78 were dissolved in 75 ml of 95% ethanol and 3.4 gms of sodium borohydride in 15 ml of 95% ethanol were added slowly to the stirred solution. The mixture was stirred for 3 hours at 60-70°. After cooling, the excess sodium borohydride was carefully decomposed with 1:1 acetic acid. The residue obtained after evaporation was extracted with chloroform; the extract was washed with water, saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to yield 5 gms of an oil.

Infrared: ν_{max}^{film} 3400 cm^{-1} broad (O-H); 2250 cm^{-1} (-C≡N); 1050 cm^{-1} (C-OH).

3-Methyl-4,9-dihydroxybicyclo[3.3.1]nonan-1-carboxylic acid amide, (82).

5 gms of the crude diol 81 were dissolved in 20 ml of ethanol and 13 ml of 30% hydrogen peroxide were added[91]. The pH of the solution was adjusted to 8 with 6N NaOH and the mixture was stirred at 50-60° overnight. An additional 10 ml of 30% hydrogen was added and the mixture was stirred again at 50-60°C for 18 hours. The pH of the solution was kept at 8 throughout the reaction. After cooling and acidification (1:1 acetic acid) to a pH of 6 the solvent was evaporated and the residue was dissolved in chloroform. The chloroform extracts were washed with water and brine. Concentration of the chloroform solution gave 1.7 gms of an oil. The amide was recrystallized from ethanol-petroleum ether (80/100), m.p. 178-180°C.

Infrared: ν_{max}^{Nujol} 3200-3500 cm^{-1} and 3350 cm^{-1} (O-H and N-H); 1665 cm^{-1} (amide-I); 1590 cm^{-1} (amide-II); 1050 cm^{-1} (C-OH).

Calculated for $C_{11}H_{19}NO_3$: C, 61.94 H, 8.98

Found: C, 61.84 H, 8.82

1-Amino-3-methyl-4,9-dihydroxybicyclo[3.3.1]nonane, (83).

0.43 ml of bromine was added dropwise to a solution of 1.7 gms of sodium hydroxide in 14 ml of water cooled to 0°. To the clear solution 1.5 gms of the amide (82) were added immediately; stirring was continued for 20 minutes after all of the amide was dissolved. During this time a white solid precipitated from the solution.* The reaction mixture was then heated to 70°C and it was stirred at this temperature for 20 minutes. At the end of this time it was cooled to room temperature. The solution was filtered to remove the insoluble material (see below). The remaining solution was thoroughly extracted with ether; the combined ether extracts were washed with water and brine. The amine crystallized readily after concentration of the organic phase. It was recrystallized from ethanol, m.p. 152°.

Infrared: ν_{max}^{Nujol} 3350 cm^{-1} (N-H and O-H) 1610 cm^{-1} ($-NH_2$ scissor).

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* See Discussion, page 88.

Calculated for $C_{10}H_{19}NO_2$: C, 64.83 H, 10.34 N, 7.56

Found: C, 65.02 H, 9.82 N, 7.59

C, 64.43 H, 10.32 N, 7.59

Picrate: m.p. 203-205°C

The insoluble material, m.p. 286-290°C, was recrystallized from ethylacetate.

Calculated for $C_{22}H_{36}N_2O_6$: C, 62.24 H, 8.55

Found; C, 62.35 H, 8.21

4-Ethylenedioxycyclohexanone.

It was prepared from quinitol according to the methods of Prins et al[92].

Attempted selective ketalization of 1,4-cyclohexanedione.

A mixture of 10.5 gms (0.95 moles) 1,4-cyclohexanedione and 5.9 gms (0.95 moles) of ethyleneglycol in 110 ml of benzene containing a few crystals of p-toluenesulfonic acid was refluxed for 3 hours using a water trap. 1.6 ml of water were collected. After cooling, the benzene solution was washed with dilute sodium bicarbonate and dried (Na_2SO_4). Evaporation of the solvent gave 12 gms of an oil. It was a mixture of starting material, 4-ethylenedioxycyclohexanone, and 1,4-bisethylenedioxycyclohexane.

N.m.r.: see Table 2c.

2-Hydroxymethylene cyclohexanonane.

The method followed in this procedure was essentially that of Woodward et al.[93].

Preparation of 4,5,6,7-Tetrahydro-1,2-benzisoxazole

A solution of 16.9 gms of 2-hydroxymethylene cyclohexanone, 10 gms of hydroxylamine-hydrochloride and 500 ml of an acetic acid-sodium acetate mixture with a pH of 5 (0.9 ml of acetic acid/250 ml of water; 8 gms of sodium acetate/250 ml of water) was refluxed for two hours.

After evaporation of the water and acetic acid, the residue was extracted with chloroform. The organic extract was washed with ice-cold 2% sodiumhydroxide solution, saturated salt solution and dried (Na_2SO_4). 3.2 gms (19%) of the isoxazole were obtained after evaporation of the solvent.

Infrared: ν_{max}^{film} 1630 and 1610 cm^{-1} (C=C and C=N-stretch).

The isoxazole was converted by the method of Kuehne[89] into 2-cyanocyclohexanone. The infrared spectrum of the ketonitrile obtained by this procedure was identical to that obtained previously (vide supra).

2-Carbomethoxy-4-ethylenedioxycyclohexanone, (85).

This compound was prepared from furfural as described by Sarett et al.[94] .

A modification was introduced during the last step of the Sarett procedure, i.e. the base-catalyzed cyclization of dimethyl γ-ethylenedioxypimelate to 85. In the original procedure, a mixture of dimethyl γ-ethylenedioxypimelate, sodium dried ether and sodium hydride was refluxed in a nitrogen atmosphere for 5 days. However, if a trace of methanol was added the reaction was complete within 5 hours.

Infrared: ν_{max}^{film} 1730 cm^{-1}, shoulder at 1710 cm^{-1} (C=O ester and ketone); 1650 cm^{-1} (conj. C=O); 1610 cm^{-1} (C=C).

ν_{max}^{Nujol} 1655 cm^{-1} (conj. C=O) 1605 cm^{-1} (C=C).

Condensation of 2-carbomethoxy-4-ethylenedioxycyxlohexanone with α-methylacrolein.

The condensation was carried out in an analogous manner described above (see page 40). The product was a viscous oil. Various attempts to obtain a crystalline material failed. The reaction was not further investigated.

Isopropyl triphenylphosphoniumbromide[95].

A pressure bottle was charged with 3.2 gms of isopropylbromide and 6.6 gms of triphenyl phosphine; the mixture was heated at 150° for 24 hours. The crystalline precipitate was washed with benzene to remove unreacted triphenylphosphine. It was recrystallized from a small amount of ethanol, m.p. 245-249°; m.p. reported: 238-239° .

Attempted preparation of dimethyl-γ-isopropylidenepimelate.

Sodium methylsulfinylcarbanion was prepared according to the method of Corey and Chaykovsky[96]. It was reacted with one equivalent (1.96 m moles) of isopropyltriphenylphosphonium bromide at room temperature. The solution turned deep red immediately. 1.96 m moles of dimethyl-γ-ketopimelate in 2 ml of dry dimethylsulfoxide were added and the reaction mixture was heated under nitrogen at 50° for five hours.

Ethylether was added to the reddish solution. After washing with water and saturated salt solution the solvent was evaporated. The solid obtained was treated with petroleum ether (30/60) and the solution was separated from the solid material. The infrared spectrum of the solution obtained after evaporation, indicated that it was largely starting material. The remaining solid gave a spectrum which was identical with triphenyl phosphine oxide. Repeated washings of the crystalline fraction with petroleum ether and evaporation of the solvent gave an oil in very low yield. Its infrared spectrum indicated the formation of some olefinic material: band at 1650 cm^{-1} (C=C). This reaction was not further investigated.

Benzyl-diethylphosphite[97].

A mixture of triethylphosphite (20 gms, 0.12 moles) and benzylchloride (15.2 gms, 0.12 moles) was heated under reflux for 10 hours. The reaction mixture was distilled at 167-168°/16-17 mm. The yield of the colorless oil was 70% (reported 74%).

Infrared: ν_{max}^{film} 1600 cm^{-1} (aromatic ring); 1500 cm^{-1} (aromatic ring); 1250 cm^{-1} (P → O); 1020-1040 cm^{-1} (P-OR).

Attempted preparation of dimethyl-γ-benzylidenepimelate.

The procedure used was essentially that of Wadsworth et al.[98]. Sodiumhydride (50%; 0.6 gms) was placed in 20 ml of dry 1,2-dimethoxy ethane. The slurry was cooled to 20° and benzyl-diethylphosphite (2.85 gms) was added dropwise with stirring. After the addition was complete, the solution was stirred at room temperature for one hour.

To the solution, maintained below 25°, were added dropwise 2.5 gms of the ketoester and the solution was then heated to reflux for 45 minutes. After cooling, a large excess of water was added and the mixture was thoroughly extracted with ether. The ether solution after being dried over magnesium sulfate was evaporated. Only starting material was obtained.

De-ketalization of 2-carbomethoxy-4-ethylenedioxycycloxanone.

Method a.

A mixture of 1 g of 85, 10 ml of methanol and 5 ml of 1 N sulfuric acid was refluxed on the steam bath for one hour. The methanol was removed under reduced pressure with the bath temperature maintained at 40°C. The residual oil was extracted with ether. After washing with dilute sodium carbonate solution, water and drying, the solution was evaporated to dryness in vacuo.

The completeness of the reaction was inferred from the absence of the band in the infrared spectrum typical for the ketal grouping; 1050-1150 cm^{-1}.

Method b.

In another approach, a mixture of 3 gms of 85 in 50 ml of acetone and 10 drops of concentrated hydrochloric acid was refluxed for one hour. The solution was cooled and 1 gm of sodium acetate dissolved in 10 ml of water was added. After removal of the acetone, the remainder was extracted with ether. The ether solution was washed with water, saturated salt solution and dried. Evaporation yielded 2.15 gms (90%) of an oil. The infrared spectrum was identical with that obtained in the preceding method.

Attempted preparation of 2-carbomethoxy-4-hydroxycyclohexanone, (87).

0.13 gms of sodium was dissolved in 3 ml of methanol. To this solution 0.7 gms of 2-carbomethoxy-1,4-cyclohexanedione in 5 ml of methanol was added and the mixture was cooled in ice-water. After the addition of 0.2 gms of $NaBH_4$ the mixture was kept another hour in the cold. The excess of the sodium borohydride was destroyed by the addition of a small amount of acetone. The solution was neutralized with acetic acid and evaporated. After work-up and evaporation of the solvent 2-carbomethoxy-4-hydroxycyclohexanone was obtained in low yield.

Infrared: ν_{max}^{film} 3450 cm^{-1} (O-H); 1730 and 1710 cm^{-1} (C=O ester and ketone); 1650 cm^{-1} (conj. C=O) 1610 cm^{-1} (C=C).

The reaction was not further investigated.

Attempted preparation of dimethyl-γ-hydroxypimelate.

To a cold solution of 2 gms of dimethyl-γ-ketopimelate in 30 ml of methanol 2 gms of sodium borohydride were added in small portions. After six hours at 0-5°C the solution was neutralized with acetic acid. The oily residue after evaporation was extracted with chloroform. The chloroform solution was washed with water, saturated salt solution and dried. The infrared spectrum of the oil after evaporation of the solvent showed bands at 1770 cm^{-1} (C=O γ-lactone) and 1730 cm^{-1} (C=O ester).

The reaction was repeated with the pH of the solution maintained at 8-9. Again, only γ-lactone was obtained. (See Discussion, page 96).

The same result was obtained when 50% aqueous dimethylformamide was chosen as the reaction medium.

The reaction was not further investigated.

Potassium salt of 2-carbomethoxy-4-ethylenedioxycyclohexanone.

Following the general procedure of Mayer et al.[99], 2.33 gms of potassium hydroxide were dissolved in 20 ml of methanol and the solution was cooled to 0-5°C. 8.85 gms of 2-carbomethoxy-4-ethylenedioxycyclohexanone were added with rapid stirring to the solution over a 2 minute period. After the addition was complete, 60 ml of ether were added to the clear solution; the potassium salt which precipitated was filtered immediately. After washing with cold methanol and ether, the salt was dried at 50-60° for two hours.

2-Methyl-2-carbomethoxy-4-ethylenedioxycyclohexanone, (88a).

0.6 gms of the potassium salt was dissolved in 5 ml of dry dimethylformamide (distilled over CaH_2). 0.34 gms of methyliodide was added. After 19 hours at 40-50° under nitrogen, the mixture was poured into 75 ml of cold ether. The ether solution was washed twice with 10 ml of a 5% sodium hydroxide solution, water and saturated salt solution. Removal of the solvent from the dried solution gave 0.42 gms of an oil. The compound failed to give a test with alcoholic ferric chloride solution.

Infrared: ν_{max}^{film} 1730 cm^{-1} (C=O ester); 1700 cm^{-1} (C=O ketone); 1000-1150 cm^{-1} (ethylene ketal group)

N.m.r.: see Table 2d.

1-Chloro-2-methyl-3-bromopropane.

This compound was prepared in 97% yield, by Burgin et al.[100] using 2-methyl-3-chloro-propene-1, anhydrous HBr and benzoylperoxide. However, the article did not give any further details.

In a 500 ml flask, equipped with a gas inlet tube reaching almost to the bottom and a gas outlet connected to a water valve, were placed 100 ml of n-pentane (free from olefinic material), 10 gms of 2-methyl-3-chloro-propene-1 and o.1 gms of benzoylperoxide. The mixture was cooled in an ice-bath and dry HBr-gas was bubbled through the solution as fast as the gas was absorbed. At the end, the pentane solution was washed successively with cold water, dilute sodium bicarbonate solution and brine. After the solution was dried and concentrated the residual material was distilled (44°/11 mm) to give 12.7 gms (67%) of a colorless liquid.

Infrared: ν_{max}^{film} 1450 cm^{-1} (CH_3, unsymm, bending vibration) 1420 cm^{-1} (CH_2, scissor); 1370 cm^{-1} (CH_3, symm. bending vibration).

N.m.r.: see Table 2d.

Condensation of 1-chloro-2-methyl-3-bromopropane with 2-carbomethoxy-4-ethylenedioxycyclohexanone.

11.4 gms of 1-chloro-2-methyl-3-bromopropane were condensed with 8 gms of 85 as previously described. The crude product, 88b (7 gms), was re-distilled at 132°/0.05 mm. The alcoholic ferric chloride test was negative.

Calculated for $C_{14}H_{21}O_5Cl$: C, 55.2 H, 6.95

Found: C, 55.9 H, 6.6

When the crude sodium salt of 2-carbomethoxy-4-ethylenedioxy-cyclohexanone, obtained from the Dieckmann ring closure of dimethyl-δ-ethylenedioxypimelate with NaH in ether (vide supra), was condensed with 1-chloro-2-methyl-3-bromopropane the yield and the product were identical to those above.

Attempted cyclization of methyl-2-(β-chloroisobutyl)-4-ethylenedioxy-cyclohexanone-2-carboxylate.

Method a.

Methylsulfinylcarbanion as base:[96]

A suspension of the base in dry dimethylsulfoxide was cooled in ice-water and 2 gms of 88b in 10 ml of dry dimethylsulfoxide were added slowly to the cold solution. After heating at 70-75° for four hours under nitrogen, the mixture was poured into excess ether; the ethereal extract was washed with water, saturated salt solution and dried. After evaporation of the solvent the residue was distilled by short-path distillation (125° C/0.025 mm). The material obtained gave a strong Br_2/CCl_4 test.

Infrared: ν_{max}^{film} 3100 cm^{-1} (vinyl H); 1735 and 1715 cm^{-1} (C=O ketone and ester); 1670 cm^{-1} (C=C for enolether).

N.m.r.: see Table 2e.

Method b.

Potassium-t-butoxide as base:

To 0.31 gms of 88b in 10 ml of dry benzene was added 2 ml of 0.48 N potassium-t-butoxide and the solution was refluxed for three hours. After work-up the product obtained was identical to that above (method a).

Condensation of the K-salt of 2-carboethoxycyclohexanone with 1-chloro-2-methyl-3-bromopropane and attempted cyclization.

The preparation of the potassium salt and its condensation with 1-chloro-2-methyl-3-bromopropane was done under conditions used previously. The compound, 90, was purified by distillation, 105° C/0.03 mm.

Infrared: ν_{max}^{film} 1705 cm^{-1}, shoulder at 1730 cm^{-1}

(C=O ester and ketone)

N.m.r.: see Table 2e.

2 gms of 90 were dissolved in 50 ml of dry benzene and 16 ml of 0.48 N potassium t-butoxide were added to the solution. The procedure was analogous to that used for method b above. 1.8 gms of an oil were isolated. It gave a strong Br_2/CCl_4 test.

Infrared: ν_{max}^{film} 3050 cm^{-1} (vinyl H); 1720 cm^{-1}

(C=O); 1670 cm^{-1} ($>C=C<$ for enolether).

β-(1-ethoxycarbonyl-2-keto-5-methylcyclohexyl) propionaldehyde.

This compound was prepared following essentially the method of Cope and Synerholm[49c].

A mixture of 2-carboethoxy-4-methyl-cyclohexanone (41.0 gms) and freshly distilled acrolein (15.2 gms) was added at -70° during one hour to a strongly stirred solution of sodium ethoxide (from sodium (0.26 gms) in 75 ml of ethanol containing 0.2 gms of hydroquinone). After stirring for another half hour without cooling, glacial acetic acid was added to bring the pH of the mixture to 7. The solvent was removed under reduced pressure. The crude product was dissolved in

ether, washed with water, 5% sodiumbicarbonate solution and dried (Na_2SO_4). After evaporation of the ether, the product was fractionated to give some unchanged ketoester (5 gms) and 29 gms (54%) of an oil, b.p. 109-111°/0.05 mm.

Infrared: ν_{max}^{film} 2720 cm^{-1} (C-H stretch aldehyde); center at 1730 cm^{-1} (C=O aldehyde, ketone, ester).

N.m.r.: see Table 2f.

Ethyl-7-methylbicyclo[3.3.1]non-3-en-9-one-1-carboxylate, (91a).

Method a.

28.5 gms of the above aldehyde were added dropwise with strong stirring to 85 ml of concentrated sulfuric acid[49c]. The temperature was maintained at 0-5°C throughout the addition. Upon completion of the addition the reaction mixture was stirred for one-half hour in the cold and it was then left at room temperature for 6 hours. The dark red solution was poured in a thin stream on 160 gms of crushed ice. The product was isolated by thorough extraction with ether-chloroform (1:1). After washing and drying ($MgSO_4$) the solvent was removed in vacuo. The crude product was chromatographed on 70 gms of neutral alumina (Fluka). Elution with petroleum ether-chloroform (4:1) and evaporation of the solvent left 5.3 gms (19%) of the ester. It was further purified by molecular distillation, 75° C/0.2 mm.

Infrared: ν_{max}^{film} 3050 cm^{-1} (vinyl H); 1730 cm^{-1} (C=O ester); 1705 cm^{-1} (C=O ketone); 1650 cm^{-1} (C=C disubst.); multiplet centered at 1240 cm^{-1} (C-O-C stretch ester)

N.m.r.: see Table 2f.

Calculated for $C_{13}H_{18}O_3$: C, 70.24 H, 8.16

Found: C, 70.16 H, 8.53

Method b.

2.5 gms of the aldehyde were added to a vigorously stirred solution of polyphosphoric acid - prepared from 22.5 gms of phosphorous pentoxide and 15 ml of 85% phosphoric acid. After being stirred for 6-7 hours, the dark red mixture was treated with an excess of ice water. The aqueous solution was extracted with several portions of ethyl ether, and the organic layer was washed with water and saturated aqueous sodium chloride. The ethereal solution was dried and evaporated to yield 1.2 gms (52%) of the crude ethyl-7-methylbicyclo[3.3.1]non-3-en-9-one-1-carboxylate. After chromatography on neutral alumina the material obtained had an infrared spectrum identical with that obtained above.

7-Methylbicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid (91b).

The acid was prepared from the corresponding ester following essentially the procedure of Cope and Synerholm[49c].

N.m.r.: see Table 2g.

Ethyl-4-hydroxy-7-methylbicyclo[3.3.1]nonan-9-one-1-carboxylate.

3 gms of β-(1-ethoxycarbonyl-2-keto-5-methylbicyclohexyl) propionaldehyde were added to a mixture of 12 ml acetic acid, 6 ml water and 3 ml concentrated hydrochloric acid[49c]. The solution was heated a short time on the steam bath and it was then kept at room temperature for 20 hours. After this time the solution was neutralized with aqueous sodiumbicarbonate and extracted with ether. The extracts were dried over $MgSO_4$ and concentrated to give 1.88 gms of an oil.

Infrared: ν_{max}^{film} 3510 cm^{-1} (O-H); 1725 cm^{-1} (C=O ester and ketone) 1240 cm^{-1} (C-O-C stretch ester) 1050 cm^{-1} (C-OH stretch).

An attempt to dehydrate this material with an ethanol-P_2O_5 (5:2) mixture failed. Only starting material was recovered.

Bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid.

The acid was prepared according to the method of Cope and Synerholm[49c].

Infrared: ν_{max}^{Nujol} 2400-3500 cm^{-1} (O-H acid); 1720 cm^{-1} (C=O acid); 1690 cm^{-1} (C=O ketone, hydrogen bonded).

N.m.r.: see Table 2g.

Iodolactonization reaction of bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid[101].

Method a.

A solution of 0.9 gms (5 m moles) of bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid in 30 ml of 0.5 N $NaHCO_3$ and a solution of 10 m moles of iodine and 30 m moles of potassium iodide in 15 ml of water were mixed and allowed to stand in the dark for 24 hours. The solution was then shaken with $CHCl_3$ and aqueous sodiumthiosulfate, washed with aqueous sodium bicarbonate, water and dried (Na_2SO_4). Evaporation of the solvent furnished a solid which after recrystallization from acetone-hexane was identified as starting material by melting point, mixed melting point and infrared spectrum (nujol).

Method b.

0.87 gms of the acid were dissolved in sodium hydroxide solution (0.19 gms sodium hydroxide dissolved in 2 ml of water). The solution was heated to 60°C and bromine was added dropwise with stirring until the color remained. The mixture was then extracted with ether. After washing and drying (Na_2SO_4), removal of the ether afforded a sticky oil. Its infrared spectrum did not indicate any γ-lactone.

1-Aminobicyclo[3.3.1]non-3-en-9-one, (92).

The amine was prepared following essentially the modified Curtius reaction of Weinstock[102]. 4.25 gms of bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid were suspended in 4.3 ml of water; sufficient acetone was added to complete the solution. The solution was cooled to 0° and 2.81 gms of triethylamine in 48 ml of acetone were added. To the cold stirred solution, 3.43 gms of ethylchloroformate in 12 ml of acetone were added dropwise and the mixture was stirred at 0° for 30 minutes. After this time 2.36 gms of sodium azide in 8.3 ml of water were added slowly and stirring was continued for one hour at 0°. The mixture was then poured into excess of ice water. The acid azide was extracted with toluene. After drying ($MgSO_4$), the toluene was added dropwise to a heated flask (steam bath). The heating was continued until the evolution of nitrogen had ceased. The toluene solution was concentrated in vacuo to give 3.93 gms of an oil. This material was shown by infrared spectroscopy to be substantially pure isocyanate.

Infrared: ν_{max}^{film} 3080 cm^{-1} (vinyl H); 2260 and 2240 cm^{-1} (-N=C=O); 1735 cm^{-1} (C=O); 1650 cm^{-1} (disubstit. C=C).

The isocyanate was suspended in 25 ml of 20% hydrochloric acid and the mixture was heated for 5 hours under reflux and then left overnight at room temperature. Evaporation of the solution gave a dark semi-solid residue. It was dissolved in 28 ml of water and enough 40% sodium hydroxide was added to make the solution strongly alkaline. The oil which separated was extracted with ether; the ether extracts were washed with water, brine and then dried (Na_2SO_4). Evaporation of the ether gave 2.09 gms (58%) of the amine as a yellowish oil.

Infrared: ν_{max}^{film} 3250-3650 cm^{-1} (N-H); 3080 cm^{-1} (vinyl H); 1720 cm^{-1} (C=O); 1650 cm^{-1} (disubst. C=C); 1600 cm^{-1} ($-NH_2$ scissor).

The amine crystallized on standing overnight. The infrared spectrum of the crystalline material indicated that dimerization of the α-amino ketone had occurred. The compound was purified by sublimation, m.p. 178-179.5°C. Molecular weight calculated for $C_{18}H_{22}N_2$:266; molecular weight determined (Rast): 252.

Infrared: ν_{max}^{Nujol} 3050 cm^{-1} (vinyl H); 1670 cm^{-1} (C=N-stretch); 1645 cm^{-1} (disubst. C=C)

Calculated for $C_{18}H_{22}N_2$: C, 81.16 H, 8.33

Found: C, 81.27 H, 8.34

1-Acetaminobicyclo[3.3.1]non-3-en-9-one, (94).

1.75 gms of 1-aminobicyclo[3.3.1]non-3-en-9-one were dissolved in 30 ml of anhydrous pyridine and 3 ml of acetic anhydrided were added. The mixture was left at room temperature for 18 hours. The pyridine was evaporated. The residual oil crystallized at once.

Infrared: ν_{max}^{Nujol} 3320 cm^{-1} (N-H); 3050 cm^{-1} (vinyl H); 1715 cm^{-1} (C=O); 1650 cm^{-1} (amide-I); 1500 cm^{-1} (amide-II).

N.m.r.: see Table 2g

Recrystallization from cyclohexane gave a pure compound, m.p. 86-88°C.

Calculated for $C_{11}H_{15}NO_2$: C, 68.37 H, 7.82 N, 7.25

Found: C, 68.84 H, 8.12 N, 7.30

N-methylation of 1-acetaminobicyclo[3.3.1]non-3-en-9-one.

To 0.384 gms of sodium hydride (50% in oil) in 8 ml of anhydrous xylene 1.52 gms of 94 in 35 ml of dry xylene were added. The mixture was refluxed under nitrogen with stirring for 20 hours. After cooling 3.13 gms of methyl iodide were added and the mixture was refluxed for 5 hours. The oil obtained after removal of the solvent was distilled at 108°/0.04 mm. Upon standing, a crystalline compound was obtained. It was purified by sublimation, m.p. 101-103°C.

Infrared: ν_{max}^{Nujol} 3050 cm^{-1} (vinyl H); triplet poorly resolved at 1630 cm^{-1}, 1660 cm^{-1} and 1695 cm^{-1}.

Ultraviolet: only endabsorption, λ^{EtOH} 225 mμ (ε 6250).

N.m.r.: see Table 2h.

Calculated for $C_{12}H_{15}NO$: C, 76.15 H, 7.99

Found: C, 76.35 H, 8.31

Acrylic anhydride, (97).

To a cold stirred solution of 5 gms (0.024 moles) of dicyclohexyl carbodiimide in 50 ml of anhydrous ether 3.2 gms (0.045 moles) of acrylic acid were added dropwise. Within a few minutes N,N'-dicyclohexylurea began to precipitate. After 90 minutes at 15-20° the urea was collected on a sintered glass funnel and the remaining solution was concentrated to dryness. Short path distillation (0.05 mm) gave 2.4 gms of the anhydride as a clear liquid.

Infrared: ν_{max}^{film} 1725 and 1785 cm^{-1} (C=O);
1625 cm^{-1} (monosubst. C=C).

Condensation of 3-methyl butylamine with acrylic anhydride, (98).

A mixture of 0.62 gms of the amine in 6 ml of dry pyridine and 0.9 gms of acrylic anhydride was allowed to stand overnight at room temperature. Evaporation of the pyridine yielded a yellow oil which was dissolved in ether. The ether solution was washed with water, cold 5% sodium bicarbonate solution and brine. After drying and evaporation, the residual oil was purified by molecular distillation 70° C/0.025 mm.

Infrared: ν_{max}^{film} 3300 cm^{-1} (N-H); 3100 cm^{-1} (vinyl H); 1650 cm^{-1} (amide-I); 1620 cm^{-1} (monosubst. C=C); 1550 cm^{-1} (amide-II); 985 cm^{-1} (C-H out of plane bending).

Ultraviolet: λ_{max}^{EtOH} 227 mμ (ε 4980).

N.m.r.: see Table 2h.

Ethyl-bicyclo[3.3.1]non-3-en-9-one-1-carboxylate.

The crude ketoester was prepared as described by Cope et al.[49c]. For purification, the compound was dried, dissolved in Skelly C and filtered through a column of neutral alumina (Fluka). Removal of the solvent gave the pure ketoester in 70% yield.

Ethyl-3-hydroxy-4-bromobicyclo[3.3.1]nonan-1-carboxylate (99b).

Method a.

33.5 gms of the pure ketoester were suspended in 300 ml of water and 40 ml of 1 N sulfuric acid. The mixture was heated to 70°C and 29.5 gms of N-bromosuccinimide were added to the stirred solution over a period of 30 minutes. The reaction mixture was then stirred for one hour at 70°C. In order to destroy traces of N-bromosuccinimide, sodium bisulfite was added until the potassium iodide starch test was negative; the aqueous solution was extracted with several portions of ether. The combined ether extracts were washed with water and dried (Na_2SO_4). When the solvent was evaporated, 39 gms of the crude bromohydrin were obtained as a yellow oil.

The bulk of the crude product was converted directly to the bromo-diketoester 101. Some of the oil was dissolved in ether and petroleum ether 30/60 was added. After cooling to 0° for 3 to 5 hours the crystalline bromohydrin (yield 40%) was collected. Recrystallization from ether gave the pure bromohydrin, m.p. 98-100°C.

Infrared: ν_{max}^{Nujol} 3540 cm^{-1} sharp (O-H); 1720 cm^{-1} (C=O ester) 1700 cm^{-1} (C=O ketone); multiplet between 1000-1100 cm^{-1} (C-OH).

Calculated for $C_{12}H_{17}O_4Br$: C, 47.24 H, 5.56 Br, 25.9

Found: C, 46.51 H, 5.36 Br, 26.4

Method b.

To a solution of 1.53 gms of the ketoester in 70 ml of dioxane, 39 ml of 0.167 N $HClO_4$ were added. N-bromosuccinimide was then added with swirling until it dissolved completely. The solution was left in the dark at room temperature for one hour. Most of the dioxane was then thoroughly extracted with ether. The ether solution was washed with water, saturated salt solution and dried (Na_2SO_4). After evaporation of the solvent in vacuo, the crude product (2.0 gms) was treated with ether-petroleum ether (30/60) in the cold. 0.9 gms of crystalline bromohydrin (99b) was collected. The bromohydrin after recrystallization from ether melted at 97.5-99.5°C undepressed on admixture with the bromohydrin obtained by method a. The infrared spectrum of the crude product further confirmed the identity.

Attempted ether ring closure of the bromohydrin[103].

0.415 gms of $CaCO_3$ (dried over P_2O_5) and 4.15 gms of $Pb(OAc)_4$ (dried under high vacuum) were added to 0.850 gms of the bromohydrin (99b) 120 ml of cyclohexane; the mixture was refluxed for 18 hours. After cooling the solution was filtered through Celite. The filtrate was washed successively with 5% potassium iodide solution, 10% sodium thiosulfate solution and water. The ethereal layer was dried ($MgSO_4$) and evaporated to give 0.810 gms of a crystalline material. The infrared spectrum (nujol) and the melting point were identical with those of the starting material.

Ethyl-3-acetoxy-4-bromobicyclo[3.3.1]nonan-1-carboxylate (100a).

One gram of the pure bromohydrin (99b) was dissolved in 14 ml of dry pyridine. To the solution 7 ml of acetic anhydride were added and the mixture was kept at room temperature overnight. After concentration, the residue was re-crystallized from ether, m.p. 118-120°C.

Infrared: ν_{max}^{Nujol} 1730 cm^{-1} (C=O ester); 1700 cm^{-1} (C=O ketone); 1215-1230 cm^{-1} (C-O-C stretch, ester).

N.m.r.: see Table 2i.

Calculated for $C_{14}H_{19}O_5Br$: C, 48.43 H, 5.23 Br, 23.02

Found: C, 48.16 H, 5.22 Br, 23.42

Ethyl-4-bromobicyclo[3.3.1]nonan-3,9-dione-1-carboxylate (101).

Method a.

A solution of 41 gms of the crude bromohydrin* in 500 ml of benzene was added over a 40 minute period with cooling (15-20°C) to a mixture of 70 gms of crystalline sodium dichromate, 52 ml of glacial acetic acid and 92 ml of concentrated sulfuric acid in 300 ml of water in a 3-necked flask.

The mixture was thoroughly stirred for eight hours at 25°C. The benzene solution was separated and washed twice with water, twice with sodium chloride solution and dried (Na_2SO_4). The benzene was removed by distillation to give 37.5 gms of a yellowish oil. The oil was dissolved in ether and petroleum ether (30/60) was added. The mixture was left in the cold overnight, whereupon 9.64 gms (23.4%) of crystals separated. The bromo-diketoester was recrystallized from cyclohexane and acetone, m.p. 89-91°C.

* (99b)

Infrared: ν_{max}^{Nujol} 1735 cm^{-1} (C=O ester); 1710 cm^{-1} (C=O ketone); 1230 cm^{-1} (C-O-C stretch ester).

Ultraviolet: λ_{max}^{EtOH} 307 mμ (ε 145).

N.m.r.: see Table 2j.

Calculated for $C_{12}H_{15}O_5Br$: C, 47.54 H, 4.99 Br, 26.36

Found: C, 47.71 H, 4.81 Br, 26.21

Method b.

The crude bromohydrin* (41.0 gms) was dissolved in warm glacial acetic acid (130 ml). The solution was cooled to room temperature and chromic acid (17.4 gms) dissolved in water (9 ml) and acetic acid (90 ml) was added. The temperature was kept below 25° throughout the addition of the chromic acid solution. The reaction mixture was allowed to stand at room temperature overnight and the solvent was removed under reduced pressure. The oily residue was dissolved in methylene chloride and the solution was washed with water, dilute sodiumcarbonate solution and saturated sodium chloride solution. After drying (Na_2SO_4) and removal of the solvent, the residual oil was dissolved in a little ethanol and kept at 0° for six hours. 10.6 gms (26%) of essentially pure bromodiketoester were collected. It was identical in every respect with the material obtained in Method a.

Method c.

The procedure followed here was essentially that of Jones et al.[104]. A cold solution of chromic acid (2.67 gms) in concentrated sulfuric acid (2.3 ml) and water (4 ml) was made up to 10 ml (8 N with respect to oxygen).

---

* (99b)

The compound to be oxidized (0.39 gms) was dissolved in pure acetone (distilled over $KMnO_4$) at 20°C and the reagent was added dropwise from a microburette until a persistent orange brown coloration indicated that oxidation was complete. The infrared spectrum and yield of the crude and the recrystallized material were identical with those of the previous two methods.

Method d.

The bromohydrin* was oxidized using the usual Sarett conditions[90]. Again, the product was identical with that obtained before. However, there was no improvement in yield of the crystalline fraction.

The crude bromodiketoester showed an absorption at 6μ, either as a distinct sharp peak (methods a and b) or as a pronounced shoulder (methods c and d). This band was absent in the crystalline fraction; it disappeared on zinc-acetic acid reduction of the mother liquor (vide infra).

Reductive debromination of ethyl-4-bromobicyclo[3.3.1]nonan-3,9-dione-1-carboxylate (102).

80 ml of glacial acetic acid were added slowly to a cooled mixture of 4 gms of the pure bromodiketoester 101, 16 gms of anhydrous sodium acetate and 22 gms of powdered zinc. The mixture was heated with stirring under reflux for one hour. The zinc was removed by filtration and the filtrate was concentrated in vacuo; azeotropic distillation with toluene was used to remove excess acetic acid.

* (99b)

The product, isolated in the usual manner gave 2.7 gms (92%) of an oil which crystallized readily. Most of the crude crystalline material was used in the following step. The remaining portion was recrystallized from ether, m.p. 75-77°C.

Infrared: ν_{max}^{Nujol} 1730 cm^{-1} (C=O ester);
1715 cm^{-1} (C=O ketone); multiplet
centered at 1240 cm^{-1} (C-O-C stretch ester).

Ultraviolet: λ_{max}^{EtOH} 287.5 mμ (ε 41).

N.m.r.: see Table 2k.

Calculated for $C_{12}H_{16}O_4$: C, 64.3 H, 7.2
C, 63.9 H, 6.8
H, 7.1

5.1 gms of the mother liquor of the bromodiketoester were treated in a similar manner to give 3 gms of an oil. The infrared spectrum no longer had an absorption at 6μ. The oil was chromatographed on neutral alumina. Elution with benzene gave 0.3 gms of ethyl-bicyclo[3.3.1]non-3-en-9-one-1-carboxylate; see Discussion, page 114. The remainder of the eluate (benzene-chloroform) did not crystallize. It was not further investigated.

Ethyl-4-hydroxybicyclo[3.3.1]nonan-9-one-1-carboxylate.

It was prepared by the method of Cope et al.[49c].

Ethyl-bicyclo[3.3.1]nonan-4,9-dione-1-carboxylate, (103).

5 gms of CrO_3 were added gradually to 50 ml of anhydrous pyridine cooled in ice water; 5 gms of ethyl-4-hydroxybicyclo 3.3.1 nonan-9-one-1-carboxylate in 50 ml of pyridine were added with swirling and the mixture was kept at room temperature for 19 hours[90]. The dark brown mixture was poured into water and filtered through a Celite pad. The filtrate was extracted with ether. After washing, drying ($MgSO_4$) and evaporation of the ethereal solution the oily residue (4.3 gms) was chromatographed on neutral alumina and eluted with benzene. The clear oil was further purified by molecular distillation, 100° C/0.01 mm.

Infrared: ν_{max}^{film} 1725 cm^{-1} (C=O ester and ketone) multiplet centered at 1230 cm^{-1} (C-O-C stretch, ester).

Ultraviolet: λ_{max}^{EtOH} 287 mμ (ε 45.5).

Bicyclo[3.3.1]nonan-3,9-dione-1-carboxylic acid, (104).

The crude crystalline ester 102 (2.63 gms) was heated in an oil bath (80-90°C) with 15 ml of 5% potassium hydroxide for 45 minutes. After cooling, the clear solution was made strongly acidic with hydrochloric acid and extracted with several portions of ether. The combined ether extracts were washed with water, brine and dried ($MgSO_4$). After evaporation to dryness the crude crystalline acid, 1.64 gms (71%), was recrystallized from acetone-hexane; m.p. 183-188°C, softening at 178°C.

Infrared: ν_{max}^{Nujol} 2400-3500 cm^{-1} (O-H, acid) 1725 cm^{-1} (C=O acid); 1705 cm^{-1} (C=O ketone) 1670 cm^{-1} (C=O ketone hydrogen-bonded).

Calculated for $C_{10}H_{12}O_4$: C, 61.21 H, 6.17

Found: C, 60.40 H, 5.97

H, 6.05

When the acid was heated for a few degrees beyond its melting point, the infrared spectrum was different from that of the starting material: $\gamma_{max}^{CHCl_3}$ 1705 cm^{-1}, shoulder at 1750 cm^{-1}.

TABLE 2a PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

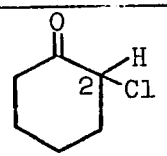
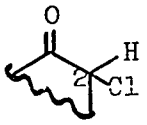
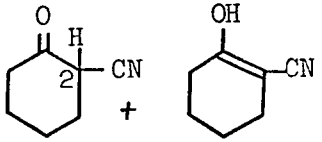
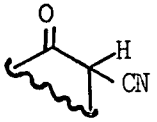
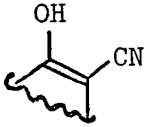
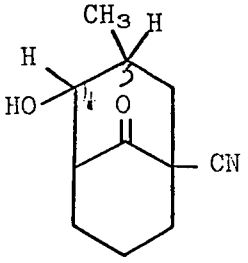
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multiplicity	Splitting c.p.s.	Integrated Area	Remarks
 C_6H_9ClO		5.75	T	5		Solvent: CCl_4
 C_7H_9NO	 	6.36 6.53	T S	5		Solvent: CCl_4
 $C_{11}H_{15}NO_2$		8.93 6.46 5.94	D Q T	6.2 10 (Jaa) 4.5(Jae) 3 (Jea) 3 (Jee)	3 protons 1 proton Rest: 11 protons	Solvent: $CHCl_3$ Ketol exists as a 1:1 mixture Chromatography on alumina and elution with chloroform-pet ether (4:1) gave partial separation: greater area for axial proton.

TABLE 2b PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS(SPLITTINGS)

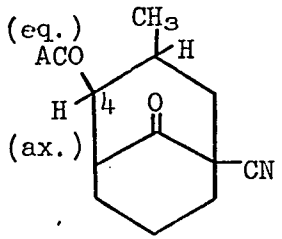
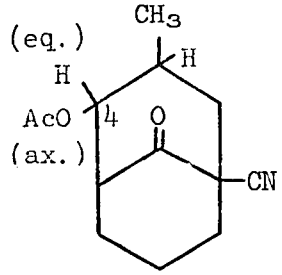
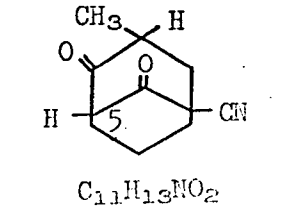
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multiplicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_{13}H_{17}NO_3$	$-\underset{\underline{CH_3}}{\overset{H}{\underset{|}{\overset{|}{C}}}}-$	8.98	D	5.2		Solvent: $CHCl_3$
	$-O-\overset{O}{\overset{\|\|}{C}}-\underline{CH_3}$	7.89	S			Equatorial (high melting) acetate.
	$\underline{H}-C_4-OAC$	5.2	Q	12 (Jaa) 6 (Jae)		
 $C_{13}H_{17}NO_3$	$-\underset{\underline{CH_3}}{\overset{H}{\underset{|}{\overset{|}{C}}}}-$	9.03	D	6.2		Solvent: $CHCl_3$
	$-O-\overset{O}{\overset{\|\|}{C}}-\underline{CH_3}$	7.95	S			Axial (low melting) acetate.
	$\underline{H}-C_4-OAC$	4.79	T	3.1 (Jea) 3.1 (Jee)		
 $C_{11}H_{13}NO_2$	$-\underset{\underline{CH_3}}{\overset{H}{\underset{|}{\overset{|}{C}}}}-$	8.8	D	7.2		Solvent: $CHCl_3$
	$-\underset{\underline{H}}{\underline{C_5}}-$	6.52	T	3 (Jea) 3 (Jee)		

TABLE 2c PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

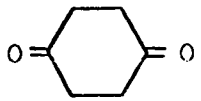
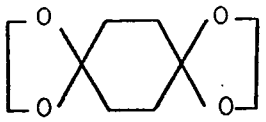
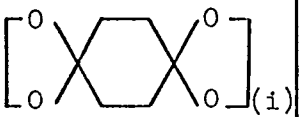
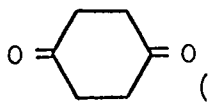
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multi-plicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_6H_8O_2$	all CH_2's	7.3	S			Solvent: $CHCl_3$
 $C_{10}H_{16}O_4$	ring CH_2's ketal CH_2's	8.23 6.07	S S			Solvent: $CHCl_3$
 (i) +  (ii) +  (iii) Mixture	ring CH_2's ketal CH_2's ring CH_2's of (ii) ring CH_2's of (iii)	8.23 6.09 6.03 8.04 7.49 7.31	S S S M M S			Solvent: $CHCl_3$

TABLE 2d PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

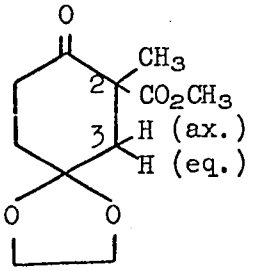
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multiplicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_{11}H_{16}O_5$	C_2-$\underline{CH_3}$	8.79	S			Solvent: CCl_4
	H-C_3-$\underline{H}$ (ax.)	8.41	D	13.9		
	$\underline{H}$(eq)-C_3-H	7.42	D	12.7		
	-C(=O)-O-$\underline{CH_3}$	6.27	S			
	ketal $\underline{CH_2}$'s	6.01	S			
$BrCH_2$-C(H)(CH_3)-CH_2Cl (γ β α) C_4H_8BrCl	H-C-$\underline{CH_3}$	8.87	D	7.4		Solvent: CCl_4
	$\underline{H}$-C-CH_3	~ 8.05	M			
	$Br\underline{CH_2}$-C-$\underline{CH_2}Cl$	6.52	T	6.0		α- and γ-protons are slightly non-equivalent

TABLE 2e PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

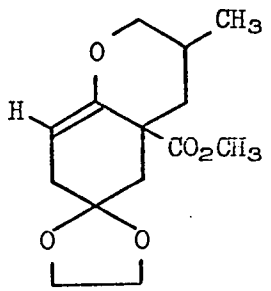
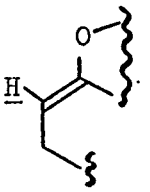
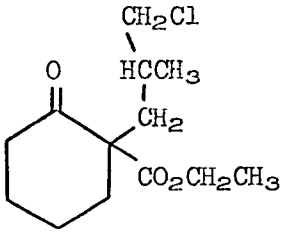
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multiplicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_{14}H_{20}O_5$	$-C(=O)-O-CH_3$	6.4	S			Solvent: CCl_4
	ketal CH_2's	6.18	S			
		5.03	T	4		
 $C_{13}H_{21}O_3Cl$	$H-\underset{\displaystyle O}{\overset{\displaystyle \|}{C}}-CH_3$	9.03	D	6.8		Solvent: CCl_4
	$-C(=O)-OCH_2CH_3$	8.7	T	7.0		
	$-CH_2Cl$	6.59	T	4.8	2 protons	$-CH_2-Cl$ protons are slightly non-equivalent
	$-C(=O)-OCH_2CH_3$	5.82	Q	6.8	2 protons Rest: 17 protons	

TABLE 2f PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

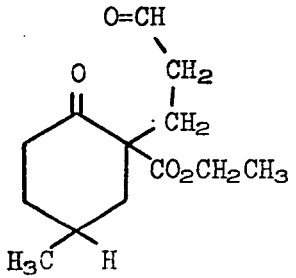
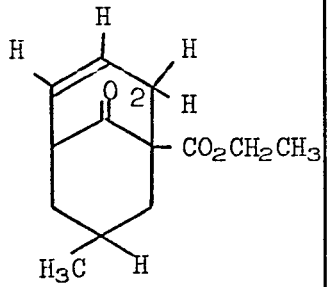
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multi-plicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_{13}H_{20}O_4$	H-C-CH_3	8.96	M			Solvent: CCl_4 poorly resolved
	-C(=O)-OCH_2CH_3	8.74	T	6.9		
	-C(=O)-OCH_2CH_3	5.78	Q	6.9		
	-C(=O)-H	0.1	S			shows splitting during slow sweep rate
 $C_{13}H_{18}O_3$	H-C-CH_3	9.01	D	5.8	6 protons	Solvent: CCl_4 sharp
	-C(=O)-OCH_2CH_3	8.71	T	6.7		
	H-C_2-H(eq)	6.58	D	2.0		
	-C(=O)-OCH_2CH_3	5.82	Q	6.7	2 protons	
	-HC=CH-	4.31	M		2 protons	
					Rest: 8 protons	

TABLE 2g PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

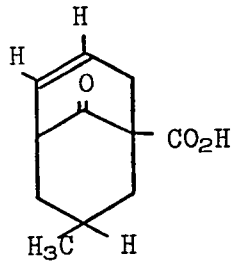
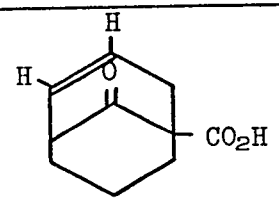
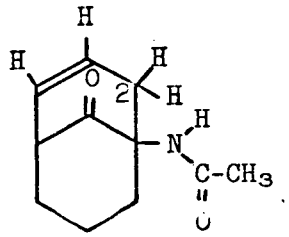
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multi-plicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_{11}H_{14}O_3$	$H-\underset{|}{C}-CH_3$	9.04	D	6.3		Solvent: $CHCl_3$ sharp
	$-HC=CH-$	~ 4.27	M			
	$-CO_2H$	- 1.9	S			
 $C_{10}H_{12}O_3$	$-HC=CH-$	~ 4.2	M			Solvent: $CHCl_3$
	$-CO_2H$	- 1.8	S			
 $C_{11}H_{15}NO_3$	$-N-\overset{O}{\overset{\|}{C}}-CH_3$	8.18	D	2		Solvent: CCl_4
	$H-\underset{|}{C}-H$ (ax.)	7.51	D	21.1		peaks show further splitting: ~3 c.p.s.
	$H_{(eq)}-\underset{|}{C}-H$	6.38	D	20.0		
	$-HC=CH-$	~ 4.13	M		2 protons	
	$>NH$	3.1	broad		1 proton	
					Rest: 12 protons	

TABLE 2h PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

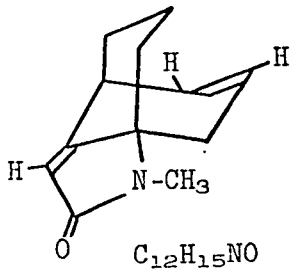
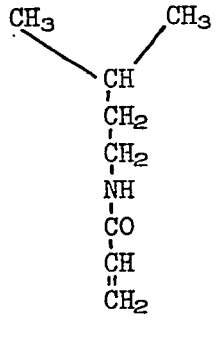
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multi-plicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_{12}H_{15}NO$	$\rangle N-CH_3$	7.17	S			Solvent: $CHCl_3$
	$-HC=CH-$ + $\rangle C=C\langle$ (H, O)	~ 4.17	M			
 $C_8H_{15}NO$	$H_3C-\overset{H}{C}-CH_3$	9.12	D	6.1	6 protons	Solvent: CCl_4
	$\rangle CH-CH_2-$	8.57	M	6.1	3 protons	
	CH_2-N-	6.77	Q	6.1	2 protons	
	$O=C$, $C=C$, H(B), (A)H, H(X)	4.57	Q	$J_{AX} > 8.2$, $J_{BX} < 4.4$	1 proton	X-part of ABX
		3.8	M	$J_{AB} \sim 18.6$	2 protons	AB-part of ABX
	$\rangle N-H$	1.95				broad

TABLE 2i PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

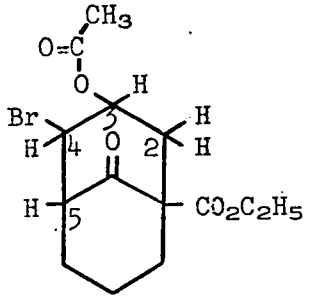
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multi-plicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_{14}H_{19}O_5Br$	$-\overset{O}{\overset{\|}{C}}-OCH_2\underline{CH_3}$	8.68	T	6.8	3 protons	Solvent: $CHCl_3$
	$-O-\overset{O}{\overset{\|}{C}}-\underline{CH_3}$	7.87	S			
	$H-\underset{\|}{\overset{\|}{C_2}}-\underline{H(eq.)}$	6.97	Q	13.6(Jgem) 6 (Jea)	2 protons	
	$-\underset{\|}{\overset{\|}{C_5}}-\underline{H}$	6.78	M			
	$-\overset{O}{\overset{\|}{C}}-O-\underline{CH_2}CH_3$	5.72	Q	7	3 protons	
	$Br-\underset{\|}{\overset{\|}{C}}-\underline{H}$	5.63	Q	10.5(Jaa) 3.4(Jae)		
	$\underline{H}-\underset{\|}{\overset{\|}{C}}-OAc$	4.9	M	11;10.5(Jaa) 6 (Jae)	1 proton	M ≡ sextet
					Rest: 10 protons	

TABLE 2j PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

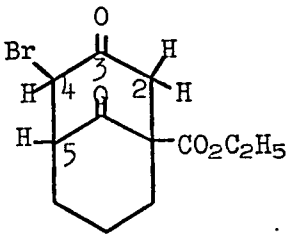
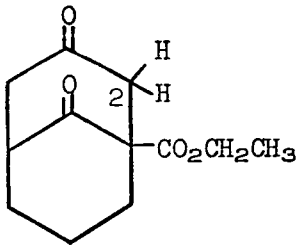
Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multi-plicity	Splitting c.p.s.	Integrated Area	Remarks
 $C_{12}H_{15}O_4Br$	$-\overset{O}{\overset{\|}{C}}-OCH_2\underline{CH_3}$	8.64	T	7.1	3 protons	Solvent: $CHCl_3$
	$H-\dot{C}_2-\underline{H}$(ax.)	7.25	D	17.2		peaks further split: 2 c.p.s.
	$-\dot{C}_5-\underline{H}$	6.85	M			
	$H-\dot{C}-H$ (eq)	5.79	D	16.2		
	$-\overset{O}{\overset{\|}{C}}-OCH_2\underline{CH_3}$	5.69	Q	7.1	4 protons	
	$Br-\dot{C}_4-\underline{H}$	5.49	T	2-3	Rest: 8 protons	

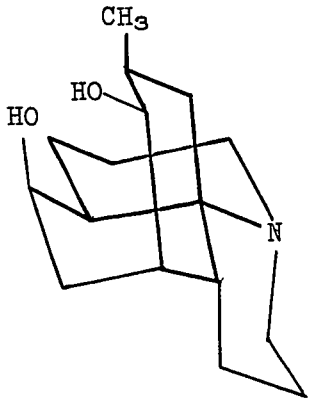
TABLE 2k PROTON CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS (SPLITTINGS)

Compound	Functionality	Chemical Shift (τ) rel. to TMS	Multi-pli-city	Splitting c.p.s.	Integrated Area	Remarks
 $C_{12}H_{16}O_4$	$-\overset{O}{\overset{\|}{C}}-OCH_2\underline{CH_3}$	8.7	T	7.9	3 protons	Solvent: $C Cl_4$
	$H-\overset{'}{C_2}-H$ (eq.)	6.59	D	17	1 proton	
	$-\overset{O}{\overset{\|}{C}}-O\underline{CH_2}CH_3$	5.83	Q	7	2 protons	
					Rest: 10 protons	

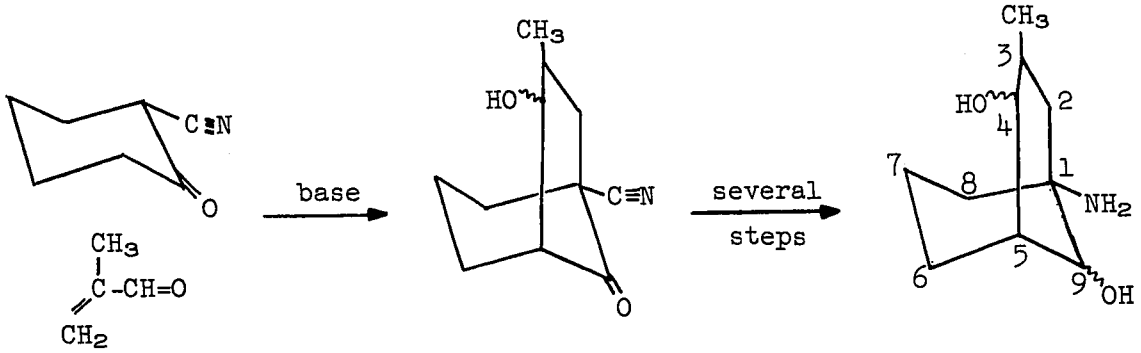
DISCUSSION

The chemistry, the stereochemistry and the interrelation of a number of Lycopodium alkaloids has been studied extensively in recent years; this was outlined in Part I of the Introduction. Our interest in this field was concerned primarily with the preparation of suitable intermediates for the synthesis of some of these alkaloids.

As a first attempt we chose 1-amino-3-methyl-4,9-dihydroxy-bicyclo[3.3.1]nonane as a model for



The sequence which we had planned for the preparation of the bicyclo-nonane derivative is shown in the following scheme:

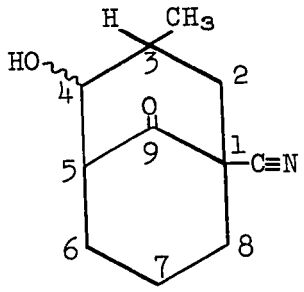


There is a variety of methods available for the preparation of β-ketonitriles.[105] Kuehne[89] prepared 2-cyanocyclohexanone from the pyrrolidine enamine of cyclohexanone and cyanogen chloride in a 54% yield. Our attempt to replace cyanogen chloride by the readily available cyanogen bromide gave an oil, which did not show any absorption for the nitrile group in the infrared spectrum. In another approach, we reacted 2-chlorocyclohexanone with anhydrous sodium cyanide in an aprotic solvent such as dimethylsulfoxide.[88] The infrared spectrum of the product (yield 11%) was identical with that of the material obtained from a modified procedure of Winternitz et al.[87] The latter method gave a reasonable yield of the ketonitrile (35-40%).

The infrared spectrum of 2-cyanocyclohexanone showed a carbonyl absorption at 1725 cm^{-1} with a pronounced shoulder on the high frequency side, which is related to the neighboring nitrile group. This is analogous to the shift observed with equatorial halogen substituents.[86] In addition to a nitrile absorption at 2275 cm^{-1}, there is a smaller peak at 2220 cm^{-1}, which is attributed to the enolic form of the compound. In the n.m.r. spectrum there is a singlet at 6.53 τ and a triplet centered around 6.36 τ, corresponding to the enolic and ketonic form of the compound, respectively.

Addition of α-methylacrolein to the ketonitrile using Triton-B as a base, yielded a yellow, viscous oil. The infrared spectrum of the crude product lacked a band for an aldehydic hydrogen at 2750 cm^{-1}. Instead, the compound showed a strong absorption in the 3400-3500 cm^{-1} region (O-H stretch), indicating that addition and cyclization might have occurred. On standing, a crystalline compound was formed in a 56%

yield. The elemental analysis indicated an empirical formula of $C_{11}H_{15}NO_2$. Its infrared spectrum showed a sharp band at 3460 cm^{-1}, a single band at 2255 cm^{-1} and a sharp, intense band at 1720 cm^{-1}, attributable to a hydroxyl, a nitrile and a carbonyl group, respectively. From these data we assigned to it the bicyclic structure shown:

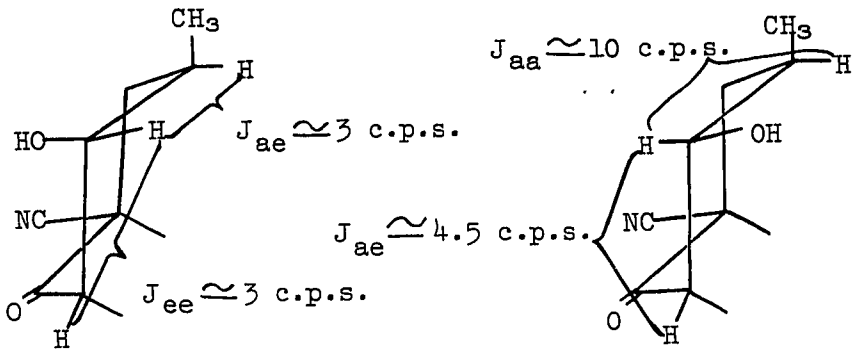


78

The apparently pure ketol melted sharply at 125°C.

The n.m.r. spectrum showed a 3-proton signal at 8.93 τ (doublet, splitting 6.2 c.p.s.) for the C-methyl group; a quartet centered at 6.46 τ and a triplet at 5.94 τ were assigned to the proton on the hydroxyl-bearing carbon atom. The resonance lines associated with this proton are displaced downfield from the other protons of the molecule because of the unshielding effect of the hydroxyl group. It has frequently been noted that equatorial protons on six membered ring compounds exhibit chemical shifts that appear at lower fields than their axial counterparts.[106, 107] Therefore, the quartet at 6.46 τ was assigned to an axial proton on C-4, flanked by an axial proton on C-3 and an equatorial proton on C-5, which would give the splitting actually

observed, whereas the triplet at 5.94 τ is due to an equatorial proton, which is flanked by two gauche protons; these are less strongly coupled, resulting in the broadened triplet (vide infra). The areas under the axial and equatorial proton signal could be shown by integrated intensity measurement to correspond to one proton each; from this it was concluded, that the ketol existed as a 1:1 complex with respect to the configuration of the hydroxyl group. The apparent coupling constants J_{aa}, J_{ae} and J_{ee} are in qualitative agreement with the values that would be calculated from the Karplus equation[108], assuming dihedral angles of 180° and 60° between the coupling protons. These results are summarized in the partial structures (i) and (ii) below:



(i) (ii)

Attempts to separate the ketol-complex by chromatography, using either alumina or florisil, were only partially successful. From the n.m.r. spectrum of the early fractions it was clear, that the equatorial isomer was preponderant. A compound with an equatorial polar group is, in general, more strongly adsorbed on a chromatographic column than its epimer with an axial substituent.[109] It can be seen from the

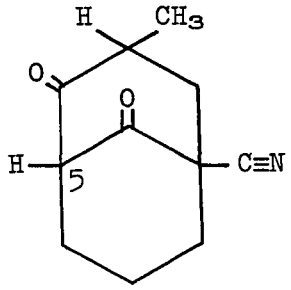
preceding partial structure (i) that the axial hydroxyl group is more exposed and thus more available for adsorption than the equatorial hydroxyl group. This may explain the reversal of the more common trend.

When the 1:1 complex was treated with pyridine-acetic anhydride, a mixture of the corresponding acetates was obtained; it was readily separated by fractional crystallization into a fraction (needles) of m.p. 119-120°C, and a fraction (hexagonal prisms) of m.p. 156-158°C. In the n.m.r. spectrum, the low melting isomer exhibited a triplet of lines at 4.79 τ , while the higher melting isomer was characterized by a quartet at 5.2 τ , much like the hydroxy compound; however, the lines are better resolved. It is well established that acetylation of a secondary hydroxyl group causes a paramagnetic shift of 1.0 - 1.5 ppm of the proton alpha to the hydroxyl group. From the foregoing remarks concerning the position and splitting pattern of these signals, the low-melting fraction was identified with the axial isomer, while the high-melting fraction corresponded to the equatorial isomer. Attempts to hydrolyze the individual isomers under mild conditions to the corresponding ketols showed little promise.

Experiments designed to obtain the $\Delta^{3,4}$-compound, using various dehydration procedures were unsuccessful. When thionylchloride or phosphorous-oxychloride were used, the hydroxyl group was replaced by a chlorine atom.

Oxidation of the 1:1 ketol mixture with the CrO_3-pyridine complex[90] gave a crystalline compound in a very good yield. The infrared spectrum of this compound showed a doublet at 1740 cm^{-1} and 1690 cm^{-1},

which is typical for a β -diketone. The compound did not have any enolic properties; this was expected since the enol of the expected dione, viz.

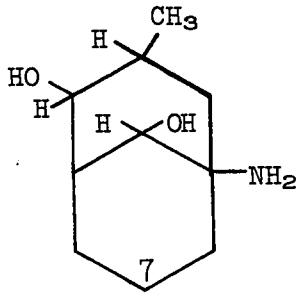


80

would have a double bond at a bridgehead, in violation of Bredt's rule.[110] The elemental analysis was in good agreement with compound 80. Its ultraviolet spectrum in alcohol solution exhibited a maximum at 291.5 mμ (ε 72). In the n.m.r. spectrum, there was a triplet at 6.52 τ, which was assigned to the bridgehead hydrogen at C-5; the splitting arises from the neighboring methylene protons at C-6.

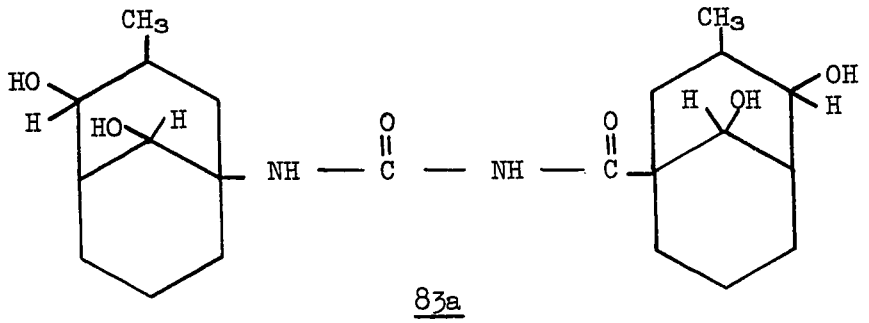
We turned our attention now to the conversion of the nitrile group in 78 into a bridgehead amine. The hydrolysis of the nitrile to an amide using hydrogen peroxide in an alkaline medium was chosen as the first step. This reaction was known to proceed satisfactorily with aromatic nitriles.[111] It was anticipated that the alkaline conditions of this hydrolysis might cause a re-opening of the bicyclic system via a reverse aldol reaction. By reducing the 9-keto group in 78 with sodium borohydride to the corresponding alcohol (81) this possibility was eliminated. The hydrolysis of 81 with alkaline hydrogen peroxide yielded 3-methyl-4,9-dihydroxybicyclo [3,3,1] nonan-9-one-1-carboxylic acid amide (82, $C_{11}H_{19}NO_3$), m.p. 178-180°C, which, after rearrangement

gave an amine, m.p. 152°C, in a reasonable yield. The structure assigned to it, viz:



83

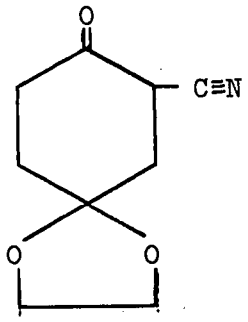
was confirmed by elemental analysis and by its infrared spectrum: 3350 cm^{-1} (sharp) for non-bonded N-H and O-H stretch, strong absorption between 2500-3300 cm^{-1} for hydrogen bonded N-H and O-H; 1610 cm^{-1} for the NH_2-scissoring mode. During the formation of the amine, a small amount of a white substance precipitated. The elemental analysis of this compound was in agreement with the following alkyl acyl urea:



83a

In order to utilize this reaction sequence for the synthesis of a more general intermediate, it became necessary to prepare a ring

system which would contain a carbonyl group at C-4*, protected in such a way that it could easily be removed afterwards. Therefore, 4-ethylenedioxycyclohexanone was prepared by known procedures.[92] Next we intended to introduce a nitrile group via the isoxazole to give the following compound:



84

The presence of the acid-labile ketal grouping made it necessary to modify the usual conditions ($H_2NOH.HCl$) for the preparation of the isoxazole from the corresponding hydroxymethylene derivative. 2-hydroxymethylene cyclohexanone served as a useful model compound for this work. Attempts to convert it into the isoxazole with hydroxylamine hydrochloride using a NaOAc-HOAc buffer gave the isoxazole in a 19% yield only.

A simpler approach to a similar compound involved the synthesis of 2-carbomethoxy-4-ethylenedioxycyclohexanone (85); this compound was prepared by the method of Sarett and co-workers.[94] It was expected that condensation with α-methylacrolein by the Michael method would proceed in a manner similar to that observed previously with 2-cyano-

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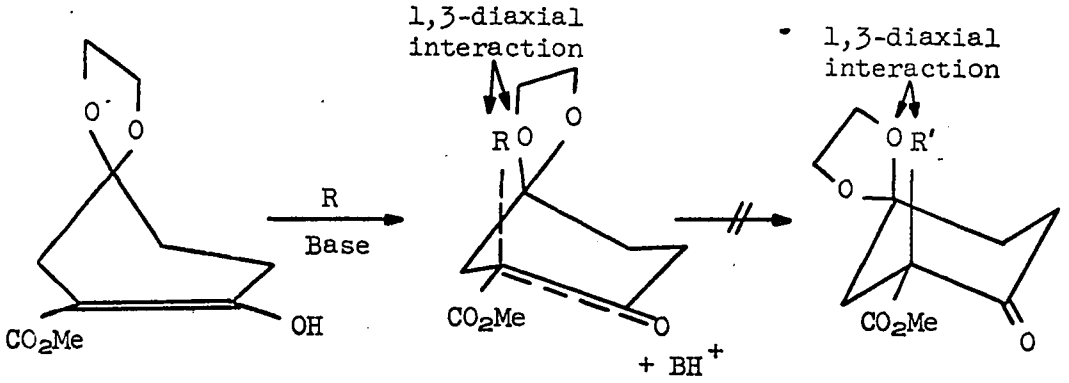
* This corresponds to C-7 in the bicyclo-compounds 78 and 83, respectively.

cyclohexanone. However, a number of variations of the reaction conditions did not bring about the desired result.

In general, additions to the double bond of a cyclohexene derivative lead to products which arise from diaxial addition, by passing preferentially through a transition state with a quasi-chair conformation.[112] Therefore, an approach by the alkylating agent (α-methylacrolein) from the top-side (cis-approach) of the half-chair enol A should give a transition state with a geometry such as B. However, this introduces a destabilizing 1,3-diaxial interaction between one of the oxygen atoms of the ethylenedioxy group and the R-group as shown. Therefore, the preference for the quasi-chair form is outweighed by this steric repulsion.

Conversely, a transition state such as D might be expected for a trans-approach of the acrolein molecule, leading to a boat form (E) for the product or its conformationally flipped version (F). In the latter case the 1,3-diaxial interaction between the ketal group and the carbomethoxy group destabilizes this form relative to E, i.e. the kinetic product would be expected to retain a conformation which is closely analogous to that of the transition state.

In the foregoing discussion it was assumed that the transition state resembles the product rather than the reactant. If the geometry of the transition state resembles the reactant (G), the most probable approach should be from the least hindered side (ii). However, the product obtained from the latter is destabilized by a 1,3-diaxial interaction as shown (H).

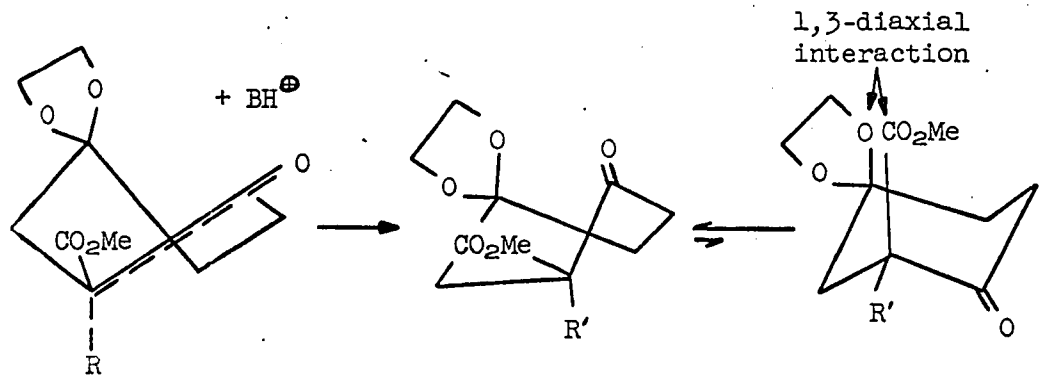


A B C

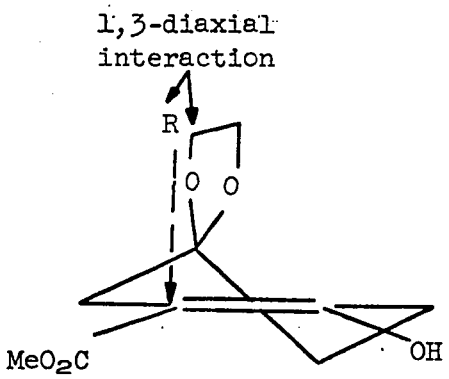
R
Base

R: $CH_2 = C(CH_3)CH = O$

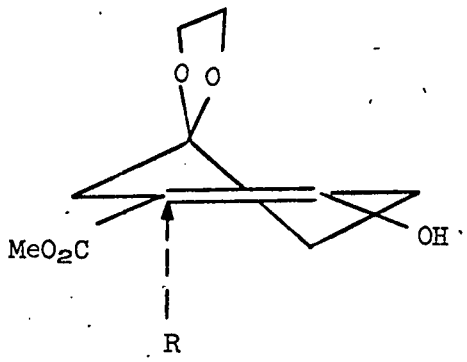
R′: $CH_2 - CH(CH_3)CH = O$



D E F



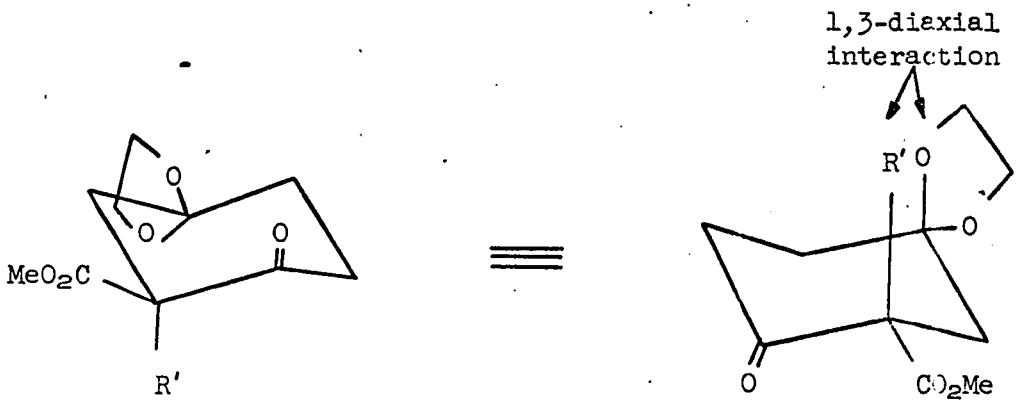
(i)



(ii)

R: $CH_2 = C - CH = O$ (with CH_3)

G

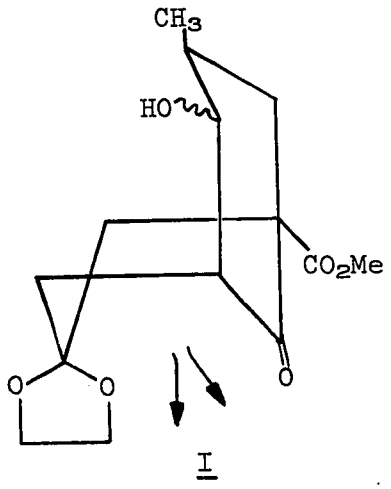


R': $CH_2 - CH - CH = O$ (with CH_3)

H

Therefore, the assumption that the addition to the enolate ion proceeds via a transition state which closely resembles the product is quite reasonable. Also, the pathway A→D→E seems to be a plausible mechanism.

From the foregoing discussion it might be anticipated that the ring closure would take place in a similar manner to yield I.



I

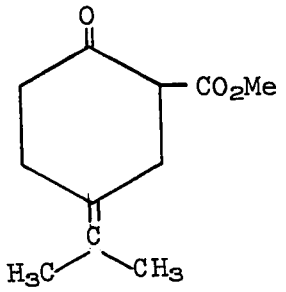
However, in contrast to 1-cyano-3-methyl-4-hydroxybicyclo [3.3.1] nonan-9-one above, the analogous compound I could not be isolated.

The formation of the two cyclization products, 78 and I, involves reversible reactions. The fact that I, is not formed, may be attributed to the bowsprit-flagpole interaction shown. Although this is modified by the trigonal geometry of the carbonyl carbon, it seems to destabilize this compound sufficiently to prevent its formation and other, intermolecular aldol-type condensations supervene.

In view of the failure to find conditions which would give the desired results, it became necessary to make modifications, eliminating

gross steric factors, while maintaining the necessary functionality at carbon 4*. For instance, introducing an exocyclic double bond at C-4 would flatten the molecule because of the trigonal nature at C-4 and non-bonded interactions would be greatly minimized. Alternatively, a single substituent such as benzylether group, would be expected to assume an equatorial configuration giving again the desired result.

It was planned to prepare



86

starting from dimethyl-γ-isopropylidene pimelate. The justification for choosing the isopropylidene group rather than the more accessible methylene group was based on the fact, that a double bond exocyclic to a six-membered ring is considered to be thermodynamically unstable with respect to the isomeric alkylcyclohexene;[113] this tendency was thought to be less pronounced for an isopropylidene group.

Attempts to introduce the isopropylidene group via the Wittig reaction,[114] using dimethyl γ-ketopimelate and the ylide from isopropyl triphenylphosphoniumbromide were unsuccessful. The interaction of sodium methylsulfinylcarbanion[96] with one equivalent of isopropyl triphenylphosphoniumbromide at room temperature led to the formation of

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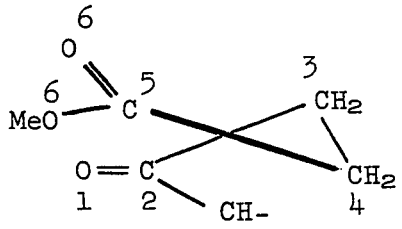
* For numbering used, see footnote on page 89.

the corresponding phosphorane, as shown by a color change to deep red. However, this intense color of the phosphorane solution was not discharged upon addition of the carbonyl component, even after five hours at 50°C. After work-up, only a very small amount of the expected product was detected in the reaction mixture, as inferred from a band at 1660 cm^{-1} (C=C) in the infrared spectrum.

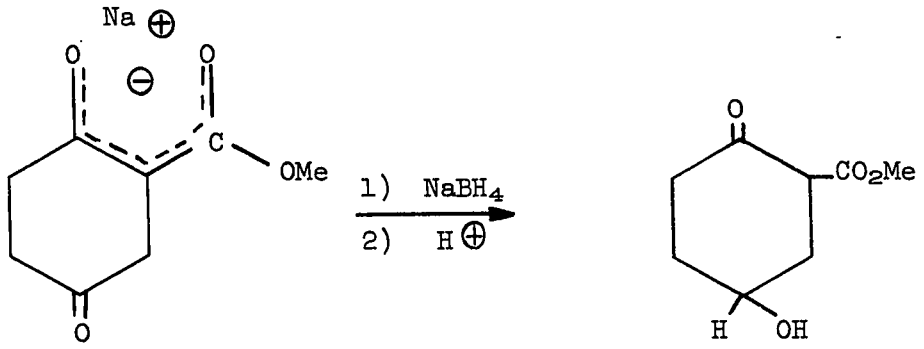
Wadsworth and Emmons[98] have recently introduced a useful supplement to the Wittig olefin synthesis, using the reaction of phosphonate carbanions with ketones and aldehydes. This reaction was shown to proceed under much milder conditions. However, the reaction of the diethyl benzylphosphonate anion with dimethyl- δ -ketopimelate in refluxing xylene gave starting material only.

The reason why no reaction occurred under any of these conditions may perhaps be due to the fact that the atoms in the pimelate molecule are arranged in a non-planar, coiled structure, viz.



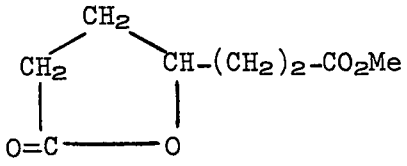
In such a coiled form the chain might be sterically effective in hindering addition. Steric effects of this kind have been summarized by Newman in an empirical rule, usually referred to as the "rule of six".[115]

In another approach, the ketal grouping in 2-carbomethoxy-4-ethylenedioxycyclohexanone was removed in acetone which contained a trace of acid, and the diketo ester so obtained was selectively reduced at the 4-position under basic conditions, viz.



87

However, the yield of 2-carbomethoxy-4-hydroxycyclohexanone (87) was too low to warrant any further work. Still another approach involved the sodium borohydride reduction of dimethyl-γ-ketopimelate in the cold to give dimethyl-γ-hydroxypimelate; the infrared spectrum of the product showed strong absorption at 1730 cm^{-1} (C=O, ester) and an intense band at 1770 cm^{-1}, indicating that lactonization had occurred, yielding:



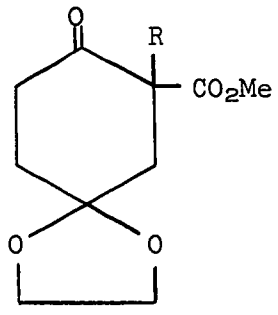
We returned to the 4-ethylenedioxy compound and investigated the feasibility of a stepwise procedure, namely alkylation followed by cyclization. A suitable alkylating agent was 1-chloro-2-methyl-3-bromopropane.

Two problems arise in connection with alkylations using substrates like 2-carbomethoxycyclohexanone:

(a). The enolate ion of this compound is an ambident anion, i.e., it is capable of covalent bond formation at either carbon atom-2 or at the carbonyl oxygen. The yield and the site of alkylation may be greatly influenced by the solvent medium.[116]

(b) If C-alkylation occurs, it may take place at either C-2 or C-6. Stork[117] was able to show that the kinetic enolate ion is the less substituted 6-enolate ion in compounds such as 2-methylcyclohexanone, which in the presence of free ketone is rapidly equilibrated to the more stable 2-enolate. Alkylation is usually slower than this equilibration and thus proceeds normally via the more stable enolate.

We undertook a preliminary experiment, using the potassium salt of 2-carbomethoxy-4-ethylenedioxycyclohexanone and methyliodide in dry dimethylformamide as a solvent. The reaction furnished the C-methylated product exclusively, namely:



a. R = CH_3

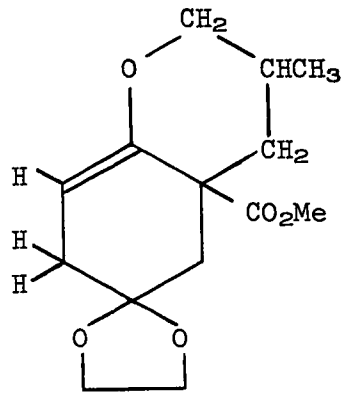
b. R = $CH_2CH(CH_3)CH_2Cl$

88a

The sharp, 3-proton signal at 8.79 τ was assigned to the tertiary methyl group. There was no evidence for a $\rangle C=C-OCH_3$ group, which would have resulted if O-alkylation had taken place.

Next, 1-chloro-2-methyl-3-bromopropane was prepared. The n.m.r. spectrum of this compound shows a doublet at 8.87 τ for the CH-methyl group and a multiplet centered at 8.05 τ for the β-CH proton. The signals for the α- and the γ-protons at 6.52 τ are somewhat complicated by the fact that these protons are adjacent to an asymmetric carbon atom and are slightly non-equivalent, due to hindered rotation about the αC-βC and the βC-γC bond, respectively.

Condensation with the potassium salt of 2-carbomethoxy-4-ethylenedioxycyclohexanone, under similar conditions to those used above gave the expected product (88b) in a reasonable yield. The subsequent cyclization step, however, using either methylsulfinylcarbanion in dimethylsulfoxide[96], or potassium t-butoxide in benzene, gave largely O-alkylated product, viz.



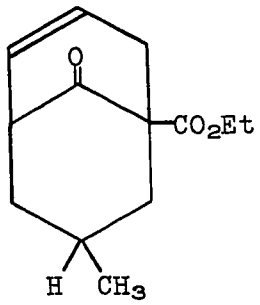
89

The compound gave a positive bromine test. Spectroscopic evidence for the presence of an enol-ether came from its infrared spectrum which showed an intense, characteristic[118] band at 6 μ. The n.m.r. spectrum gave further support to this interpretation: a triplet at 5.03 τ is

consistent with such a structure: the splitting of the vinyl hydrogen arises from the non-equivalent neighboring methylene protons.

The same reaction was attempted using the condensation product of 2-carboethoxycyclohexanone with 1-chloro-2-methyl-3-bromopropane. Again, mostly O-alkylated product was obtained, regardless of the conditions used.

Finally, we abandoned this series and instead turned our attention to the following bicyclononane system:



91a

To this end, 2-carboethoxy-4-methylcyclohexanone was prepared from 4-methylcyclohexanone, which was subsequently condensed with acrolein at low temperature. The infrared spectrum of the product showed an absorption at 2720 cm^{-1} for the aldehydic hydrogen as well as an absorption in the carbonyl region. Aside from the signals for the carboethoxy group, the n.m.r. spectrum showed a poorly resolved signal for the C-methyl group centered at 8.96 τ and a sharp signal at 0.1 τ, characteristic for an aldehydic proton. Coupling with the protons on the adjacent carbon atom was observed for slower sweep rates, which resulted in a poorly resolved doublet. An attempt to effect cyclization using

concentrated sulfuric acid gave the desired compound in low yields only. A much more satisfactory approach involved the use of polyphosphoric acid, which gave this compound in a 52% yield.

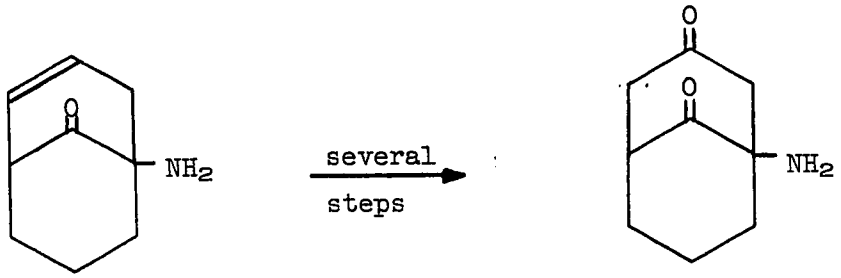
The n.m.r. spectrum of the bicyclic compound is in agreement with the structure shown above. Signals for the carboethoxy group are at 8.71 τ (triplet) and 5.82 τ (quartet), respectively. A doublet at 6.58 τ (splitting 20 c.p.s.) was assigned to the C-2 equatorial hydrogen atom, the large splitting arising from a strong geminal coupling with the C-2 axial proton. The peaks of this doublet are relatively broad, which is due to further splitting to the C-3 olefinic proton and to a lesser degree to the C-4 olefinic proton through long-range coupling. Observable couplings across four or five bonds in unsaturated systems are rather common and have been measured in many cases. Banwell and Sheppard[119] have recently reviewed the present experimental and theoretical situation with regard to long range (H,H) coupling constants. The signal for the axial proton lies at higher field and occurs together with other signals. The olefinic protons gave rise to multiplet at 4.31 τ. The signal at 9.01 τ for the C-methyl group deserves some comment. In contrast to the uncyclized material this signal is now sharp, and it is split distinctly into a doublet with a splitting of 5.8 c.p.s.

In compounds with a $CHCH_3$ group adjacent to a methylene group, the appearance of the methyl signal depends on the difference in the chemical shift of the CH-proton relative to the adjacent methylene protons.[84] The band of the methyl group is a fairly good doublet if the CH-proton is chemically shifted from the adjacent methylene protons,

as for instance in 2-methylcyclohexanone. On the other hand, the methyl group gives a very poor "doublet" if these protons are only slightly separated, as for instance in 3-methylcyclohexanone.

The differences noted for the C-methyl group in the uncyclized and the cyclized product above may be explained in a similar manner. However, an assignment of the factors involved (e.g. long range shielding effects) is not possible without further data.

While experiments for the improvement in yield for ethyl-7-methylbicyclo [3.3.1] non-3-en-9-one-1-carboxylate were in progress, we were at the same time trying to find a workable procedure for the conversion of ethyl-bicyclo [3.3.1] non-3-en-9-one-1-carboxylate into 1-aminobicyclo [3.3.1] non-3-en-9-one (92), as well as a method to achieve the following:



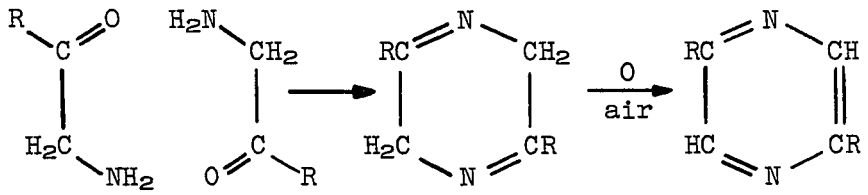
92 92a

It seemed, that 92a - lacking only a methyl group - might serve as a suitable intermediate for a partial synthesis.

Ethyl-bicyclo[3.3.1]non-3-en-9-one-1-carboxylate was chosen as a starting substance since it was readily available by known methods.[49c] The elegant procedure used by Weinstock[102] for the preparation of cis-2-phenylcyclopropylamine from cis-2-phenylcyclopropyl carboxylic acid was applied to bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid, which in turn was obtained by mild hydrolysis of the corresponding ethyl ester.

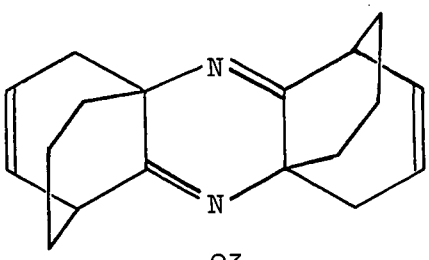
Thus, when this acid was treated with triethylamine, ethylchloroformate and sodium azide in aqueous acetone solution, followed by extraction of the acid azide with toluene and thermal rearrangement of the latter, the isocyanate was obtained in a good yield. The infrared spectrum of the oily product showed a strong absorption at 2240 cm^{-1}, characteristic for the -N=C=O group. Hydrolysis, followed by the usual work-up, gave 1-amino-bicyclo[3.3.1]non-3-en-9-one (92) as an oil in a 58% yield. The compound was characterized by its infrared spectrum: the bands at 3450 cm^{-1}, 3080 cm^{-1}, 1725 cm^{-1}, 1650 cm^{-1}, and 1600 cm^{-1} were assigned to the stretching vibrations for N-H, C=C-H, C=O, and C=C and to the NH_2 scissoring mode, respectively.

The amine solidified on standing. The infrared spectrum of the compound showed no absorption for the N-H or C=O stretching vibration, but instead had bands at 1660 cm^{-1} and 1640 cm^{-1}. This suggested that the compound might contain a C=N linkage beside the C=C bond. A molecular weight determination of the pure crystalline compound, m.p. 178-179.5°C, showed that dimerization with the loss of two moles of water had occurred. This was not entirely unexpected since it is known, that free amino-ketones rapidly undergo condensation to give pyrazines, viz.



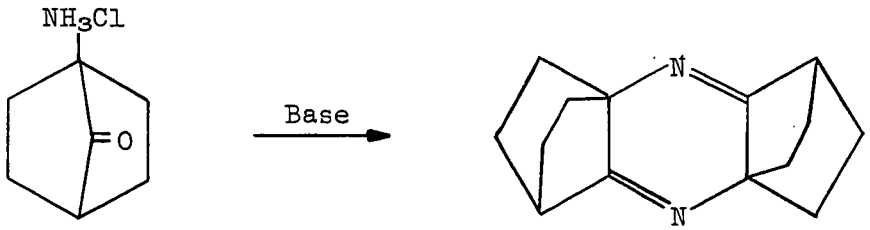
(a) (b) (c)

However, in our case the second step (b → c) cannot take place because of the fact, that the remaining two carbon atoms are quarternary in nature. Therefore, the dimerized structure may be formulated as follows:



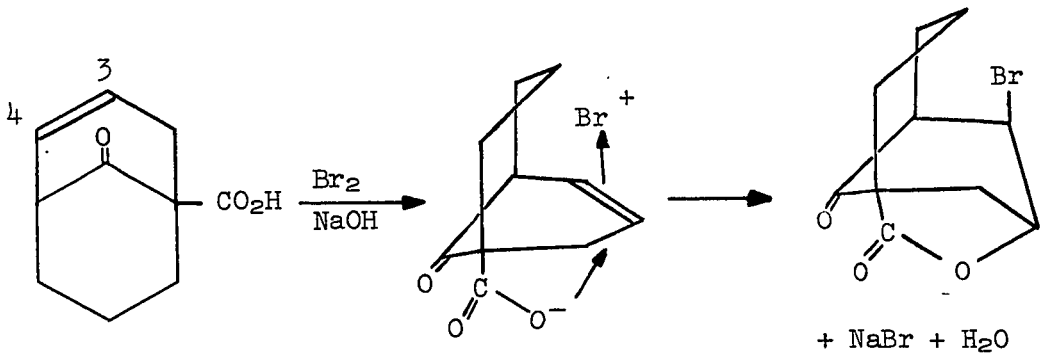
93

The elemental analysis, $C_{18}H_{22}N_2$, is also in excellent agreement with this structure. The results of this study compare well with those of Applequist and Klieman.[120] They obtained the dihydropyrazine (ii) upon treating the amine hydrochloride (i) with aqueous sodium hydroxyde.

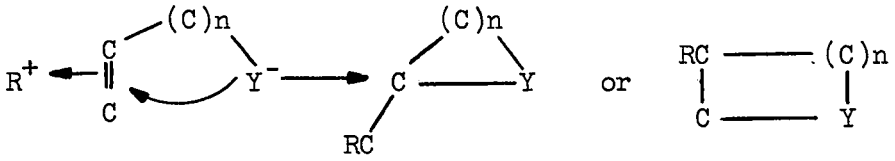


(i) (ii)

During the formation of ethyl-bicyclo[3.3.1]non-3-en-9-one-1-carboxylate a migration of the $\Delta^{3,4}$-bond to the 2,3-position under the strongly acidic conditions of the cyclization cannot be entirely ruled out. Therefore, we tried to find out if such a migration had actually occurred. It might be anticipated, that the bromination of the $\Delta^{3,4}$-bond in bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid is anchimerically assisted by participation of the carboxylate ion with the formation of a γ-lactone, viz.



It was shown by Johnson[121] and van Tamelen[101] that this is a rather general reaction:



where Y^- is a nucleophilic function and R^+ a cationic species.

However, in the above experiment no γ-lactone formation was observed. This might be due to the strain involved in the formation of this compound.

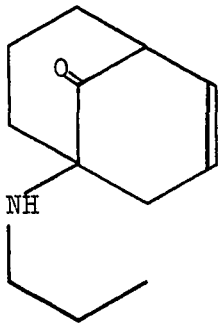
With the amine readily obtained, the first objective was completed. At this point it became necessary to prepare a suitable 3-carbon unit such as:

$CH_2=CH-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH=CH_2$ (a)

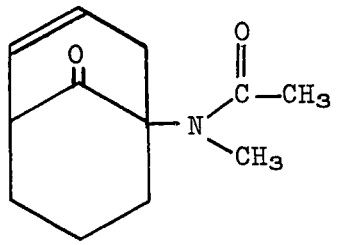
$Br(CH_2)_2OTs$ (b)

$Br-CH_2-\underset{O\ O}{\overset{/\ \backslash}{C}}-CH_3$ (c)

which, after condensation with the amine would lead to an assembly of the type:



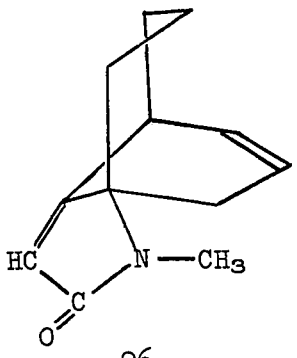
In order to find a procedure for the alkylation of the amine, using either (b) or (c), the N-acetyl derivative (94) was treated with sodium hydride and methyliodide in refluxing xylene. The infrared and n.m.r. spectrum were not in agreement with the expected structure shown below:



95

The alkylation product did not show a carbonyl absorption in the infrared spectrum. Its n.m.r. spectrum had only one strong (3-proton), sharp signal at 7.17 τ . N-methyl groups normally absorb near 7.8 τ . However, a paramagnetic shift accompanies N-acylation or lactam formation. From these observations and the mode of preparation it was concluded that

ring formation had occurred to give:

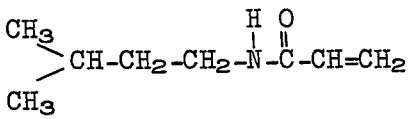


96

through an intra-molecular aldol condensation. The elemental analysis, $C_{12}H_{15}NO$, further corroborated this conclusion. The ultraviolet spectrum of this compound in the 220-340 mμ region showed only end absorption, λ^{EtOH} 225 mμ (ε 6250).

Next we turned our attention to the preparation of (a). The condensation of acrylic acid with dicyclohexylcarbodiimide led in a reasonable yield to the desired compound (97). The clear, mobile liquid had a doublet in the carbonyl region of its infrared spectrum at 1790 cm^{-1} and 1730 cm^{-1}, respectively, and a strong C=C stretching absorption at 1630 cm^{-1}. The n.m.r. spectrum of the anhydride showed a multiplet centered at approximately 3.69 τ.

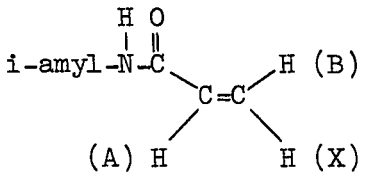
A cursory experiment was made for finding conditions to condense the anhydride with a primary amine, e.g. iso-amylamine. The usual acylating conditions gave a good yield of the expected amide:



98

The evidence for this compound was derived solely from spectral evidence. In the infrared spectrum, this compound showed bands at 3300 cm^{-1} (N-H), 3100 cm^{-1} (vinyl H), 1650 cm^{-1} (Amide I), 1620 cm^{-1} (C=C) and 1545 cm^{-1} (Amide II), in full agreement with the structure shown above. The

nuclear magnetic resonance spectrum showed a doublet at 9.12 τ (splitting 6.1 c.p.s., 6 protons), a multiplet centered at 8.57 τ (3 protons) and a quartet at 6.77 τ (2 protons), accounting for all the protons of the isoamyl portion of the molecule; a quartet at 4.57 τ and a multiplet at approximately 3.8 τ belong to the vinyl system; they arise from an ABX-system of nuclei in the notation of Bernstein, Pople and Schneider,[122] where A and B are spin coupled nuclei having J_{AB} and J_{AB} of comparable magnitude, which are also spin coupled with another nucleus, X, having a large chemical shift relative to A and B. On the basis of their coupling constants J_{AB} = 18.6 c.p.s., $J_{AX} > 8.2$ c.p.s. and $J_{BX} < 4.4$ c.p.s. the A, B and X protons were assigned as follows:



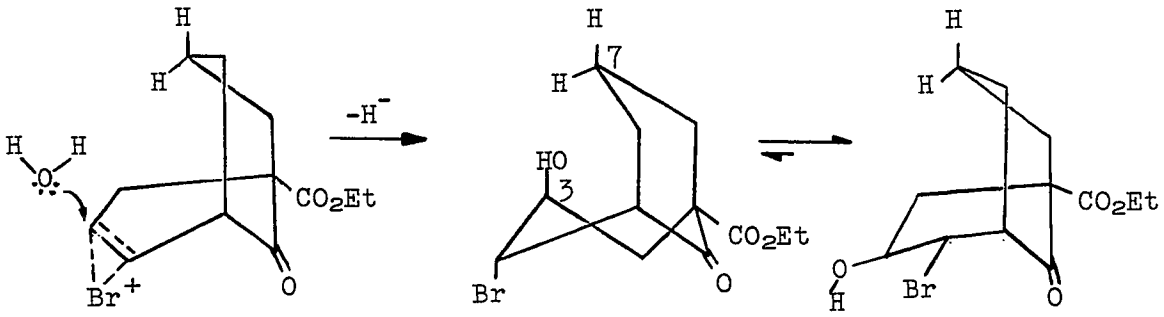
The splittings agree well with the general observation of proton coupling constants across double bonds, viz.

J_{trans}(11-18 c.p.s.) > J_{cis}(6-14 c.p.s.) > $J_{vicinal}$(0-3.5 c.p.s.)

The conversion of the double bond to a keto-group at C_3 posed a major obstacle. There are several methods known which convert olefinic compounds into oxygenated saturated compounds. One such reaction is the well known but recent hydroboration reaction[123], which in many cases yields the ketone without the isolation of any intermediate. Another approach involves the formation of an epoxide, followed by reduction with lithium aluminum hydride to yield an alcohol. Still

another course of action is the hydroxylation of olefins using N-bromosuccinimide. Each of these methods has found wide application in various fields.

The last method was chosen for the following reason: it was anticipated that the formation of the halohydrin would be stereospecific, on the reasonable assumption that approach of the bromonium ion would occur from the least hindered side as shown:

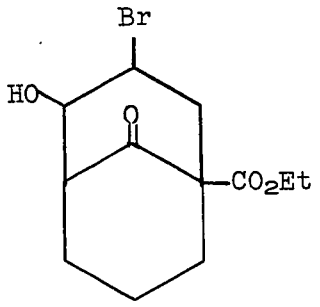


(i) (ii) (iii)

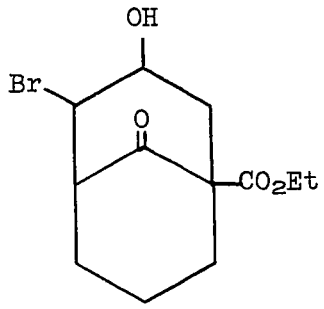
An inspection of a molecular model of this compound suggests that there is a very large transannular interaction between the axial hydrogen on C-7 and the axial hydroxyl group at C_3 in (ii). It would be expected, therefore, that the axial OH-group makes the chair form (ii) energetically very unfavorable; consequently, its content should be negligible in contrast to the boat (iii) in which both the hydroxyl group and the bromine atom are equatorially oriented.

When ethyl-bicyclo[3.3.1]non-3-en-9-one-1-carboxylate was treated with aqueous N-bromosuccinimide in the presence of sulfuric acid at 80°C, a viscous, yellow oil was obtained in over 80% yield; this product exhibited a strong absorption in the O-H region of the infrared

spectrum. After addition of petroleum ether, a crystalline compound, m.p. 98-100°C, was obtained in a 40% yield. Its elemental analysis, $C_{12}H_{17}O_4Br$, was in agreement with the bromohydrin, 99a or 99b:



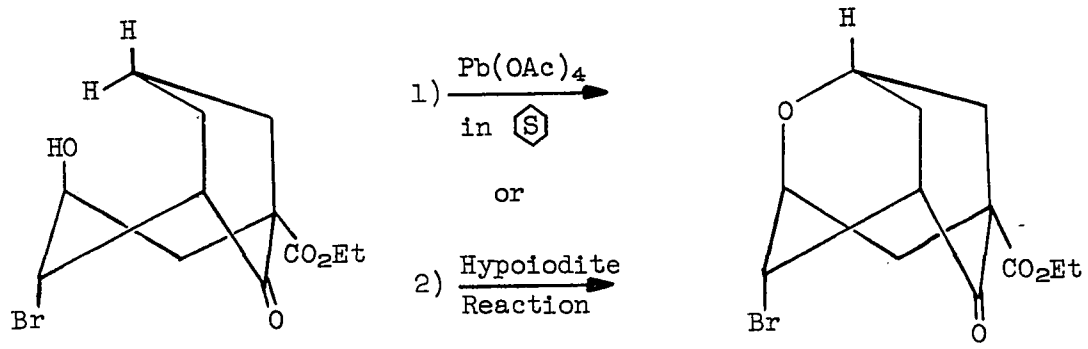
99a



99b

That it was the "correct" isomer 99b was shown by its conversion to ethyl-bicyclo[3.3.1]nonan-3,9-dione-1-carboxylate (vide infra). The low yield of this isomer seems to indicate that the formation of the bromonium ion can occur to a considerable extent from the opposite side to that shown in (i), thus giving a mixture of isomers. The pure bromohydrin shows no absorption in the range 3600-3650 cm^{-1}, which would correspond to a free hydroxyl group on the diaxial (chair) conformation (ii). Its O-H stretching frequency at 3540 cm^{-1} may be due to hydrogen bonding which can occur with a diequatorial bromohydrin (iii above).

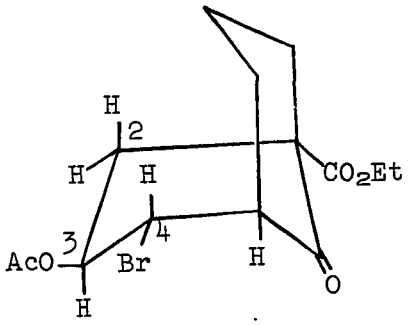
Also, in the chair-chair conformation (ii), functionalization of the unactivated C-7 methylene group should be possible using the known intramolecular substitution reactions of Jeger[103] or Wettstein,[124] since hydrogen abstraction would be very favorable in this conformation.



However, only starting material was recovered (see Experimental, page 64).

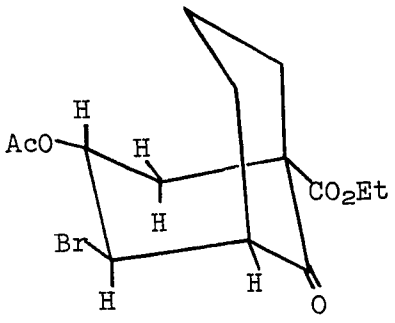
Acetylation of the bromohydrin under mild conditions yielded the corresponding O-acetate in good yield; this is a further indication for an equatorial configuration of the hydroxyl-group, as shown for structure (iii) above. The n.m.r. spectrum of the acetate is also in favor of a structure with an equatorial acetoxy group. A quartet centered at 5.72 τ (splitting 7 c.p.s.) and a triplet at 8.68 τ (splitting 6.8 c.p.s.) belong to the ethylester grouping. The acetoxy-methyl group appears as a 3-proton singlet at 7.87 τ . Centered at about 4.9 τ is a sextet, representing the proton on the acetoxyl bearing carbon atom; the splitting arises from the C-2 methylene protons (11 c.p.s. and 6 c.p.s.) and from the proton on C-4 (10.5 c.p.s.). The proton on C-4 appears as a quartet at somewhat higher field at 5.63 τ . The poorly resolved signal at 6.78 τ was assigned to the bridgehead hydrogen atom. The equatorial proton at C-2 ($\delta \simeq 6.97\ \tau$) is split by a large gem-coupling to its axial counterpart (13.8 c.p.s.) and by approximately 6 c.p.s. to the C-3 proton. The signal for the axial proton occurs together with the remaining protons of the molecule at higher field.

The integrated intensities indicate a total of 19 protons, in agreement with the value found by elemental analysis. These data can be accommodated if one assumes a boat form for the ring bearing the acetoxy - and bromine group, viz.



100a

It should be noted that the n.m.r. spectrum also fits the following structure:



100b

However, evidence against this is the fact, that the bromine atom in ethyl-4-bromobicyclo[3.3.1]nonan-3,9-dione-1-carboxylate (vide infra) has an axial configuration, whereas the corresponding bromoketone derived from 100b would have an equatorial bromine atom.

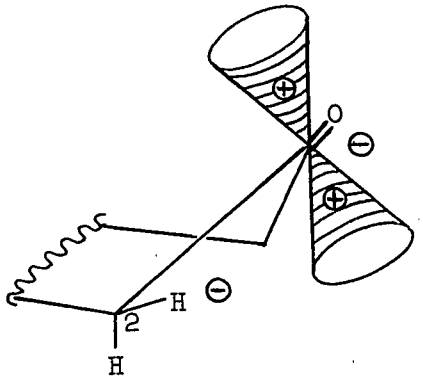
Oxidation of the crude bromohydrin with sodium dichromate in sulfuric acid gave a yellow oil in good yield. The oil was dissolved in ethyl ether and petroleum ether was then added. After standing in the cold overnight, a crystalline compound, m.p. 89-91°C, separated out in 23% yield. Its elemental analysis, $C_{12}H_{15}O_5Br$, was in good agreement with ethyl-4-bromobicyclo[3.3.1]nonan-3,9-dione-1-carboxylate (101). Similar results were obtained using acetone-chromic acid[104] or pyridine-chromic acid.[90] The low yield of the crystalline bromoketone (axial bromine atom, vide infra) could be due to partial isomerization to a compound in which the bromine has an equatorial configuration. This was not further investigated.

The n.m.r. spectrum of the crystalline bromoketone showed a triplet at 8.64 τ for the 3 protons of the ester methyl group. The C-2 protons formed an AB system: the axial proton gave a signal at 7.25 τ (doublet, splitting 17.2 c.p.s.); the peaks were further split by approximately 2 c.p.s., presumably through long range coupling. The corresponding doublet for the C-2 equatorial proton appeared at 5.79 τ (splitting 16.2 c.p.s.). The magnitude of the coupling constants is consistent with geminal coupling. The bridgehead proton gave a multiplet at 6.85 τ and the equatorial proton on the bromine carrying carbon atom showed a poorly resolved signal at 5.49 τ . The methylene protons of the ester group gave the expected quartet at 5.69 τ .

The appreciable downfield shift of the C-2 equatorial proton in this compound* may be explained by the anisotropy effect of the neighboring carbonyl group.[125] Protons lying in conical regions extending above and below the plane of the trigonal carbon atom of the

* Similar shielding effects, although less pronounced, were observed for the C_2 equatorial proton in compounds 91a, 94 and 102.

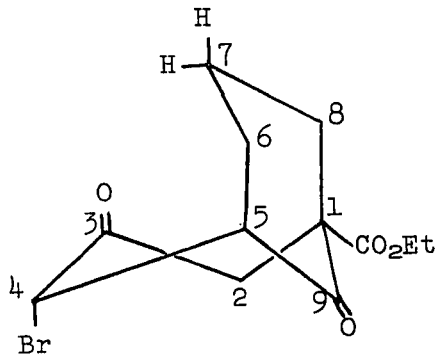
carbonyl group are shielded by this function, while those lying elsewhere, and particularly those in the plane of the trigonal atom will be de-shielded.



Unequivocal proof for an axial bromine atom came from the ultraviolet spectrum of this compound. It was shown by Cookson[126] that in the cyclohexanone series an equatorial bromine atom has an absorption band $n \rightarrow \pi^*$ (R-band) in position as well as in intensity in the neighborhood of the non-brominated ketone, i.e. around 289 mμ(ε 20-30). An axial bromine atom on the other hand causes an appreciable bathochromic shift, accompanied by a strong hyperchromic effect (300 mμ; ε 120). The value obtained, 307 mμ(ε 145), is in good agreement with this. A similar relationship exists in the infrared spectrum of compounds of this type. Here the axial isomer[127] absorbs around 1710 cm^{-1}, equal to the simple ketone, while its equatorial counterpart absorbs at a higher frequency, around 1735 cm^{-1}. However, this effect was masked because of the presence of the ester group.

These observations, together with the fact that non-bonded interactions between C-3 and C-7 are greatly reduced because of the

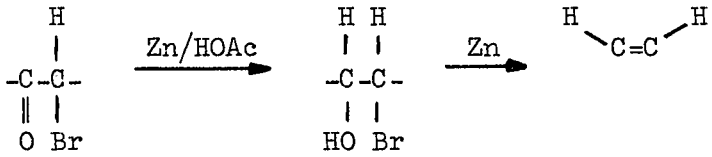
trigonal configuration of carbon atom-3, lead to the very reasonable assumption of a chair-chair form for this compound as shown:



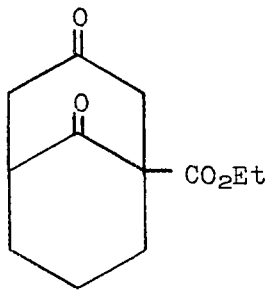
101

Reductive removal of the bromine atom with zinc in glacial acetic acid led in a good yield to ethyl-bicyclo[3.3.1]nonan-3,9-dione-1-carboxylate (102), a solid melting at 75-77°C. Aside from signals typical for the $-\overset{\overset{O}{\|}}{C}-O-CH_2CH_3$ grouping, the n.m.r. spectrum showed a doublet at 6.59 τ (splitting 17 c.p.s.); it was assigned to the equatorial proton at C-2 (vide supra).

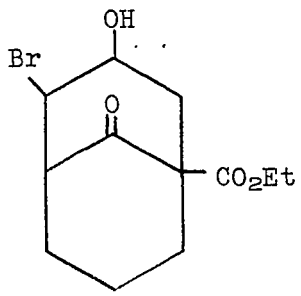
If the reduction was carried out with the crude bromoketone, some starting material, i.e. ethyl-bicyclo[3.3.1]non-3-en-9-one-1-carboxylate was recovered. The formation of the olefin from the bromoketone can be explained as follows:



In order to show that the reduction of the bromoketone 101 did in fact give the 3,9-dione 102 rather than the 4,9-isomer, it became necessary to synthesize the latter compound by an unambiguous method. When β-(1-ethoxycarbonyl-2-ketocyclohexyl) propionaldehyde was treated with acid under mild conditions, ethyl-4-hydroxybicyclo[3.3.1]non-9-one-1-carboxylate was obtained in good yield. Oxidation of the latter compound with the pyridine-CrO_3 complex[90] gave the 4,9-dione as a clear, viscous oil, which did not crystallize on seeding with the 3,9-isomer. Furthermore, these compounds differed in their ultraviolet and infrared absorption. It follows, that the diketoester described above, and consequently the bromohydrin, have structures 102 and 99b, respectively.



102



99b

Hydrolysis of the diketoester gave bicyclo[3.3.1]non-3,9-dione-1-carboxylic acid (104), m.p. 183-188°C. The infrared spectrum was in agreement with this compound. The three distinct peaks in the carbonyl region were assigned to the acid (1730 cm^{-1}), the free keto-group at C-3 (1705-1710 cm^{-1}) and the C-9 carbonyl group (1670 cm^{-1}) respectively.

The large shift to lower frequency must be due to strong hydrogen bonding between the acid and this carbonyl group. Although signals from the ethyl ester group were absent in the n.m.r. spectrum, no signals for the carboxylic acid proton - using a number of solvents - could be detected.* In comparison, both bicyclo[3.3.1] non-3-en-9-one-1-carboxylic acid and its 7-methyl analogue exhibited a sharp signal at -1.8 τ and 1.9 τ , respectively. This difference may be due to some exchange process.

Several attempts were made to prepare the amine 92a from the acid 104 by methods described above. However, we were unable to obtain any amine from the complex reaction mixture.

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* The n.m.r. spectrum of o-hydroxybenzoic acid in acetone showed a very broad peak for the carboxylic acid-hydroxyl proton on the low frequency side of the ring protons.

CLAIMS TO ORIGINAL RESEARCH

1. The following compounds have been synthesized:
   (a) 1-cyano-3-methyl-4-hydroxybicyclo[3.3.1]nonan-9-one.
   (b) The C_4-epimers of 1-cyano-3-methyl-4-acetoxybicyclo[3.3.1]nonan-9-one.
   (c) 1-cyano-3-methylbicyclo[3.3.1]nonan-4,9-dione.
   (d) 3-methyl-4,9-dihydroxybicyclo[3.3.1]nonan-1-carboxylic acid amide.
   (e) 1-amino-3-methyl-4,9-dihydroxybicyclo[3.3.1]nonane.
   (f) Ethyl-7-methylbicyclo[3.3.1]non-3-en-9-one-1-carboxylate.
   (g) 1-aminobicyclo[3.3.1]non-3-en-9-one.
   (h) 1-acetaminobicyclo[3.3.1]non-3-en-9-one.
   (i) Ethyl-3-hydroxy-4-bromobicyclo[3.3.1]nonan-1-carboxylate.
   (j) Ethyl-3-acetoxy-4-bromobicyclo[3.3.1]nonan-1-carboxylate.
   (k) Ethyl-4-bromobicyclo[3.3.1]nonan-3,9-dione-1-carboxylate.
   (l) Ethyl-bicyclo[3.3.1]nonan-3,9-dione-1-carboxylate.

2. An improved procedure for the base-catalyzed cyclization of dimethyl-γ-ethylenedioxypimelate is claimed.

3. The use of polyphosphoric acid instead of concentrated sulfuric acid for the cyclization of compounds like β-(1-ethoxycarbonyl-2-keto-5-methylcyclohexyl)propionaldehyde gives improved yields.

4. The existence for a boat-chair form for a [3.3.1]bicyclononane system has been established for ethyl-3-acetoxy-4-bromobicyclo[3.3.1]nonan-1-carboxylate by chemical means and through n.m.r. evidence.

5. A pronounced de-shielding effect through magnetic anisotropy has been observed for the C_2-equatorial proton in the following compounds:

   (a) Ethyl-7-methylbicyclo[3.3.1] non-3-en-9-one-1-carboxylate.

   (b) 1-acetaminobicyclo[3.3.1] non-3-en-9-one.

   (c) Ethyl-4-bromobicyclo[3.3.1] nonan-3,9-dione-1-carboxylate.

   (d) Ethyl-bicyclo[3.3.1] nonan-3,9-dione-1-carboxylate.

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