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THE UNIVERSITY OF ALBERTA

TOWARDS THE SYNTHESIS OF COCCINELLIN AND LUCIDULINE

by

© ROBIN DAWE

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
FALL, 1974

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

TOWARDS THE SYNTHESIS OF
COCCINELLIN AND LUCIDULINE

submitted by ROBIN DAWE in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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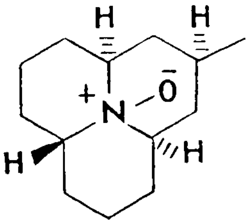
ABSTRACT

Because of their appetities for aphids and mites, ladybugs are now the subject of much research. The defensive secretion of the ladybug Coccinella septempunctata has been found to contain the alkaloid coccinellin, to which has been assigned structure 5. This compound is responsible for the exceedingly bitter taste of the ladybug.

There are certain similarities in stereochemistry between coccinellin and compound 15. The latter compound has been synthesized previously in these laboratories and certain aspects of that synthesis were employed in an attempted total synthesis of coccinellin. This work is described in the first part of the thesis.



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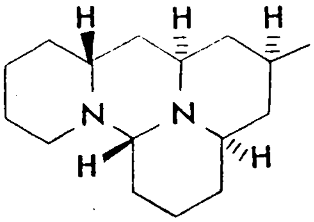

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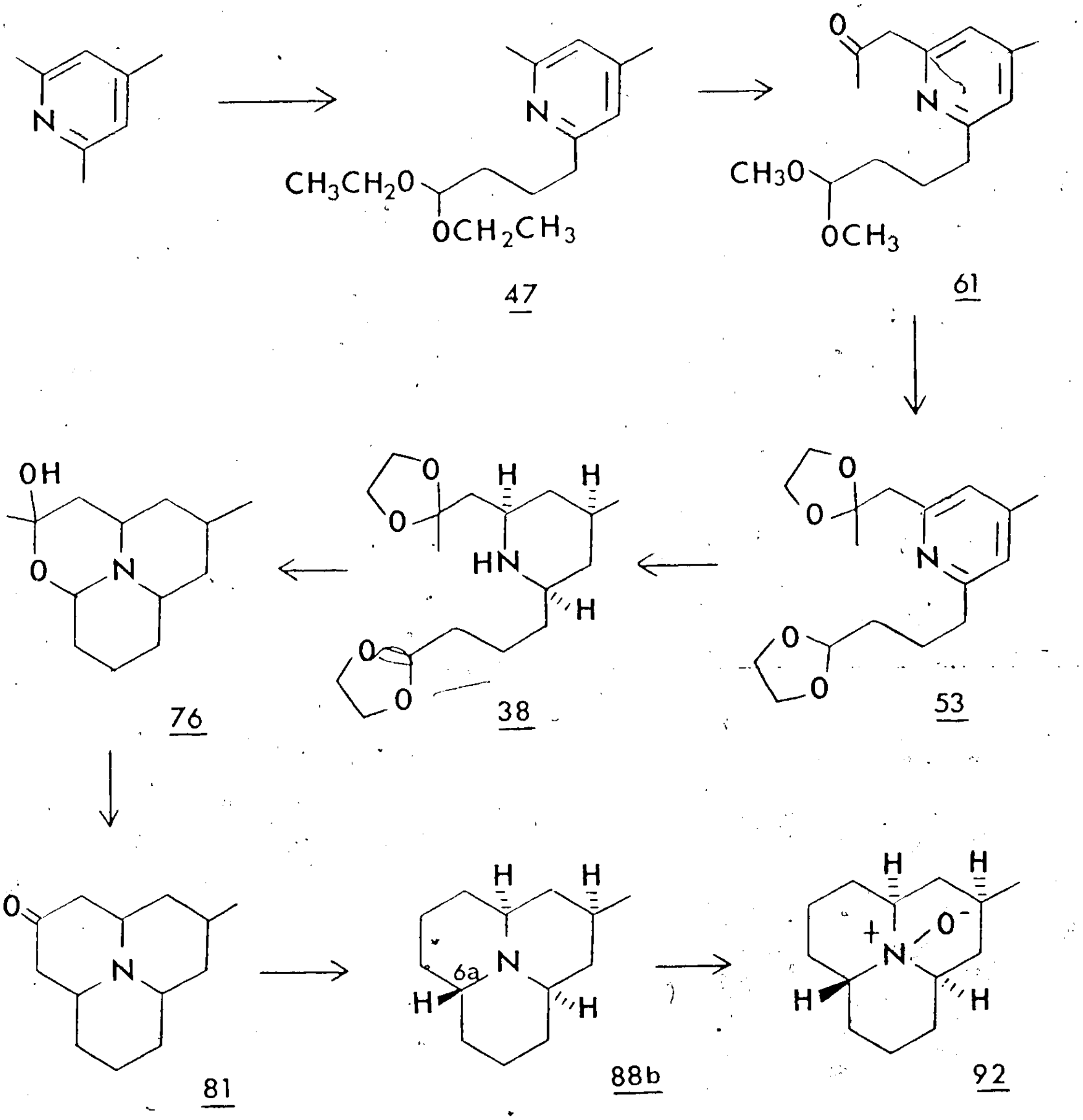
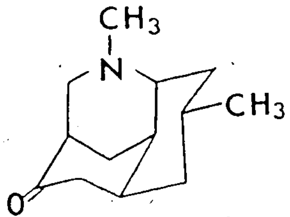
2,4,6-Collidine may be lithiated at the 2-methyl group and then alkylated with β-chloropropionaldehyde diethylacetal to give 47. After acetal exchange to the dimethylacetal this compound was treated with phenyllithium and the anion alkylated with acetonitrile to give 61. Protection of the ketone (with concomitant acetal exchange) as the ethylene ketal gave 53 which was reduced to the all *cis* piperidine derivative 38 using sodium in *iso*-amyl alcohol.

Hydrolysis of the protecting groups produced hemiketal 76 which was treated with pyrrolidine and acetic acid in tetrahydrofuran to produce keto-amine 81. The oxygen functionality was removed by thioketalization followed by desulphurization with Raney-Nickel to produce 88b and the compound epimeric at C-6a. Amine 88b was oxidised with *m*-chloroperbenzoic acid to give the N-oxide to which has been given structure 92. It has not been possible to establish identity between 92 and natural coccinellin.

The second part of the thesis describes work directed towards the synthesis of bicyclic keto-lactam 17 which is a potential precursor of luciduline 9. Conceptually, 17 is available *via* internal Michael cyclization of 22. Several possible methods of synthesizing 22 have been examined.


N
CH$_3$CH$_2$O
OCH$_2$CH$_3$
47
O
N
CH$_3$O
OCH$_3$
61
O
O
N
O
O
53
O
O
H
H
HN
H
O
O
38
OH
O
N
76
O
N
81
H
H
6a
N
H
H
88b
H
H
+
N
O$^-$
H
H
92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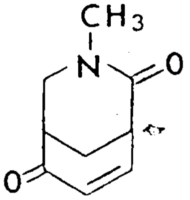
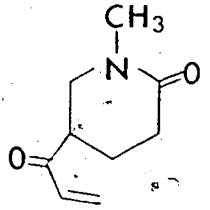

17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Dr. W. A. Ayer for his encouragement and enthusiasm throughout the work described herein. He was always happy to share his knowledge and offer enlightening suggestions.

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I: TOWARDS THE SYNTHESIS OF COCCINELLIN

INTRODUCTION

"Ladybug, ladybug, fly away home.
Your house is on fire and your children alone".

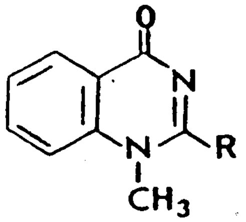
The Coccinellidae (or ladybugs) have long been known for their appetites for plant pests such as aphids and mites.[1] However the use of insecticides to control these plant pests resulted in little interest being shown in the coccinellids. The realization that insecticides are harmful to the environment in general has led, in the last decade or so, to tremendous developments in biological control. Thus the ladybugs are now the subject of much scientific research and a monograph by Hodek[2] describes the recent advances in the knowledge of this group of insects.

All organisms are chemosensitive and all of them produce substances to which others can potentially respond[3]. When the organisms belong to the same species the compounds responsible for the signals are the pheromones. These compounds which are very important for courtship and mating and other social activities among animals have been the subject of much intensive research and of excellent reviews[4].

Of equal importance to the lives of certain organisms are those substances which carry information between organisms of different species. If two species coexist in harmony or they coexist in conflict their interactions seem to depend to a large extent on the chemical compounds which they produce. When two organisms exist in conflict the weaker of the species often uses defensive secretions to dissuade the stronger from attacking.

Arthropods have most diverse and probably the best evolved chemical defences[4a]. The chemical compounds used by these animals may be ejected in gaseous form or as a fine spray, simply ooze out as a liquid or they may be foams. However it is of no consequence how the compounds are discharged, the predators have no doubt as to their meaning. The defensive compounds are not usually fatal, but they cause the predators sufficient discomfort to allow the attacked animal to escape.

Unlike pheromones which are often produced in microgram quantities thus making isolation and characterization difficult, the defensive secretions may be detected with relative ease since they are often strongly smelling and ejected in substantial amounts. Compounds which have been isolated from arthropods and are claimed to be defensive substances vary in complexity from hydrogen cyanide or formic acid to terpenes, quinones and miscellaneous polycyclic molecules. For example, the secretion of the whipscorpion *Mastigoproctus giganteous* consists of 84% acetic acid[5]. Work by Schildknecht, Wenneis, Weiss and Maschwitz[6] and by Meinwald, Meinwald and Eisner[7] has demonstrated that the secretion from the millipede *Glomeris marginata* contains the two dialkyl-quinazolinones 1 and 2.

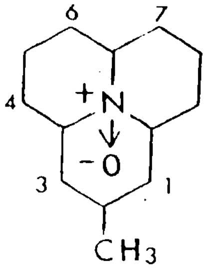


1 R = CH_3

2 R = CH_2CH_3

In 1971 Tursch and co-workers[8,9] published work on the chemical defenses of the common European ladybug *Coccinella septempunctata* L. When this insect is molested it releases droplets of orange haemolymph at its articulations. The ejection of this liquid by the insect provides it with immunity from predators, notably ants and birds.

From a blend of 1600 insects, 135 mg of a colourless crystalline compound, empirical formula $C_{13}H_{23}NO$, was isolated. These workers coined the name coccinellin for this compound. From spectroscopic data they were able to suggest either structure 3 or 4 for coccinellin.



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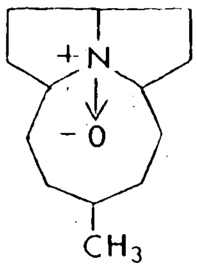

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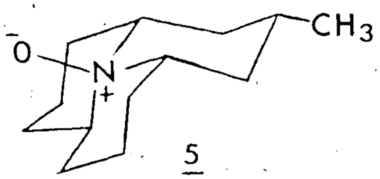
A single-crystal X-ray diffraction study of the hemihydrochloride of coccinellin showed that the compound possesses the structure 5[10].



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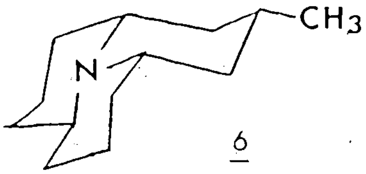


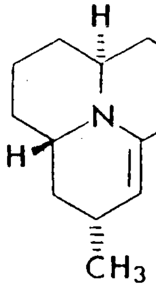
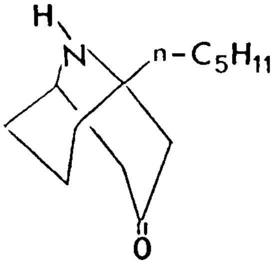
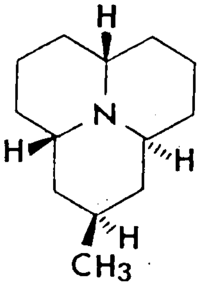
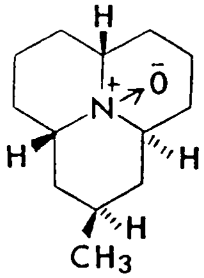
6

In addition to this compound, 10 mg of compound $C_{13}H_{23}N$ was isolated from the haemolymph. This latter compound was shown to possess structure 6, and the relationship between it and coccinellin was demonstrated by reduction of coccinellin to this second compound, precoccinellin, by treatment with ferrous sulphate. The reverse reaction was accomplished using monoperphthalic acid.

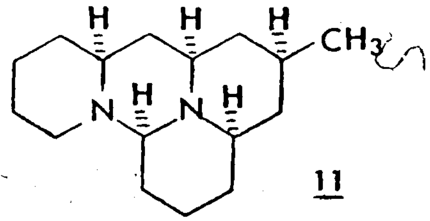
Tursch and co-workers[8] were able to demonstrate that coccinellin is responsible for the bitter taste of the insect but not for its smell. The defensive utility of coccinellin was shown by the complete refusal of water containing 0.5% of the N-oxide by the ant Myrmica rubra. This concentration is much smaller than that of the compound in the haemolymph. It was shown that the ant can be dissuaded from attack without direct contact between the secretion and the mouth of the ant: a [illegible] mg quantity of coccinellin around their food prevented hungry ants from reaching it.

Other work by Tursch and co-workers has shown that the haemolymphs of several related Coccinellidae contain alkaloids of similar skeleta. These are listed in Table 1.

TABLE 1

Species	Alkaloid	Name	Reference
Propylaea quatuordecim-punctata		Propylein 7	11
Adalia bipunctata L.		Adaline 8	12
Hippodamia Convergens		Hippodamine 9	13, 14
"		Convergine 10	13, 14

In 1967 Ayer and Piers published the synthesis of dihydrodeoxyepiallocernuine, 11[15].



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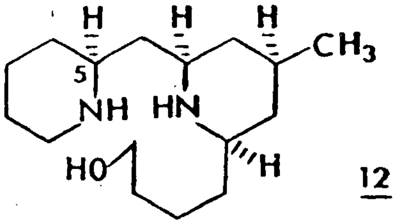
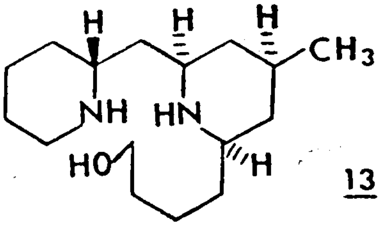


12

This tetracyclic compound was synthesized by oxidation of alcohol 12 to the corresponding aldehyde which cyclized spontaneously under the reaction conditions to the desired tetracyclic compound. Compound 12 had been synthesized in such a way that the compound epimeric at C-5, 13, was produced as well.



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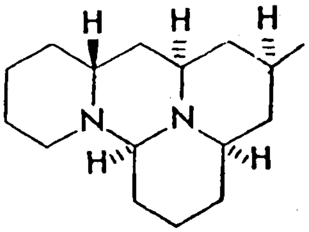
Treatment of 13 under conditions identical to those used for the oxidation of compound 12 produced a mixture of compounds which were epimeric at C-9, 14 and 15.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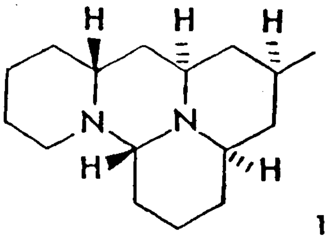
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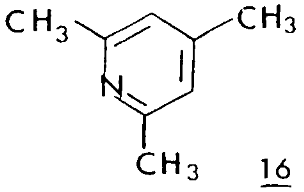
The stereochemistry at all positions in the B, C and D rings of 15 is identical with that reported for coccinellin, 5, and precoccinellin, 6.

Therefore it was decided to investigate the synthesis of precoccinellin and coccinellin along lines similar to those used for the synthesis of 11, 14 and 15. It was expected that certain aspects of the previous synthesis could be utilized most profitably. The synthesis of 11 started with 2,4,6-collidine, 16.

It was shown that treatment of 16 with one molar equivalent of phenyllithium produced the carbanion at the



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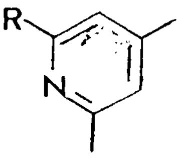

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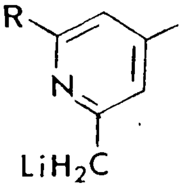
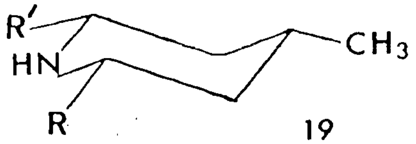


18

2-methyl and that this could be alkylated with a suitable alkylating agent to produce a compound such as 17. Treatment of this with a further equivalent of phenyllithium resulted in metalation at the 6-methyl, 18, and this could be alkylated with a suitable reagent.

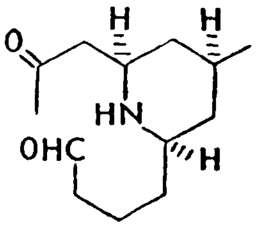
Thus it was expected that the collidine ring would serve as the A-ring in precoccinellin. As in dihydrodeoxyepiallocernuine all the asymmetric centres in the methyl-substituted ring are in the *cis* configuration and, as was observed in that synthesis, reduction *via* catalytic hydrogenation or dissolving metal should lead to this configuration. The desired skeleton, 19, has all the ring-substituents in the equatorial configuration and thus this should be the thermodynamically most stable product. Catalytic hydrogenation of aromatic systems usually



19

produces the compound resulting from all cis addition of hydrogen[16]. Even though catalytic dehydrogenation-hydrogenation has been observed to cause isomerization at the carbon α to nitrogen in nitrogen heterocycles this generally results in the thermodynamically most stable product[17,18]. Dissolving metal reduction usually leads to formation of the most stable product[19] and thus either of the reduction techniques mentioned could be used to produce the required product.

After elaboration of the side-chains, ketoaldehyde 20, should be available (although probably only transiently). This compound would be expected to cyclize readily to 21 in a manner similar to that observed for the cyclization of 13 to 14 and 15. It was expected that this product would be a mixture of isomers about the new asymmetric centre 21a, 21b.



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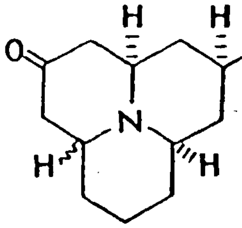

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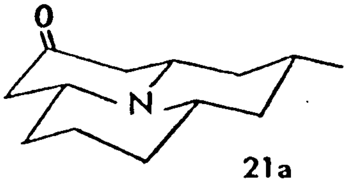
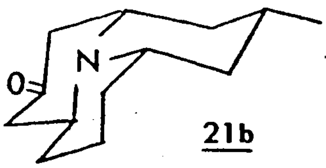
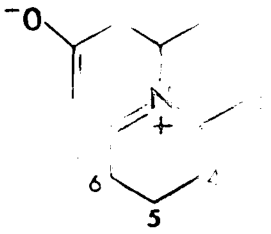


21a



21b

The intermediate in the cyclization of 20 to 21 would be expected to be 22 = 22a.



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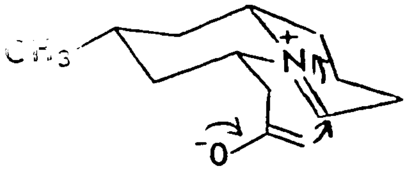
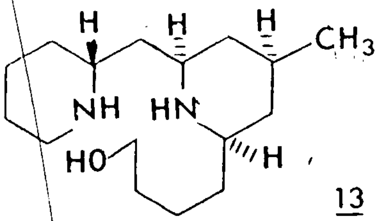


22a

Cyclization from the bottom-side would result in compound 21a, the more stable product, whereas attack by the enolate from the top would produce the desired compound, 21b. Removal of the keto-functionality would then produce precoccinellin, 6, which could be oxidized with facility to the N-oxide, coccinellin.

DISCUSSION

In the synthesis of dihydrodeoxyepiallocernuine[15] compounds 14 and 15 had been formed by oxidation of diaminoalcohol 13 with chromium trioxide in pyridine.



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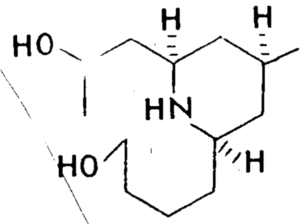
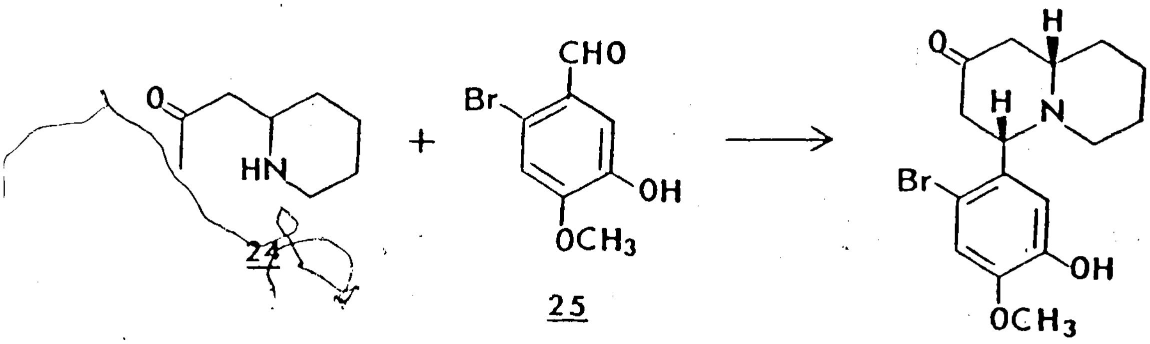
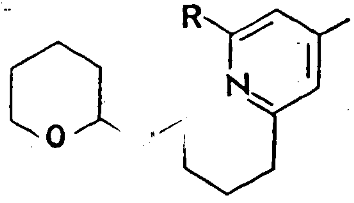


23

The initial experiments described in this part of the thesis were directed towards the synthesis of a compound which could possibly be oxidised in a similar manner. Thus the first synthetic goal was the aminodiol, 23. Oxidation could possibly form the ketoaldehyde 20 which should cyclize to the tricyclic ketone 21 under the basic reaction conditions. There are several recent examples of the condensation of aminoketones with aldehydes under basic conditions[20,21,22]. For example, Hanaoka and co-workers[20] report the condensation of pelletierine, 24, with 6-bromoisovanillin 25 in aqueous sodium hydroxide in 76% yield.

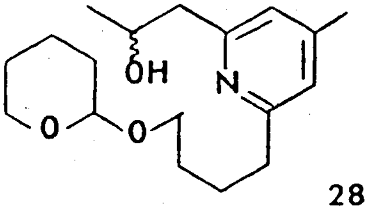


The synthesis of 13 proceeded from 2,4,6-collidine to the protected hydroxypyridine, 26. Transmetalation of this compound with phenyllithium in ether produced the compound of metalation at the 6-methyl group. This was shown by quenching the product with D_2O and observing the nuclear magnetic resonance (nmr) spectrum of the resulting compound.



26 R = CH_3

27 R = CH_2D

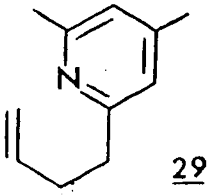


28

The nmr spectrum of 26 shows a 3-proton singlet at δ 2.25 for the 4-methyl and a further 3-proton singlet at δ 2.48

attributed to the 6-methyl group. The material quenched in D_2O now shows a singlet at δ 2.48 integrating for just over 2 protons. Thus condensation of the lithio compound from 26 with acetaldehyde should lead to the alcohol, 28. Reduction of this to the substituted piperidine followed by hydrolysis of the tetrahydropyranyl ether would lead to 23. As mentioned in the introduction it was expected that either catalytic hydrogenation or dissolving metal reduction would lead to the desired stereochemistry in which all the substituents are in the equatorial configuration.

Compound 26 was prepared according to the conditions worked out previously[15]. 2,4,6-Collidine was treated with phenyllithium in ether to form collidyllithium which is a deep blood-red colour. This anion was alkylated with allyl bromide to produce compound 29.



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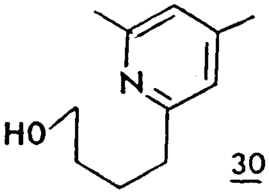
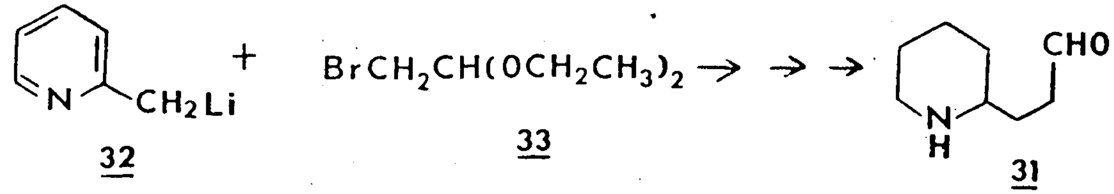


30

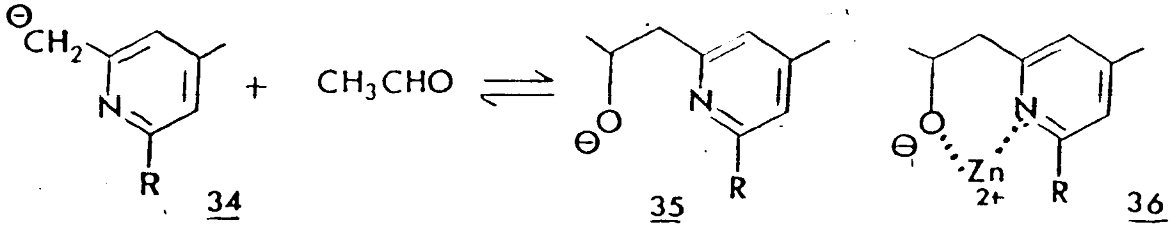
Treatment of 29 with diborane in tetrahydrofuran (THF) followed by oxidation of the intermediate organoborane with alkaline hydrogen peroxide gave the alcohol 30. Protection of the hydroxyl function was accomplished using dihydropyran in dimethoxyethane into which was bubbled an excess of dry gaseous hydrogen chloride. Thus 26 was formed in 50% overall yield from 2,4,6-collidine.

Wibaut and Beets[23] have described the synthesis of 31 *via* addition of bromoacetaldehyde diethylacetal 33 to picolyllithium 32.



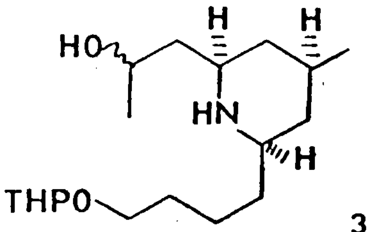
This successful addition of a relatively unactivated bromocompound (compared to allyl bromide) to the lithiated pyridine derivative led to a shortened and equally efficient synthesis of 26. 3-Bromopropan-1-ol was protected as the tetrahydropyranyl ether by treating a benzene solution of the alcohol with excess dihydropyran and a few drops of phosphoryl chloride[24]. A 95% yield of acetal was thus obtained and this was used to alkylate the collidyllithium. After distillation a 52% yield of 26 was obtained.

Transmetalation of 26 with phenyllithium gave the blood-red solution containing the collidyl anion and this was cooled to -78°. A ten-fold excess of acetaldehyde, dissolved in an equal volume of dry ether, was added dropwise and,after stirring for 15 minutes,the reaction was quenched with water and worked up. The oil which resulted showed two spots on tlc (alumina, chloroform). The two compounds were separated by chromatography over alumina. Elution with benzene gave the less polar compound which was identical with starting material (tlc, ir, nmr). Elution with ether afforded the desired alcohol, 28 in 44% yield as a colourless oil, b.p. 165 - 168°, 0.2 mm. The ir spectrum (chloroform) shows absorption at 3360 cm^{-1} which is unchanged by dilution and is consistent with the intramolecular hydrogen bonding expected for this compound. The nmr spectrum shows a 3-proton doublet, J=6Hz, at δ 1.25. Many attempts were made to improve the yield of this reaction, but the conditions quoted above led to the best yield of 28. The poor yield of this aldol-type condensation is most probably due to the equilibrium shown.



Generally the equilibrium in a reaction of this type would be expected to be well over to the side of the more stable alkoxide ion. However the aromatic ring must impart sufficient stability to carbanion 34 such that 34 and 35 are of almost equal stability. Evidence for such an equilibrium was provided by treatment of pure alcohol 28 with phenyllithium followed by quenching with water, which produced an approximately 1:1 mixture of the alcohol and the dealkylated product, 26. Subsequent to abandonment of this approach House[25,26] described the use of ethereal solutions of anhydrous zinc chloride to favour product formation in aldol condensations. By analogy this method may be useful here to trap the product as the chelate, 36, and thus increase the yield of the alcohol.

The alcohol, 28, was reduced using sodium in absolute ethanol to the substituted piperidine, 37. The ir spectrum of this material in methylene chloride shows absorption at 3610 cm^{-1} (-OH) and 3250 cm^{-1} (-NH) and is devoid of absorption at 1610 and 1570 cm^{-1} (pyridine ring). Although various attempts were made, it was never possible to reduce the pyridine ring by catalytic hydrogenation. The protecting group in 37 was removed by stirring a chloroform solution with dilute aqueous hydrochloric acid for one hour. Thus diol 23 was formed as an oil.



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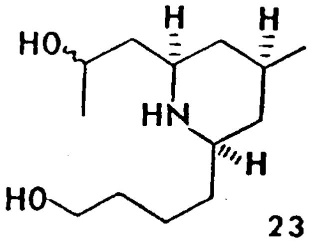
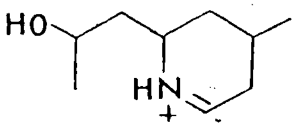


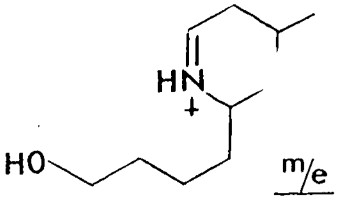
23

The ir spectrum of 23 in methylene chloride shows hydroxyl absorption at 3610 cm^{-1} which is more intense than that of 37. Again the NH absorption appears at 3250 cm^{-1}. The tlc of 23 (alumina, 95:5 chloroform-methanol) shows one spot. The mass spectrum has a very weak parent peak at m/e 229, the base peak appears at m/e 156 and there is an intense peak at m/e 170.

The structures below are assigned to these peaks.



m/e 156



m/e 170

The triacetate of 23 was prepared using acetic anhydride in pyridine. This material is a viscous oil, but since there are chiral centres at nitrogen and carbon-2 of the propyl side-chain, this is perhaps not surprising. The ir spectrum of this material shows amide carbonyl at 1635 cm^{-1} and ester carbonyl at 1735 cm^{-1}. The mass spectrum shows a parent peak at m/e 355 (exact mass for $C_{19}H_{35}NO_5$ calcd. 355.2359; meas. 355.2369). The nmr spectrum displays a well-defined doublet at δ 0.91 (J=6Hz) and an ill-defined doublet at δ 1.24 (J=6Hz). This latter signal is attributed to the side-chain methyl group and is presumably untidy because of the adjacent chiral centre. The signal attributed to the methine proton of this chiral centre occurs as a multiplet centred at δ 4.84 and irradiation at this point resulted in appreciable decoupling of the doublet at δ 1.24.

There is no direct evidence for the assignment of stereochemistry at the tertiary centres of the piperidine ring, but it was felt that the evidence from the previous synthesis[15] was sufficient to expect that the required stereochemistry had been obtained. It was expected that the assigned stereochemistry could be proven at a later stage.

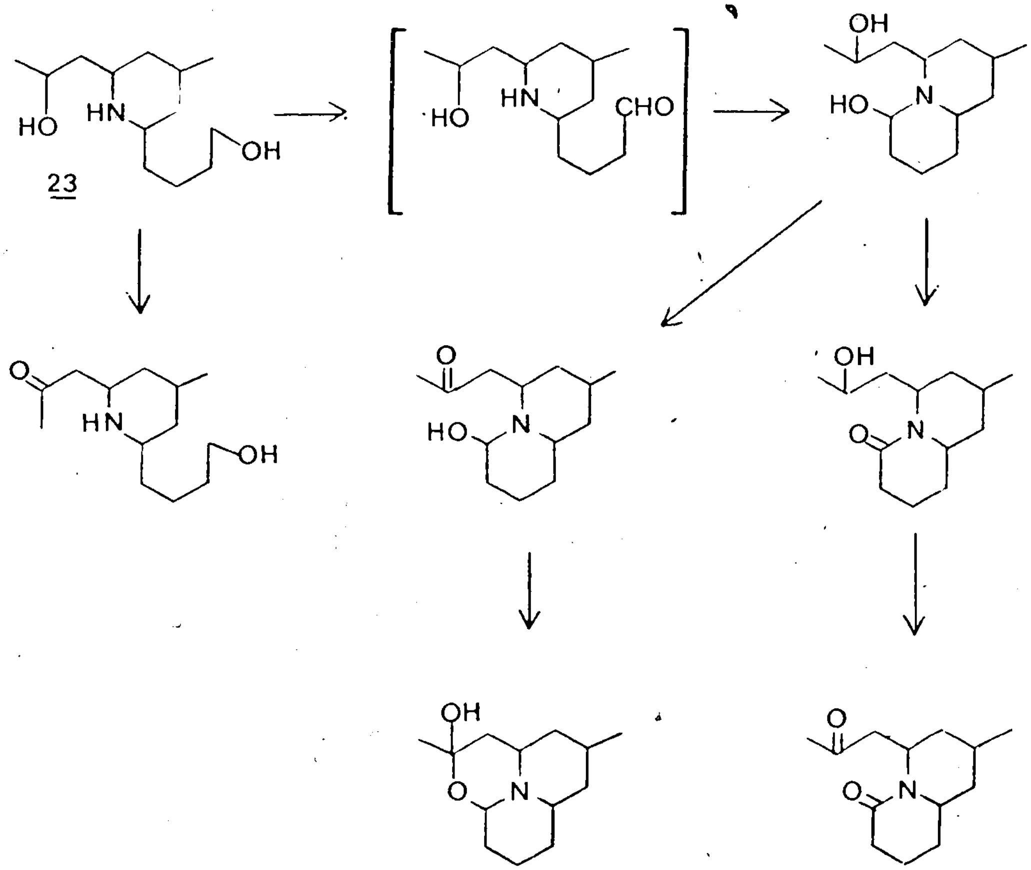
With the desired piperidinediol at hand, many attempts were made to oxidise this to the desired keto-aldehyde. The techniques which were employed are summarized in the following chart.

Attempted Oxidations of 23

	Oxidant	Reference
1.	Chromium trioxide-pyridine-acetic acid	27
2.	Chromium trioxide-pyridine(complex)-methylene chloride (Collins)	28
3.	Chromium trioxide-pyridine (Sarett)	15
4.	Chromium trioxide-pyridine-methylene chloride (*in situ* preparation of Collins' reagent)	29
5.	Silver carbonate-celite (Fétizon)	30
6.	Chromium trioxide-sulphuric acid-acetone (Jones)	31

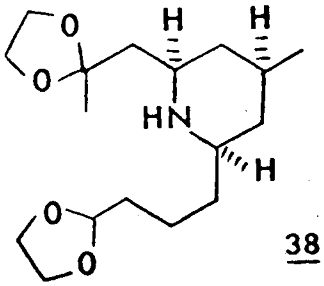
In all cases a complex mixture of products was formed (tlc). The basic material isolated from these oxidations showed little, if any, absorption in the carbonyl region of the ir spectrum. Thus it appeared that none of the desired compound had been formed.

The failure of this oxidation-cyclization can, perhaps, be explained by considering the various routes which the reaction could have taken. Several possibilities are outlined below.



Since two sites were to be oxidised, the amount of oxidant used was twice that recommended for the oxidation of a primary alcohol to the aldehyde. This amount of oxidant must have resulted in overoxidation in some parts of the molecule - most likely aldehyde to acid, which may then condense with the amine to form amide. Since the desired ketone was subsequently shown to be a very unstable substance it is also possible that it was formed and subsequently further oxidised.

The inability to form recognizable oxidation products from the diol resulted in a different route being employed to reach the ketoaldehyde, 20. It was felt that a better route would involve an intermediate in which the required oxidation level of each functionality was already incorporated. Thus the immediate synthetic goal became the protected ketoaldehyde, 38.



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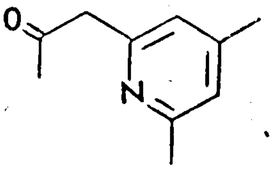
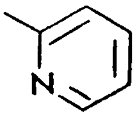


39

2,4,6-Collidine was again the starting material but it was decided that the side-chain containing the keto-function should be introduced first. Wibaut and co-workers have done substantial work directed towards transforming an α-methyl group in a pyridine ring into just the side-chain that was desired here (compound 39). In all of their work the starting material was α-picoline, 40. Transmetalation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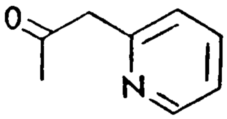
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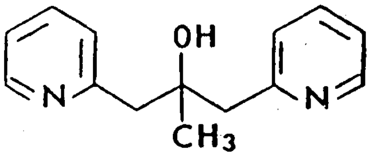

42

of this compound with phenyllithium readily forms picolyllithium and this was reacted with a variety of compounds with the view of synthesizing 41. The results of these studies are summarized in the chart on the next page.

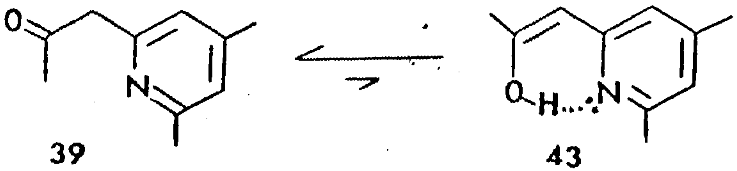
Treatment of the anion with slightly more than one molar equivalent of acetyl chloride produced the compound of double-addition, 42, in quite respectable yield. This was avoided by adding a large excess of acetyl chloride to the picolyllithium in one portion and a 24% yield of

Alkylation of α-Picolyllithium

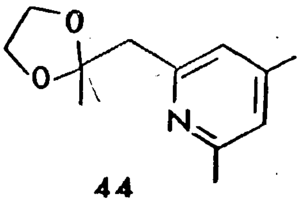
Alkylating Agent	Product	Yield (%)	Reference
$(CH_3CO)_2O$	41	16	32
$CH_3COOCH_2CH_3$	41	not quoted	33
CH_3COCl (large excess)	41	24	34
CH_3COCl (slight excess)	42	34	34
CH_3CN	41	35	35

desired compound was formed. The best conditions these workers found were those of the last entry in the chart. Alkylation with acetonitrile followed by acid hydrolysis of the resulting imine gave a 35% yield of desired ketone. These were the conditions used in the present synthesis. The low yield, thus expected in this step, predicated its use at the beginning of the sequence.

Collidyllithium was formed in the normal way and was alkylated with a ten-fold excess of freshly distilled acetonitrile. After stirring at room temperature for one and a half hours the reaction mixture was treated with excess dilute sulphuric acid. Work up followed by distillation at 105 - 109°, 4.5 mm gave a 34% yield of the desired ketone as a yellow oil. The ir spectrum of this oil as a thin film shows a carbonyl peak at 1720 cm^{-1}. However it also shows absorption at 1655 cm^{-1} and weak absorption at 3400 cm^{-1}. These peaks can be explained by an equilibrium between the keto and the enol forms of this compound. The enol form is stabilized somewhat by intramolecular hydrogen bonding between the lone pair of electrons on the nitrogen atom and the hydroxyl hydrogen, 43. The nm spectrum in deuteriochloroform shows 3-proton singlets at δ 2.20, 2.27 and 2.48. In addition there are 2-proton singlets at δ 3.83 and 6.87. There are very minor peaks possibly attributable to the enolic form and these peaks were intensified when a spectrum was determined on the neat compound. These peaks occur at δ 2.00, 2.22, 2.40, 5.22, 6.48 and 6.77.



39 43



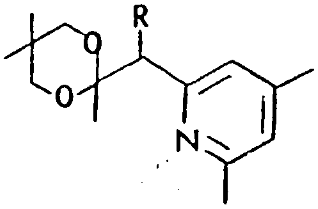
44

When the ketone was converted into the ketal 44 by treatment with ethylene glycol and p-toluenesulphonic acid in refluxing benzene under a Dean-Stark trap the nmr spectrum lost all the minor signals attributed to the enol form. The spectrum is now clean and consists only of 3-proton singlets at δ 1.36, 2.26 and 2.48 with a 2-proton singlet at δ 3.06, a 4-proton singlet at δ 3.89 and 1-proton singlets at δ 6.83 and 6.96. The ir spectrum (neat film) is devoid of signals at 3400, 1720 and [illegible] cm^{-1}, and there is a new intense peak at 1045 cm^{-1} (C-O stretch).

In an attempt to introduce the other side-chain, ketal 44 was treated with phenyllithium and to this mixture was added allyl bromide. The resultant oil displays an nmr spectrum in which the peaks due to the ketal and the adjacent methyl group at δ 3.89 and 1.36 respectively are not present. Thus, it appears that the phenyllithium attacked the ketal.

Heathcock, Ellis and Badger have reported[36] that the ethylene ketals of cyclopentanone and cyclohexanone are attacked by isopropyllithium or t-butyllithium. The products of the reactions are the result of attack of alkyllithium on the ketone, generated by E_2 elimination of the enolate of acetaldehyde from the ketal. Therefore the result observed in the reaction of 44 with phenyllithium is not surprising.

In order to prevent this reaction the ketone was protected using 2,2-dimethyl-1,3-propanediol to form ketal 45 which shows a 6-proton singlet at δ 0.95, a 4-proton singlet at δ 3.60, a 3-proton singlet at δ 1.40 and a 2-proton singlet at δ 3.18 in the nmr spectrum.

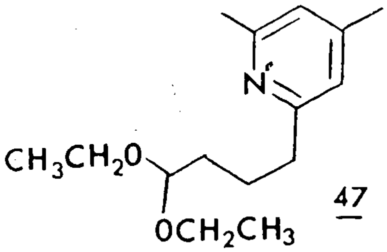


45 R=H

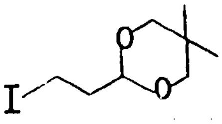
46 R=D

This ketal was treated with 1 molar equivalent of phenyllithium and a portion of the lithiated compound was quenched with D_2O. The nmr spectrum of this material shows decrease of the signal due to the methylene attached to pyridine. The singlet at δ 3.18 attributed to this group now integrates for approximately 1.1 protons. The increased acidity of the protons at this methylene, as compared to other molecules in this series, may be attributed to the presence of the two electron-withdrawing oxygen atoms in the ketal.

This disappointing result made it necessary to introduce the other functionality first. As it was felt desirable to include the required oxidation level of each chain at an early stage, the commercially available β-chloropropionaldehyde diethylacetal was chosen as the starting material for the four-carbon chain. A preliminary reaction of this alkylating agent with collidyllithium gave approximately 45% yield of the alkylated collidine 47.



47



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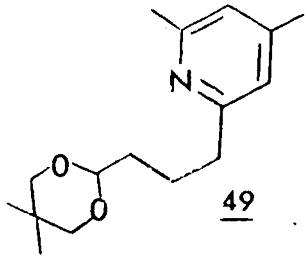


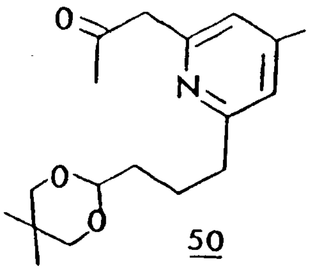
49

It was felt that this could be improved by employing a better leaving group than chloride ion. For this purpose iodide ion was chosen. After purification, this alkylated product would be treated with phenyllithium to generate the anion at the 6-methyl group. As the diethyl acetal may undergo β-elimination similar to that already observed for the ethylene acetal it was decided that the acetal should be exchanged to one which would definitely be stable under the reaction conditions. Thus the first alkylating agent chosen was 48.

This was prepared from β-chloropropionaldehyde diethylacetal by first exchanging the acetal using 2,2-dimethyl-1,3-propanediol. The chloroacetal was then dissolved in acetone and treated with a large excess of a solution of sodium iodide in acetone[37] to give the desired compound in 75% yield. Reaction of this iodoacetal with collidyllithium gave an almost quantitative yield of the desired alkylation product, 49. Before further elaboration of the molecule it was decided to prove that the aldehyde could be generated from this acetal when desirable. The methods attempted were treatment of a chloroform solution with 10% aqueous hydrochloric acid; treatment of an acetone solution with 20% aqueous hydrochloric acid; treatment with chloral (to exchange the acetal to chloral acetal); treatment with 100% sulphuric acid and ether[38]; and treatment with 40% hydrobromic acid in acetic acid. In the first three methods no reaction was observed and the latter two gave rise to dark polymeric products.

Despite the lack of success with the hydrolysis of the acetal, it was decided to continue the proposed route with 49 to verify that the route would be viable when a less stubborn acetal was used. Thus 49 was treated with phenyllithium and the anion so produced was treated with acetonitrile employing the same reaction conditions as were used for the synthesis of 39. The crude product was a mixture of starting material and desired product in approximately equal amounts (by nmr).

Both these compounds are high boiling oils and it was impossible to separate them by distillation. It was also impossible to separate them by chromatography since they have polarities on alumina only slightly different from one another. Thus it became necessary to convert one component of the mixture into a compound of a substantially different polarity thus facilitating chromatographic purification. Also, the original compound must be readily regenerated from the new compound. Conversion of the ketonic component to its oxime was the method chosen. The mixture was treated with hydroxylamine hydrochloride in 95% ethanol containing pyridine and the resulting oil was chromatographed on alumina. Elution with ether gave starting material (ir, nmr) and elution with chloroform-methanol (94:6) produced the acetal-oxime 51 as a colourless oil.



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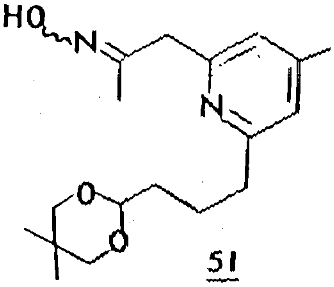

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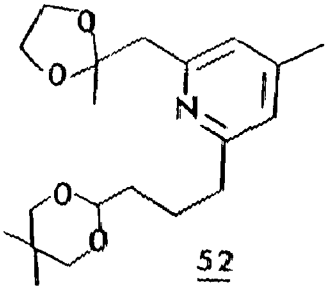


52

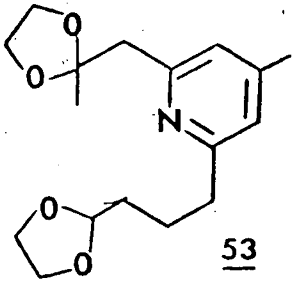
The ir spectrum of the oxime (chloroform) displays absorption at 3580 and 3290 cm^{-1} (NOH), 1665 cm^{-1} (C=N) and at 1610, 1570 cm^{-1} (pyridine), and is devoid of signals in the carbonyl region. The nmr spectrum ($CDCl_3$) in addition to the signals for the remainder of the molecule displays a singlet integrating for 1.5 protons at δ 3.67 and one at δ 3.08 for 0.5 protons. These peaks are assigned to the methylene group adjacent to the oximino carbon, with the two peaks originating from the E and Z isomers of the oxime.

The ketone, 50 was regenerated from the crude oxime by dissolution in acetone-water (2:1) and treatment with 20% aqueous titanium trichloride[39]. Thus a 37% yield of ketone (57% based on recovered starting material) was obtained.

The ketone was protected using ethylene glycol (1 ml per g. of ketone) in benzene with p-toluenesulphonic acid as catalyst under a Dean-Stark trap. The ir spectrum of the ketal 52 is devoid of absorption at 1715 cm^{-1}. The nmr spectrum displays methyl singlets at δ 0.72 and 1.19 (dioxan) and a singlet at δ 3.93 integrating for 4 protons attributed to the ethylene ketal.

On one occasion, a larger excess of ethylene glycol was used (3 ml per g. of ketone) and the tlc (alumina, chloroform) of the product showed a spot for the desired product, 52, accompanied by a less intense spot due to a slightly more polar compound. The mixture was separated by chromatography over alumina. Elution with benzene gave the product identical by nmr, tlc, ir with 52. Elution with ether gave the more polar fraction. The ir spectrum of this oil shows no peaks at 1130 and 1090 cm^{-1} (characteristic of the 1,3-dioxan moiety) but does show intense absorption at 1045 cm^{-1} (C-O). The nmr spectrum displays no absorption for the methyl groups of the dioxan ring, but shows a multiplet at δ 3.90 integrating for 8 protons for the ethylene ketal. The mass spectrum shows a parent peak at m/e 307 with strong peaks at m/e 221, and m/e 207. The base peak is at m/e 87.

These spectra are consistent with 53 for the structure of this compound. This compound must have arisen by exchange of the acetal function with the large excess of ethylene glycol employed in the reaction. It is thought that after a little more work, to optimize conditions for exchange, this method could be employed as a general method for the hydrolysis of acetals apparently too stable for direct conversion to the aldehyde. At this time the work with an alternate acetal was well under way, so this possibility was not investigated.



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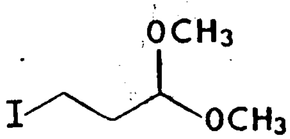

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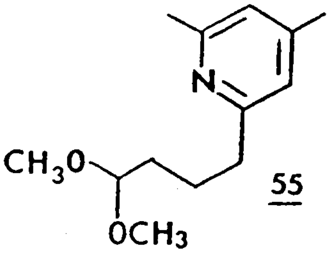
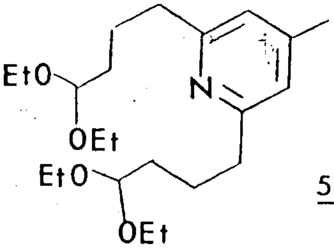


55

The other acetal chosen as precursor for the aldehyde side-chain was β-iodopropionaldehyde dimethylacetal, 54. This was synthesized from the chlorodiethylacetal in two steps. First Finkelstein reaction exchanged the halogen to iodine. In this reaction it was found necessary to add a small amount of solid sodium carbonate to ensure that basic conditions prevailed. On the first two occasions on which this reaction was attempted an excellent yield of acetone diethylketal was obtained. The crude product of this reaction was dissolved in dry methanol and *p*-toluenesulphonic acid was added as catalyst. Work up afforded the desired compound as a colourless oil in only 50% overall yield. The poor yield of these reactions is attributed to the volatility of the products resulting in loss of material during removal of solvents. The iodoacetal was used to alkylate collidyllithium in the usual manner and an overall yield of 40% of desired compound, 55, (from chlorodiethylacetal) was observed for these transformations. This yield is comparable to that previously observed for the direct alkylation of collidyllithium with the chlorodiethylacetal. It was expected that the acetal function of the product from that reaction, 47 could be exchanged in high yield. Therefore it did not appear to be advantageous to proceed with the route *via* 54. Thus the alkylation of collidyllithium with β-chloropropionaldehyde diethylacetal was investigated thoroughly.

The alkylation was performed in the usual manner, but the mixture was allowed to stir for 10 hours in order that the reaction might reach completion. This alkylation is very much slower than that for the corresponding iodoacetals. In the latter case it was necessary to add the acetal solutions very slowly because of the highly exothermic reaction with the collidyllithium, the blood-red colour of the solution disappearing within half an hour. The alkylation with the chloroacetal was very mildly exothermic and even after 10 hours the solution was still blood-red. After work up, the crude material was distilled and the desired compound, <u>47</u>, was obtained as an oil boiling at 120 - 124°, 1.2 mm. A higher boiling fraction was obtained with boiling point 170 - 174°, 1.2 mm. The nmr spectrum of this material ($CDCl_3$) displays triplets at δ 4.42 (J=5Hz) and 4.50 (J=5Hz) integrating for a total of 2 protons. There is a singlet for slightly less than 3 protons at δ 2.45 and another for slightly more than 3 protons at δ 2.25. Each signal of the triplet due to the methyl groups of the ethylacetal is split into a doublet. These characteristics are consistent with a mixture of dialkylated products <u>56</u> and <u>57</u>. From the intensities of the ring methyl groups this is approximately a 3:2 mixture <u>56</u>:<u>57</u>. The mass spectrum shows no peak for the molecular ion (381), but has a large peak corresponding to loss of $-OCH_2CH_3$ from this at <u>m/e</u> 336. A small peak at <u>m/e</u> 352 resulting from loss of $-CH_2CH_3$ is also observed.



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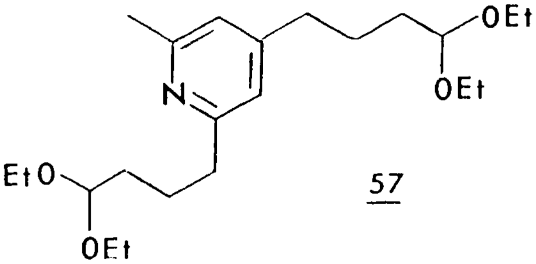
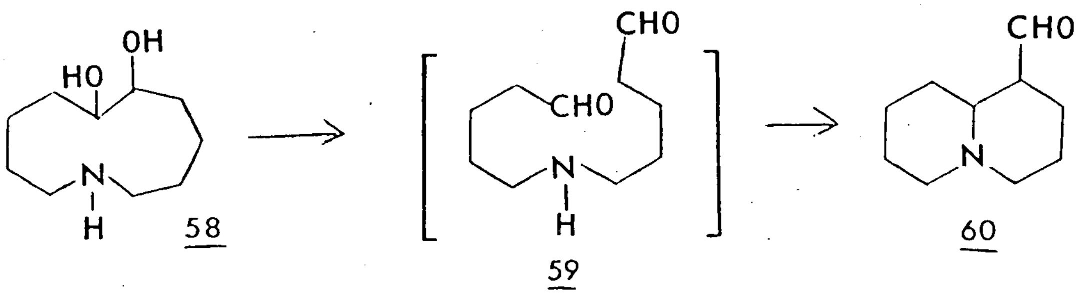
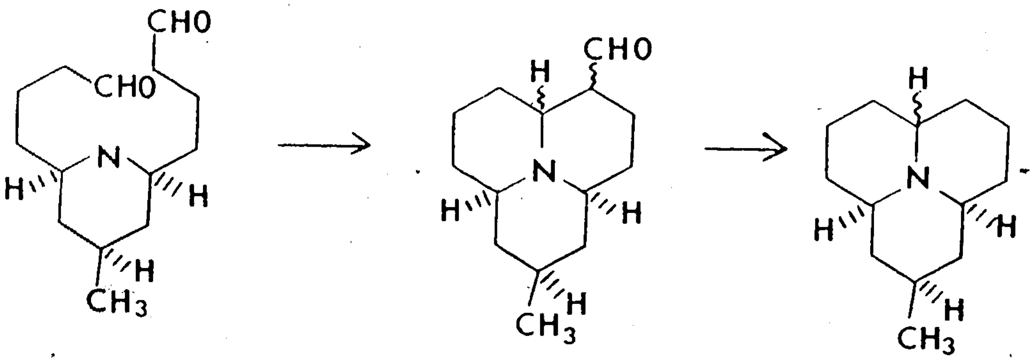


57

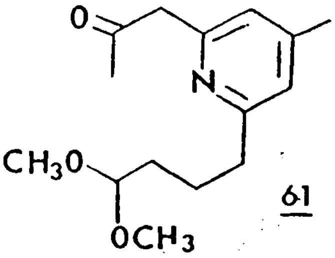
The dialkylated products must arise because the slow alkylation allows sufficient time for equilibration of the collidyl ions with alkylated material. It is interesting to speculate on whether compound 56 could be synthesized exclusively, because this compound can potentially lead to the goal of the synthesis, coccinellin. In 1960 van Tamelen reported the reaction of 58 with periodic acid at pH 5 to give the quinolizidine derivative 60[40].



This reaction presumably proceeds via oxidation of the vicinal diol to the dialdehyde 59, which cyclizes under the reaction conditions. Reduction of the pyridine ring of 56 and hydrolysis of the acetal functions should lead to a dialdehyde very similar to 59, which should lead, a priori, to a tricyclic compound, deformylation of which would give the required tricyclic amine. However this possible route has not been investigated.



The diethyl acetal 47 was transformed into the dimethylacetal using dry methanol and d-10-camphorsulphonic acid. After distillation a 78% yield of 55 was obtained. This dimethylacetal was treated with phenyllithium and the anion alkylated with acetonitrile. The reaction was quenched with methanolic hydrogen chloride with the expectation that the dimethyl ketal would be formed directly. However in every case the ketone, 61 was obtained. The reaction was worked up by basification with triethylamine followed by washing with sodium bicarbonate, etc. so it is difficult to imagine that the ketone was formed by acid catalysed hydrolysis of the ketal. It appears, therefore, that the ketone must be formed by hydrolysis of a possible carbinolamine-ether type intermediate, 62 for example.



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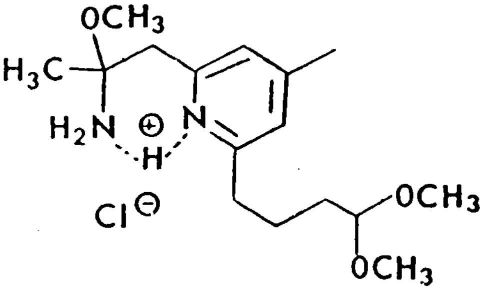


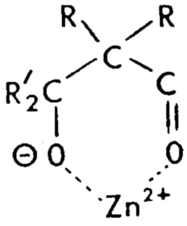
62

The crude product was distilled and, after recovered starting material (b.p. 92 - 100°, 0.1 mm), a fraction boiling at 150 - 157°, 0.1 mm was obtained. This fraction was shown to be an approximately 9:1 mixture of product and starting material and it was used without further purification in the next step. The total isolated yield of ketone was approximately 35% and recovered starting material was approximately 20%. There is a substantial residue from the distillation and the ir spectrum of this displays a strong peak at 2160 cm^{-1}. The mass spectrum of this material has large peaks at m/e 134 and m/e 121 among the multitude of peaks present. This material was not investigated further.

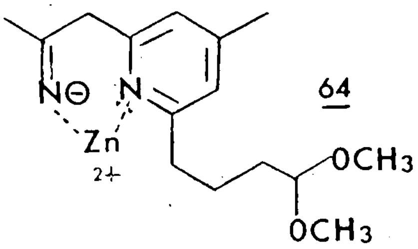
Despite the fact that this yield is comparable to those observed and reported previously in this discussion for alkylation of collidyllithium and derivatives with acetonitrile, it was felt that some effort should be made to improve on it. In addition to those already mentioned, several other methods of alkylating collidyllithium to produce the desired methyl ketone were attempted. In an attempt to form the ketal directly collidyllithium was treated with triethyl orthoacetate in ether. The blood-red mixture was stirred at room temperature for two days then worked up. The crude product appeared to be a mixture of collidine and triethyl orthoacetate (tlc, nmr), i.e., no reaction had occurred.

It is reported that N,N-dimethylamides can be used to form ketones in good yield on reaction with aryllithiums at low temperatures[41]. Thus acetal 49 was treated with phenyllithium and to the blood-red solution at -30° was added a solution of N,N-dimethylacetamide in ether. Work up produced an oil which contained approximately 15% desired ketone (nmr).

Ketones can be prepared from organolithium reagents by addition to the lithium salt of the appropriate acid[42]. Collidyllithium was prepared in the usual way and anhydrous lithium acetate was added but no detectable reaction was observed. As it appeared that no other alkylation procedure was more efficient than that using acetonitrile, House's method of trapping aldol products was investigated[25,26]. As already mentioned, the product is trapped as the zinc chelate, <u>63</u> for example. Following addition of phenyllithium to dimethylacetal <u>55</u>, a solution of anhydrous zinc chloride in ether[26] was added. This was followed by acetonitrile. The product from this reaction shows no absorption at 2160 cm^{-1} in the ir spectrum. Distillation gave starting material (about 40%) followed by the desired product (about 40%), which



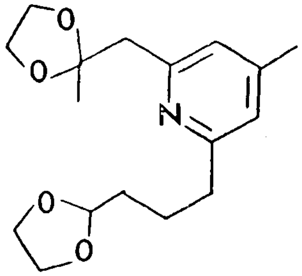
<u>63</u>



<u>64</u>

still contained a little starting material. The residue from this distillation is very small when compared to that from the reaction in which zinc chloride was not added. By analogy with House's chelate, the one involved here is probably <u>64</u>.

The methyl ketone (containing a small amount of <u>55</u>) was treated with ethylene glycol and <u>p</u>-toluenesulphonic acid in benzene under a Dean-Stark trap. The ketone was protected and, as expected, the acetal was exchanged, compound <u>53</u> being produced.

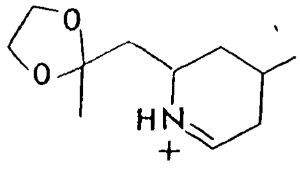


<u>53</u>

This compound was purified by chromatography over alumina, elution with benzene-ether (1:1) affording the ketal-acetal as a pale yellow oil. The nmr spectrum of this compound in deuteriochloroform shows 3-proton singlets at δ 1.36 and 2.28, an 8-proton multiplet at δ 3.90 and a 1-proton triplet at δ 4.87 (J=4Hz). The ir spectrum (methylene chloride) shows peaks at 1610 and 1570 cm^{-1} (pyridine) and 1045 cm^{-1} (C-O). The mass spectrum has a very weak parent ion at m/e 307 with large peaks at m/e 221 and m/e 207 and base peak at m/e 87. This material is identical with that obtained by acetal exchange of 52 observed earlier.

Reduction of 53 with sodium in iso-amyl alcohol gave an oil, the ir spectrum of which shows no absorption due to the pyridine ring but has a peak at 3340 cm^{-1} (NH). Tlc (alumina, chloroform) shows two spots, the more intense one being the less polar. Chromatography over alumina and elution with ether afforded the less polar material, while elution with chloroform gave the more polar. These compounds were obtained in a total yield of approximately 70% after chromatography in a ratio of about 7:2 (less polar:more polar).

The less polar compound displays absorption in the nmr spectrum for a methyl group as a doublet at δ 0.90 (J=5.5Hz). There is a methyl singlet at δ 1.35, an 8-proton multiplet at δ 3.95 (ethylene ketal and acetal) and a 1-proton triplet at δ 4.87 (J=4Hz) for the acetal proton. The mass spectrum has a weak parent peak at m/e 313. The base peak occurs at m/e 198 and there is a strong peak at m/e 212. To these peaks are assigned structures 65 and 66 respectively. These spectral characteristics are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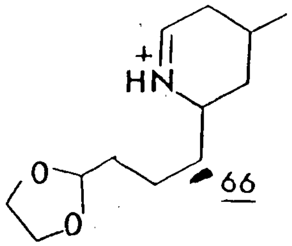
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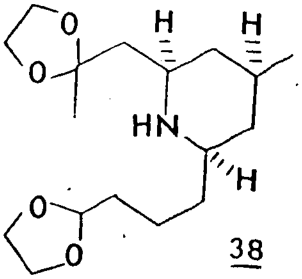

38

consistent with the assignment of the skeleton shown in 38. As discussed in the introduction it was felt that chemical reduction of 53 would produce mainly the compound of greatest thermodynamic stability, i.e., the one with all the ring substituents equatorial (and therefore cis). The less polar material was formed in the largest amount and thus it was felt that this was the compound with the stereochemistry depicted in 38. As proof of this assignment a ^{13}C nuclear magnetic resonance (cmr) spectrum of this compound was run. This spectrum shows lines for 17 carbon atoms in the completely decoupled spectrum[43,44]. By making use of the off-resonance proton-decoupled spectrum it is possible to assign the lines to methyl, methylene, methine and quarternary carbons. The signals and their assignments are shown in the following chart.

^{13}C signals of compound 38

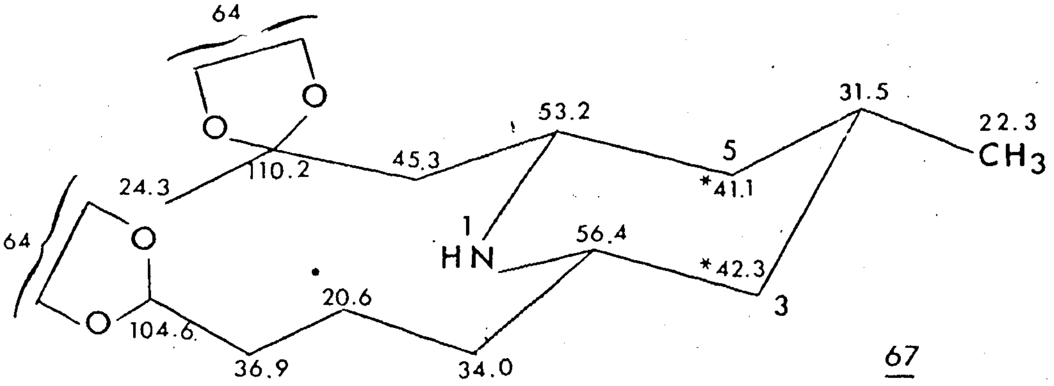
δ 20.6 (CH_2)
22.3 (CH_3)
24.3 (CH_3)
31.5 (CH)

δ 34.0 (CH_2)
36.9 (CH_2)
41.1 (CH_2)
42.3 (CH_2)

δ 45.3 (CH_2)
53.2 (CH)
56.4 (CH)
64.4 (CH_2)

δ 64.7 (CH_2)
64.8 (2 x CH_2)
104.6 (CH)
110.2 (C)

These signals are assigned to the specific carbons as shown in the following structure, by correlation of the values quoted by Stothers[43], Levy and Nelson[44], and



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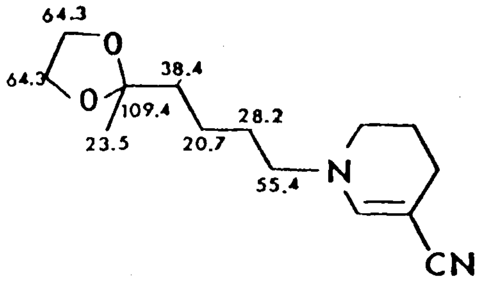
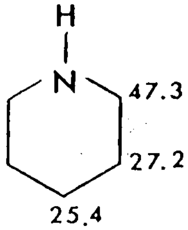
Wenkert[45]. The shifts of the side-chain carbons were assigned by direct comparison with compound 68 reported by Wenkert[45]. The shifts of the carbons of the piperidine



68

ring and the 4-methyl group were assigned by comparison of the structural features with those in compounds 69 to 75, the shifts for which are well documented[43,44]. The precision with which additivity relationships can correlate the ^{13}C shieldings of similar compounds is well known[43,44], thus it is felt that the following analysis is rigorous proof of the assigned carbon-shifts and therefore the stereochemistry depicted in 67.

Since the effect of atoms further than four bonds removed from the atom under consideration is very small[43,44], the acetal side-chain can be considered as an n-butyl substituent on C-2. The difference in shift of C-1 in n-butylcyclohexane, 75, and methylcyclohexane, 71, is 4.3 ppm. The shift of C-1 in 73 (in which all the substituents are equatorial) is only 0.4 ppm removed from the C-1 shift of methylcyclohexane, 71. Thus equatorial substituents at carbons β to C-1 have little effect on its shift. That this is also the case in substituted piperidines can be readily seen by comparing the shifts of C-4 and C-6 in piperidine 69 and 2-methylpiperidine, 72. Thus the signal at C-2 in 67 should occur at δ 56.7 (52.4, from 72, plus 4.3) providing that the substituents at C-4 and C-6 are equatorial. Initially, therefore, it is assumed that the substituents are equatorial and the signal at δ 56.4 is assigned to C-2 in 67. The methine at δ 53.2 is assigned to C-6 by exclusion. It is felt that the oxygen atoms δ to this carbon cause it to be shifted upfield, as is the case for C-2 of the butyl side-chain which is δ to two oxygen atoms and one nitrogen atom. The methyl group at δ 22.3 is assigned to the C-4 methyl group, and the methine at δ 31.5 to C-4 of the piperidine ring in the following way.



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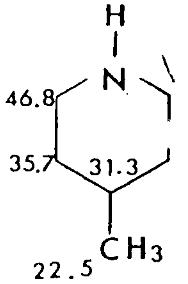

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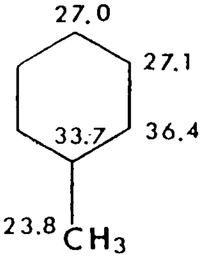

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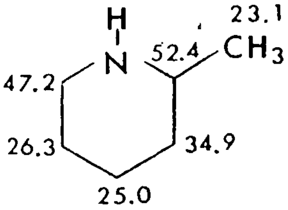

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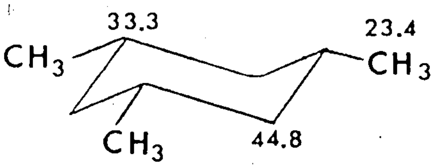

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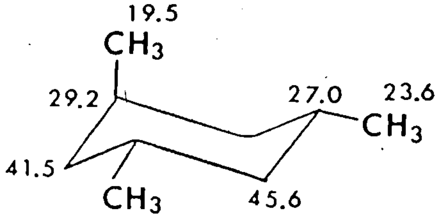

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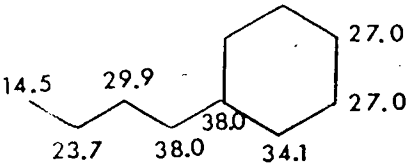


75

As already pointed out the shift of a carbon in a six-membered ring is only slightly affected by equatorial substituents at the β-carbon atoms. This should be compared with the value observed in 74 (in which the substituent at one β-carbon is axial). Thus one axial substituent at the β-carbon causes an upfield shift of 6.3 ppm for C-1 (this is the so-called γ effect[43,44]). The shift for C-4 in 4-methylpiperidine, 70, is δ 31.3. Equatorial substituents at C-2 and C-6 should have little effect on this shift, but if one of these substituents was axial there should be an upfield shift of approximately 6 ppm for C-4 resulting in a methine signal at approximately δ 25. Since the shift observed in 67 is δ 31.5 (the only other methine signals occur at δ 53.2 and 56.4 and are attributed to the carbons α to nitrogen) the substituents at C-2 and C-6 must be equatorial.

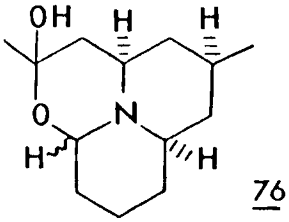
The axial methyl group in 74 occurs at δ 19.5, an upfield shift of 3.9 ppm compared to an equatorial methyl group. Also the signal for the carbon bearing this methyl group has been shifted upfield 4.1 ppm. Thus an axial methyl group at C-4 in 4-methylpiperidine would be expected to result in a signal at approximately δ 18.5 for the methyl group and δ 27 for C-4 carbon. Since these two signals occur at δ 22.3 and 31.5 respectively in 67 (very close to the values observed for 4-methylpiperidine) the methyl group must also be equatorial. An axial methyl group at C-4 would also be expected to result in upfield shifts of the signals for C-2 and C-6 of the piperidine ring. As has already been noted the signals for these carbons are consistent with an equatorial substituent at C-4.

Thus the signals of all these carbons are mutually consistent and can only result from a molecule in which all the substituents are equatorial. (The signals due to C-3 and C-5 cannot be distinguished and thus they bear a star in 67 to indicate that they may be interchanged.) Therefore it was felt that sufficient proof for the required stereochemistry of intermediate 38 was available and that the synthetic scheme could be continued with confidence.

In addition to 38 a minor amount of more polar material was produced from the chemical reduction of 53. This shows one spot on tlc (alumina, chloroform). The mass spectra of this material and compound 38 differ only in the intensities of several peaks. Thus it is felt that this material is isomeric with 38. The nmr spectrum shows a methyl doublet at δ 0.87 (J=6Hz), a methyl singlet at δ 1.33, an 8-proton multiplet at δ 3.97 and a poorly resolved

1-proton triplet at δ 4.88 (J=4Hz). The methyl doublet is further split to a very small extent. The completely decoupled cmr spectrum of this material shows lines for at least 28 carbon atoms. Thus this material appears to be a mixture of at least two components and is probably epimeric with 38 at one or more of the chiral centres. This material was not investigated further. All attempts to reduce 53 by catalytic hydrogenation were unsuccessful, starting compound being the only isolatable material.

With the desired compound, 38, at hand, the synthetic scheme was continued by removal of the two protecting groups. This was accomplished using 5% aqueous hydrochloric acid and a colourless crystalline compound resulted. This compound is quite sensitive to heat, so it was necessary to evaporate the solvent at room temperature. The ir spectrum (methylene chloride) displays strong absorption at 3570 cm^{-1} (OH) and a characteristic intense doublet at 1060 and 1040 cm^{-1}. The nmr spectrum (deuteriochloroform) shows a methyl doublet at δ 0.90 (J=6.5Hz), a methyl singlet at δ 1.43 and a 1-proton multiplet at δ 4.02. The mass spectrum has a parent peak at m/e 225 with the base peak at m/e 150 and large peaks at m/e 224 and m/e 207. These spectral characteristics are consistent with structure 76.



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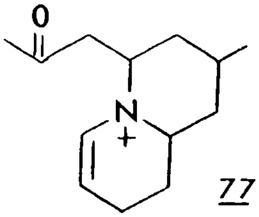

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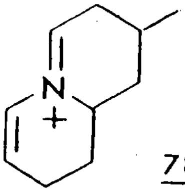
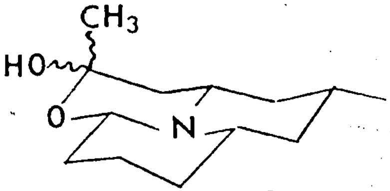


78

The peak at m/e 224 in the mass spectrum presumably arises by loss of the proton from the carbon α to both oxygen and nitrogen, resulting in an ion stabilized by both heteroatoms. The peak at m/e 207 must result from loss of water to produce 77 which then undergoes further fragmentation to the base peak at m/e 150, 78. There is a metastable peak at m*/e 109 resulting from the fragmentation 207 → 150. There are two possible conformations for the hemiketal, 79 and 80.



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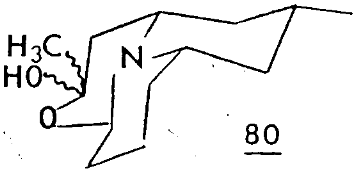
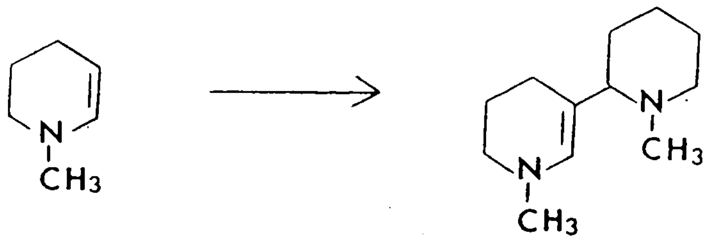


80

These conformations may be distinguished by making use of the observation noted by Bohlmann in 1958[46]. So-called Bohlmann bands are exhibited by a conformationally rigid amine in which there are at least two hydrogen atoms on the carbons α to nitrogen which are *trans*-diaxial to the lone pair of electrons on nitrogen. These bands occur as moderate absorptions in the region 2600 - 2800 cm^{-1} in the ir spectrum. *80* has only one hydrogen atom α to the nitrogen atom which is *trans*-diaxial to the lone pair on nitrogen and thus this would not be expected to show Bohlmann bands in the ir spectrum. On the other hand, *79* has three such hydrogen atoms and would be expected to show these bands. Further inspection of the ir spectrum of *76* reveals that it does indeed show peaks at 2760, 2730 and 2610 cm^{-1} and thus configuration *79* is assigned to this compound.

When this compound was first isolated it appeared to sublime a little in the flask. In an attempt to accelerate the process the material was warmed to 70°. After six hours only a very small amount of sublimate had collected. The ir spectrum of this material shows a small amount of hemiketal (3570, 1060, 1040 cm^{-1}) but there is a large peak at 1715 cm^{-1}. The substantial residue from this attempted sublimation possesses an ir spectrum which is devoid of the signals characteristic of the hemiketal. There is, however, a strong peak at 1715 cm^{-1} (C=O) and a moderate peak at 1655 cm^{-1} (C=C). The mass spectrum of this material shows a parent peak at m/e 414 with a strong peak at m/e 357. Thus it appears that the hemiketal readily dehydrates on heating to form the keto-enamine (MW = 207) which then dimerizes. Loss of 57 to m/e 357 is consistent with loss of the fragment $-CH_2COCH_3$.

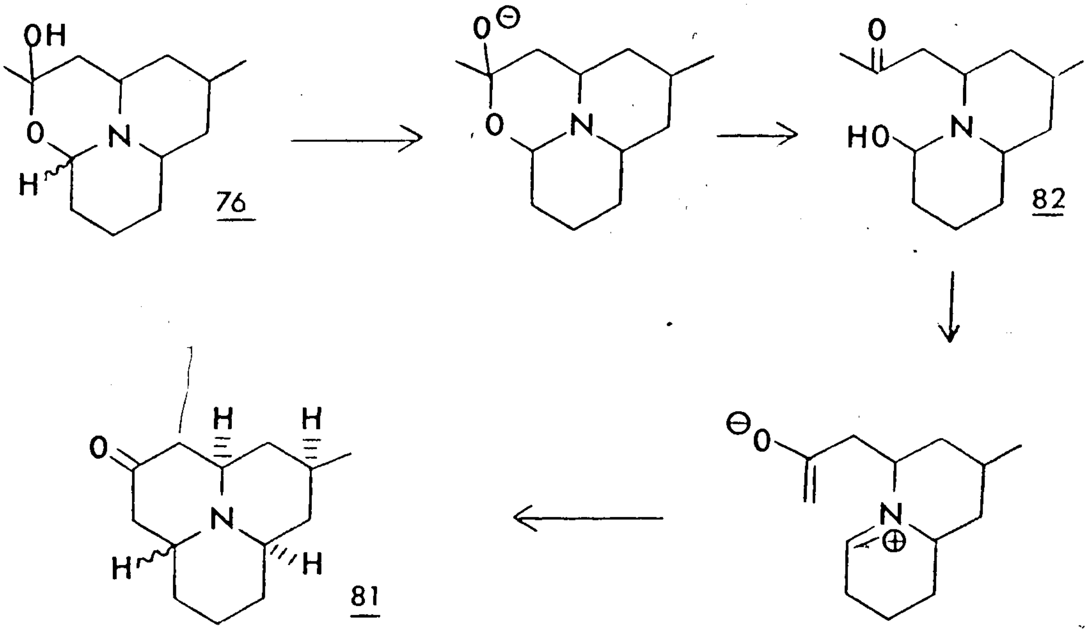
Leonard and Hauck[47] have studied the formation of derivatives of 2-piperideine and report that N-substituted piperideines tend to "dimerize" readily. For example, attempts to form 1-methyl-2-piperideine by mercuric acetate oxidation of N-methylpiperidine or by reduction of 1-methyl-2-piperidone (using lithium aluminium hydride or dissolving metal) all result in the isolation of the dimeric product shown.



Because of this apparent instability, the ketal was prepared when required and then used immediately in a subsequent step.

Conceptually there are two possible ways which could lead from the hemiketal to the desired tricyclic-ketone, 81. Treatment of 76 with base could form the alkoxide which could fragment to produce the ketocarbinolamine, 82.

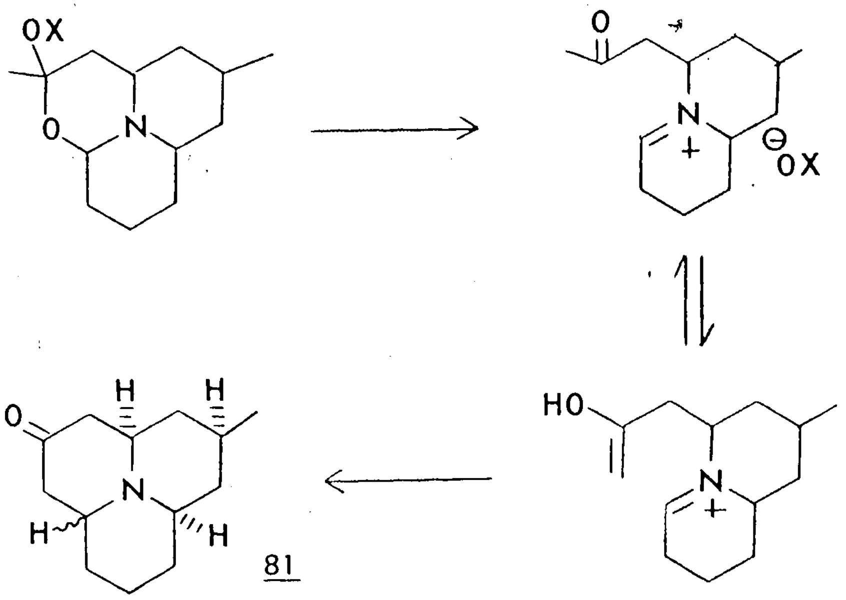
Scheme I



Elimination of hydroxide to form the immonium salt may follow, and, if this is the case, this salt could be trapped by the enolate ion to form the desired ketone, 81, as shown in Scheme I.

Alternatively, conversion of the hydroxyl function to a good leaving group may give rise to a Grob type fragmentation[48] leading to the keto-immonium salt as shown in Scheme II. Cyclization of the enol form of the ketone with the immonium salt would then produce ketone 81.

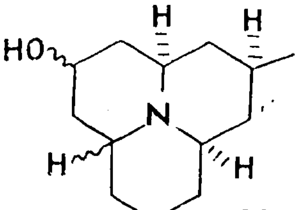
Scheme II



Initially the hemiketal was treated with sodium hydroxide in aqeuous THF at room temperature then at reflux but on both occasions the only material isolated was identical (tlc, [illegible] the starting material. Treatment of 76 with p-to[illegible]lphonic acid in refluxing benzene under a Dean-Stark [illegible] led to an oil which consists of at least three compounds by tlc (alumina, chloroform). Chromatography over alumina gave mainly material which appears to be dimeric by mass spectrum (peaks at m/e 414 and m/e 357).

Spencer and co-workers[49] have described the use of pyrrolidine and acetic acid in ether as a mild method for aldol cyclizations. It was felt that these conditions offered advantages for the case at hand. Examination of Schemes I and II reveals that both require base and acid catalysis at different stages. Thus these conditions should facilitate both processes. Treatment of 76 with one molar equivalent of pyrrolidine and two molar equivalents of acetic acid in ether at room temperature for 36 hours gave an oil which contained starting material (ir, tlc). In addition tlc showed the presence of a less polar material. The ir spectrum of this oil shows absorption at 1725 cm^{-1} in addition to the peaks for starting material. A crude separation by preparative tlc (ptlc) removed the starting material. The resultant material has in the mass spectrum an intense peak at m/e 207 accompanied by impurities with higher molecular weight. Further attempts were made to purify this material by ptlc but the mass spectra of all the fractions displayed only very small peaks at m/e 207. Suspecting that this material was desired β-aminoketone 81 (MW = 207), but that it is unstable, it was decided to reduce the reaction mixture with sodium borohydride immediately following work up. In order to accelerate the cyclization the reaction with pyrrolidine and acetic acid was performed in refluxing THF for 24 hours. The crude material, which shows strong absorption at 1725 cm^{-1} together with moderate absorptions at 2780, 2740 and 2600 cm^{-1} (Bohlmann bands[46]), was dissolved in 95% ethanol and treated with excess sodium borohydride. The colourless oil so produced in 75% yield displays absorption at 3590 (OH), 2780, 2740 and 2600 cm^{-1} (Bohlmann bands) in the ir spectrum. Tlc (alumina, chloroform-methanol, 20:1) showed two spots of very similar R_f value. The nmr spectrum displays a doublet at δ 0.88 (J=5Hz), with a poorly resolved doublet at δ 1.03 (J=7.5Hz).

The mass spectrum shows a parent peak at m/e 209. $C_{13}H_{23}NO$ calcd. 209.1780, meas. 209.1792. These spectral characteristics are consistent with alcohols 83. Since this material is probably a mixture of as many as four stereoisomers no attempt was made to obtain one or more of them pure.



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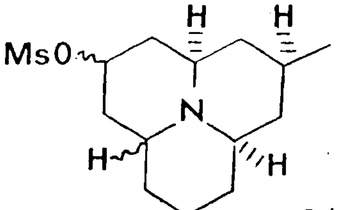

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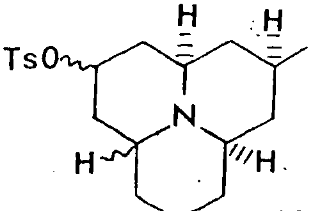
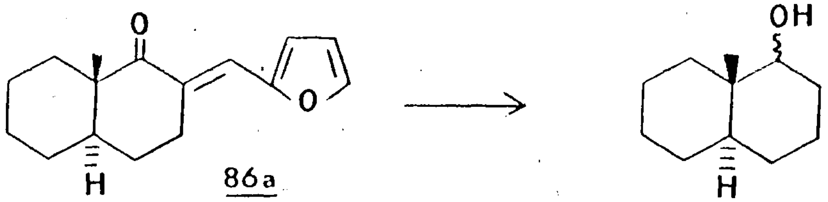


85

When hemiketal 76 was treated with sodium hydroxide in ethylene glycol at 150° a 45% yield of material identical with 83 by ir, tlc and mass spectrometry was obtained. This product could arise by Meerwein-Pondorf reduction of the ketone[50] although no precedent could be found in the literature for such a reduction in ethylene glycol. Alternatively, a crossed-Cannizzaro reaction[51] of ketone 81 with uncyclized aldehyde could result in reduction to 83. Johnson and co-workers[52] have reported a similar reaction in which the decalone 86a was transformed into the decalol 86b by reaction with sodium hydroxide in ethylene glycol at 150°. It was presumed that 86b was formed by a crossed-Cannizzaro reaction of the primary hydrolytic products, *trans*-9-methyl-1-decalone and furfuraldehyde.



86a 86b

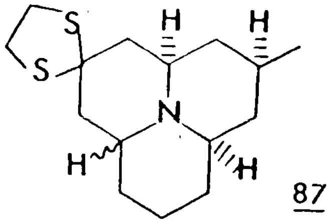
A number of experiments were performed in an attempt to remove the hydroxyl group from this mixture of alcohols. Treatment with phosphoryl chloride and pyridine in ether (attempted dehydration) led to a dark brown gum the mass spectrum of which possessed no encouraging characteristic peaks.

The mixture of alcohols was treated with *p* toluenesulphonyl chloride in pyridine and the *p*-toluenesulphonate esters, *85*, isolated[53]. The ir spectrum (methylene chloride) is devoid of a hydroxyl absorption, but shows weak absorption at 1600 cm^{-1} (aromatic) and strong absorptions at 1355 and 1170 cm^{-1} attributed to the sulphonate ester. Tlc showed only a diffuse spot less polar than starting material. The mass spectrum displays a strong parent peak at *m/e* 363, with the base peak at *m/e* 192 resulting from loss of the sulphonate group from the tricyclic moiety. It is reported that alkanes can be formed from reaction of sulphonates with lithium aluminium hydride (LAH)[54]. Treatment of this material with a solution of LAH in ether at room temperature for 24 hours did not lead to reaction. The same reaction in refluxing THF gave the alcohol 3 (ir, tlc, mass spectrum). Since methanesulphonates are equally useful as leaving groups, the reduction procedure was attempted on this functionality. The methanesulphonate esters, 84, were prepared by treatment of the alcohols with methanesulphonyl chloride in methylene chloride with triethylamine as catalyst[55]. The ir spectrum of this material (neat film) shows Bohlmann bands at 2780, 2740 and 2600 cm^{-1} together with sulphonate absorption at 1355 and 1170 cm^{-1}. The mass spectrum shows the parent peak at *m/e* 287 with the base peak at *m/e* 192. This material was treated with a solution of LAH in ether-THF (1:1) at room temperature and the product appeared to be alcohols 83 (ir, tlc, mass spectrum). The attack of hydride at the sulphur atom rather than carbon is a reaction which has been noted previously[56].

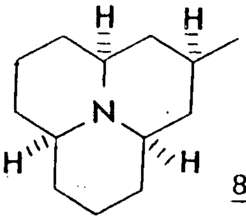
Recently Masamune[57] has described the use of a Cu(I) complex for the high yield reduction of methanesulphonate esters to alkanes. The reagent is prepared by addition of two equivalents of a freshly prepared solution of lithium trimethoxyaluminium hydride in THF to one equivalent of cuprous iodide. The methanesulphonate is then added to the dark brown reducing agent. Utilization of these conditions led only to recovered starting material.

These results led to a somewhat different approach to removing the oxygen functionality from the tricyclic compound. Ketone 81 was formed as before and the crude material was dissolved in 1,2-ethanedithiol with 1.2 equivalents boron trifluoride-etherate[58]. Work up of the reaction after four hours gave a thick oil with a sulphurous odour. The ir spectrum of the compound shows no carbonyl peak and is otherwise devoid of peaks characteristic of functionality other than C-H. The mass spectrum shows a parent peak at m/e 283 with a measured mass for $C_{15}H_{25}N^{32}S_2$. This material is a diffuse spot on tlc (alumina, chloroform) probably accounted for by the presence of two compounds. Thioketal 87 was thus formed in 50% overall yield from ketal-acetal 38.

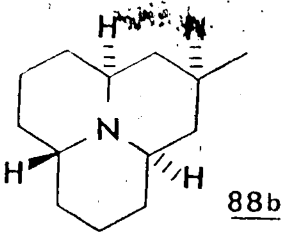
Desulphurization of the thioketal was accomplished using W2 Raney-nickel in refluxing ethanol. The tlc of the crude mixture (alumina, chloroform) shows predominantly two spots with distinctly different polarities. These compounds



87



88a

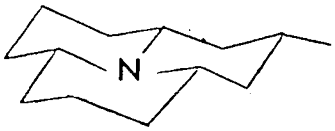


88b

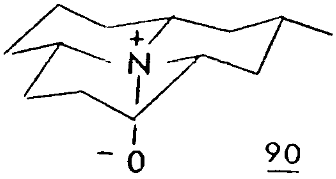
should be 88a and 88b and they were separated by ptlc on alumina with chloroform as eluent.

The less polar material shows intense Bohlmann bands at 2770, 2710 and 2600 cm^{-1} in the ir spectrum. The mass spectrum displays a parent peak at m/e 193 with a very strong peak at m/e 192 (the base peak is at m/e 41). The nmr spectrum displays a methyl doublet δ 0.87 (J=5Hz). The intense Bohlmann bands are indicative of the conformation shown in 89 for this compound. The fact that there are 3 protons *trans*-diaxial to the lone pair on nitrogen is no doubt responsible for the strength of these bands.

This amine was converted into the N-oxide 90 by reaction with one molar equivalent *m*-chloroperbenzoic acid in chloroform[59]. Work up by elution through a column of basic alumina with chloroform-methanol (3:1) provided



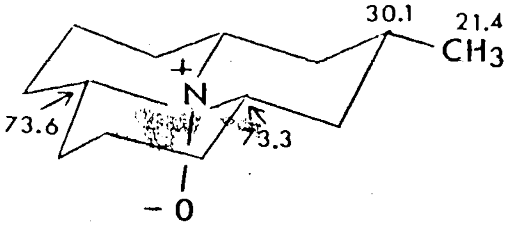
89



90

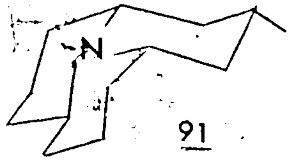
the N-oxide as pale yellow crystals, which were recrystallized from hexane-acetone. The mass spectrum of this material shows a parent ion at m/e 209 ($C_{13}H_{23}NO$ calcd. 209.1780 meas. 209.1777) with an intense peak at m/e 192 (the base peak occurs at m/e 41). The nmr spectrum displays a methyl doublet at δ 0.91 (J=6Hz) and a 3-proton multiplet centred at δ 2.84 resulting from the methine hydrogen atoms on the carbons α to nitrogen.

The completely decoupled cmr spectrum of this N-oxide (35 mg) displays only eight lines. The approximate intensities of the signals are given in parentheses and are as follows: δ 73.6 (1), 73.3 (2), 35.8 (2), 35.6(2), 30.1 (1), 27.4 (2), 23.4 (2), 21.4 (1). Several of the signals are assigned as shown in the following diagram. Since the molecule is symmetrical there are five pairs of identical carbon atoms resulting in only the eight lines

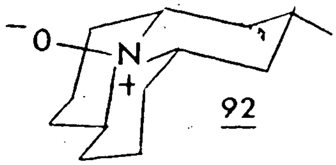


observed. Wenkert reports[60] that carbons α to an N-oxide are shifted downfield to a great extent compared to the amine and mentions one such compound in which the α carbon resonates at δ 69.6. The signals observed here are therefore expected.

Structure 91 has been assigned to the more polar fraction from the desulphurization. The ir spectrum of material (neat film) shows no Bohlmann bands indicating less



91



92

than 2 protons <u>trans</u>-diaxial to the lone pair on nitrogen. The nmr spectrum shows a methyl doublet at δ 0.85 (J=6Hz) and a 3-proton multiplet at δ 2.7 - 3.1. The mass spectrum displays a parent peak at <u>m/e</u> 193 ($C_{13}H_{23}N$: calcd. 193.1831; meas. 193.1825), an intense peak at <u>m/e</u> 192 and a base peak at <u>m/e</u> 41. These spectral data are consistent with structure <u>91</u> for this compound.

The N-oxide <u>92</u> was formed from this amine using the same conditions employed for the isomeric compound. The ir spectrum of this material in chloroform displays absorption at 3550 and 2490 cm^{-1}. These can be explained by the N-oxide forming a hydrate, as is the case for natural coccinellin. The nmr spectrum (deuteriochloroform) shows a methyl doublet at δ 0.89 (J=6Hz). The mass spectrum shows a parent peak at <u>m/e</u> 209 ($C_{13}H_{23}NO$: calcd. 209.1780; meas. 209.1788) with base peak at <u>m/e</u> 192.

The cyclization and following steps resulted in the formation of <u>89</u> and <u>91</u> in the ratio of approximately 2:1. When the cyclization of <u>76</u> was performed using azacycloheptane (rather than pyrrolidine) and acetic acid and the remaining steps performed as already described a ratio of approximately 1:1 was obtained.

The amine <u>91</u> should be precoccinellin and the

N-oxide 92 coccinellin[8]. The publication describing the isolation of these compounds contains very little experimental detail or spectroscopic data. However, the chemical shifts of the methyl group in each compound are given. The quoted values are δ 0.96 and δ 1.00 respectively. The values obtained for compounds 91 and 92 in the synthesis are δ 0.85 and δ 0.89 respectively.

At this time a sample of natural coccinellin and several ir spectra were received from Professor Tursch. The spectra sent were those of precoccinellin (film), coccinellin (KBr disc) and coccinellin hydrochloride (KBr disc). The first spectrum is not very well defined, but could be used for comparison. The ir spectrum (neat film) of 91 is largely the same as that forwarded, but there are differences. Tursch's spectrum of coccinellin is poorly defined so an ir spectrum was run of the sample which he sent. Again the spectra of coccinellin and 92 bear striking similarities but they are definitely different. The hydrochloride salt of 92 was prepared by dissolving a small amount of the compound in acetone and treating with two drops of 1N aqueous hydrochloric acid. Evaporation of the solution gave the crude salt which was recrystallized from acetone. Again the spectrum of the synthetic material had slight dissimilarities from Tursch's spectrum. The hydrochloride salt of the natural material was prepared in exactly the same fashion as for 92, but identity between this and synthetic material still could not be established. The N-oxide was recovered from both of these salts by elution through a hydroxide loaded strongly basic ion exchange column, followed by evaporation. The N-oxides show spectra which bear great similarities but are still not identical.

The mass spectra of the natural material and 92 were run sequentially and have identical peaks with identical intensities except for the peaks at m/e 194 and /e 140 which are very slightly more intense in the spectrum of 92.

Throughout the comparisons, tlc's of 92 and the natural material were run. The compounds show the same polarity on alumina when eluted with 95:5 chloroform-methanol, 80:20 ethyl acetate:methanol or 3:2:1 acetone:benzene:methanol.

An nmr spectrum was run on the remaining portion of natural material sent by Tursch. The spectrum displays a methyl doublet at δ 1.02 (J=6Hz) and a further doublet at δ 1.21 (J=6Hz). It is possible, therefore, that this material is a mixture. However, even if that is the case, the difference in the signals of the methyl groups in the nmr spectra appear to point to the fact that 92 is not identical with either one of the components of the mixture.

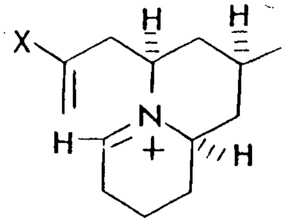
At this stage an 11 mg sample of 92 was remaining and a cmr spectrum was attempted on this material. The completely decoupled spectrum, although very weak, displays lines at δ 74.0, 58.7, 35.9, 34.0, 28.1, 27.4, 25.6, 24.6, 23.7, 21.5, 18.1. The signals quoted for coccinellin[8] occur at δ 73.4, 58.4, 35.3, 30.0, 26.9, 25.1, 20.7, 17.7.

The lines in 92, which are underlined, are consistent with the signals in coccinellin, but there appears to be no signal corresponding to the one at δ 30.0 in natural coccinellin. At present the instrumentation employed here is not sufficiently sophisticated to be used with confidence to obtain a cmr spectrum on a sample size much less than approximately 0.5 mmole. Since the results quoted above for compound 92 were obtained on 0.05 mmole, not too much emphasis can be placed upon them. However, they are quoted to point out that there are certain similarities between the cmr spectra of 92 and natural coccinellin.

The fact that it has proven impossible to establish identity between compound 92 and natural coccinellin has necessitated a review of the spectral data obtained for several compounds. The final amine and N-oxide, 91 and 92, clearly have the correct constitution (exact masses correct for $C_{13}H_{23}N$ and $C_{13}H_{23}NO$ respectively).

The isomeric N-oxide, 90, has spectral data completely in accord with the proposed structure. Of great importance is the cmr spectrum of this compound. The element of symmetry present is proven by only eight lines (from 13 carbon atoms) observed in the spectrum. The highest field signal in this spectrum occurs at δ 21.4, therefore the methyl group must be in the equatorial conformation. (An axial methyl group should result in a signal between δ 16 - 19[43,44].)

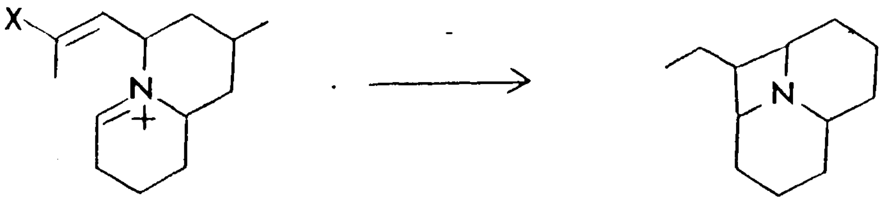
Amine 89 (the precursor of 90) and amine 91 are both formed from the same intermediate, 76, which is in turn formed from acetal-ketal, 38. The analysis of the cmr spectrum of this compound confirms the equatorial conformation of each ring substituent. The stereochemistry at these three positions is thus proven. Since there is no opportunity in later reactions for these centres to be isomerized this stereochemistry must be present in the final compound. Thus different compounds can only result from different modes of cyclization of the intermediate enol or enolate 93. As there are potentially two chiral centres, four compounds can initially arise.



93

Cyclization from the top-side produces the skeleton of 89 and the isomeric compound formed by possible inversion at nitrogen. This inversion would result in one ring being a chair, with the other two twist boats. This conformer would have a very much greater free energy, therefore this molecule should exist solely as 89.

Cyclization from the bottom-side results in 91 and the isomeric compound formed by inversion at nitrogen. The inversion would result in two rings in the chair conformation and one in a twist-boat. Again this should have much greater energy than 91 and thus the latter would be expected to be the only form of this compound observed. The complete lack of Bohlmann bands in the ir spectrum of 91 is further confirmation of the assigned skeleton.

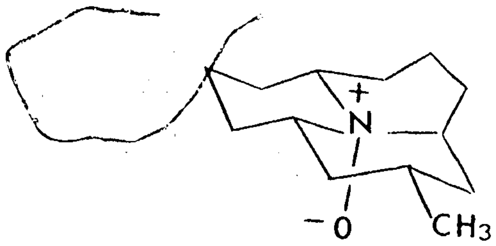


The possibility that a compound containing a 4-membered ring could be formed should be considered. However, this would result in a compound containing an ethyl group and no such functionality can be recognized in any of the nmr spectra of the products.

The cmr of ketal-acetal 38 contains no spurious peaks, thus the possibility of impurities in this compound can be discounted. As 89 and 91 are formed in approximately equal proportions via the route involving azacycloheptane, an impurity (if it did indeed lead to 91) would have to be present in 38 to a very considerable extent and would certainly give rise to prominent peaks in the cmr.

These arguments all lead to the more polar amine having the structure depicted in 91.

Obviously there is some discrepancy between the results quoted here and those reported by Tursch. One possible explanation is that the N-oxide formed from amine 91 has an inverted nitrogen atom. This would lead to at least one ring being a twist boat, 94. However, the greater free energy that would be associated with this molecule makes this seem unlikely.



94

In conclusion, it is felt that the structure of 91 and/or 92 will only be verified unambiguously when an X-ray study is completed on a suitable derivative of one or both of them. As mentioned, the sample of natural coccinellin obtained from Prof. Tursch may have been impure. The results described here have been communicated to Prof. Tursch and it is hoped that further reference samples will be obtained shortly. It now becomes important to compare natural and synthetic material at the precoccinellin stage. Since the assignment of structure to 91 appears to be well founded, failure to establish identity at this stage would suggest that the structural assignment of Tursch *et al* should be reexamined.

EXPERIMENTAL

Solutions were dried over anhydrous magnesium sulphate unless otherwise specified.

R_f value = distance moved by compound/distance moved by solvent.

Melting points were dete[illegible]d on a Fischer-Johns or Leitz-Wetzlar hot-stage m[illegible] point apparatus and are uncorrected.

Microanalyses were performed by the Microanalytical Laboratory of this department.

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer, a Unicam SP1000 grating infrared spectrophotometer, or a Perkin-Elmer Model 421 dual grating infrared spectrophotometer.

Nuclear magnetic resonance spectra were measured using a Varian Associates Model A-60 spectrometer or a Varian Model HR-100 spectrometer with tetramethylsilane as internal standard.

^{13}C nmr spectra were determined at 22.63 MHz in the Fourier mode using a Bruker HFX-90 spectrometer in conjunction with a Nicolet-1085, 20 K mercury computer or [illegible] 25.1 MHz Varian HA-100-"15 system interfaced to the Digilab FTS/NMR-3 Data System and associated pulse and proton decoupling units.

Mass spectra were recorded on an A.E.I. Model MS-9 mass spectrometer or an A.E.I. Model GC/MS mass spectrometer with a WB separator.

2-(3-butenyl)-4,6-dimethylpyridine 29

To a stirred solution of phenyllithium (40.3 g, 0.48 m) in anhydrous ether (300 ml) under an atmosphere of nitrogen at room temperature was added dropwise 2,4,6-collidine (62.5 ml, 0.48 m). The dark solution was stirred for four hours then cooled to 0° in an ice-bath.

Allyl bromide (60.25 g, 0.5 m) was dissolved in ether (75 ml) and added dropwise to the collidyllithium solution. Following addition the solution was allowed to warm to room temperature and stirred for 12 hours. Water (150 ml) was added dropwise to the mixture, then the aqueous phase was separated and extracted with ether (3 x 75 ml). The combined organic phase was extracted everal times with dilute hydrochloric acid, and the acidic solution was basified with cold aqueous ammonia and extracted several times with chloroform. The chloroform was removed and the residue distilled to give 2-(3-butenyl)-4,6-dimethylpyridine 29 (53.4 g, 70%), b.p. 58° - 60°, 1 mm, n_D^{20} 1.5045 (lit.[15] 54 - 56°, 0.5 mm, n_D^{21} 1.5042).

2-(4-hydroxybutyl)-4,6-dimethylpyridine 30

2-(3-Butenyl)-4,6-dimethylpyridine (16.1 g, 0.1 m) was dissolved in freshly distilled tetrahydrofuran (25 ml) under a nitrogen atmosphere at room temperature and a solution of diborane in tetrahydrofuran (150 ml, 1M, 0.15 m) was added dropwise to it. The slightly cloudy solution was stirred at room temperature for two hours then excess diborane was destroyed by the careful addition of small pieces of ice. 3N aqueous NaOH (60 ml) was added and the resulting solution cooled to 0°. 30% hydrogen peroxide (60 ml) was added dropwise. The solution was stirred at room temperature for two hours then was poured into water and extracted with ether (4 x 100 ml). The combined organic phase was extracted with dilute hydrochloric acid and the bases isolated as usual. Distillation gave 2-(4-hydroxybutyl)-4,6-dimethylpyridine 30 (16.5 g, 93%) b.p. 125 - 127° at 0.6 mm (lit.[15] 110 - 112° at 0.2 mm) which solidified to a low-melting solid on cooling.

4 4,6-dimethylpyridyl)butyl 2-tetrahydropyranyl ether 26

2-(4-hydroxybutyl)-4,6-dimethylpyridine 30 (16.5 g, 0.09 m) was dissolved in freshly distilled dimethoxyethane (25 ml) and freshly distilled dihydropyran (13.7 ml, 0.14 m) was added. Hydrogen chloride was bubbled into the solution, which became warm and deep orange, until 5.5 g (excess) had been absorbed. The reaction mixture was stored at room temperature for six hours, poured carefully into ice-cold aqueous ammonia and extracted with methylene chloride. The methylene chloride was removed and the residue distilled to give the tetrahydropyranyl ether 26 (20.5 g, 85%) b.p. 143 - 147°, 1.2 mm, n_D^{26} 1.5027 (lit.[15] 130 - 132° at 0.5 mm, n_D^{21} 1.5024).

3-bromopropyl 2-tetrahydropyranyl ether

3-Bromopropan-1-ol (25 g) was dissolved in freshly distilled benzene (250 ml) and dihydropyran (17 ml) was added. Phosphoryl chloride (16 drops) was added as catalyst and the colourless solution was stirred at room temperature for 1½ hours. Triethylamine (1 ml) was added, then the solution was washed with dilute sodium bicarbonate (50 ml), water (50 ml), brine (50 ml), dried and evaporated. The oil was distilled at 88 - 91°, 10 mm, and bromoacetal (38 g, 95%)

was obtained. n_D^{23} 1.4780.

ir$_{(neat)}$: no -OH; 1030 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 2.13 (quintet, 2, J=6.5Hz, $CH_2\underline{CH_2}CH_2$), 4.63 (m, 1, OC$\underline{H}$O).

mass spectrum: m/e 224(1), 223(6), 222(M$^+$, $C_8H_{15}{}^{79}BrO_2$, 1), 221(M-1, $C_8H_{14}{}^{79}BrO_2$, calcd. 221.0177, meas. 221.0178, 6) 123(9), 121(9), 120(9), 87(7), 86(6), 85(100), 84(17), 83(10), 67(5), 59(5), 57(10), 56(26), 55(20), 54(8), 43(12), 41(43), 39(11).

4-(2-[4-methyl-6-(2-hydroxypropyl)-pyridyl])butyl 2-tetrahydropyranyl ether, 28

Pyridine-acetal 26 (17 g, 0.065 m) was dissolved in 100 ml anhydrous ether under a nitrogen atmosphere and a solution of n-butyllithium in hexane (47 ml) (1.4M, 0.066 m) was added dropwise. The solution was stirred at room temperature for two hours then cooled to -78°. Acetaldehyde (25 ml) in ether (25 ml) was added dropwise to the solution. The mixture was stirred at -78° for 15 minutes then quenched at -78° by dropwise addition of water (10 ml). The mixture was warmed to room temperature and the layers separated. The aqueous solution was extracted with ether (2 x 25 ml) and the combined organic solution dried and evaporated to give an oil which by tlc (alumina, chloroform) consisted mainly of two fractions: starting material at R_f 0.7 and a more polar fraction at R_f 0.4. The oil was chromatographed over alumina (800 g). Elution with benzene gave an oil identical with starting material. Elution with ether gave hydroxyacetal 28 as a colourless oil (8.7 g, 44%) b.p. 165 - 168° at 0.2 mm, n_D^{23} 1.5072.

ir$_{(CHCl_3)}$ 3360 (unchanged by dilution, intramolecular H-bonded -OH), 1610, 1570 (pyridine) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 1.25 (d, 3, J=6Hz, -CH(OH)C$\underline{H}_3$), 2.29 (s, 3, -C$\underline{H}_3$), 4.56 (b[illegible]., 1, -OC$\underline{H}$O-), 6.77 (s, 1, -Ar$\underline{H}$), 6.83 (s, 1, Ar$\underline{H}$).

mass spectrum: $C_{18}H_{29}NO_3$, m/e calcd. 307.2147, meas. 307.2147(4), 263(10), 222(56), 207(13), 206(85), 179(23), 178(41), 165(100), 163(13), 162(40), 148(12), 147(14), 146(10), 135(13), 134(57), 121(82), 120(13), 85(70), 77(12), 57(10), 45(10), 43(13), 41(21).

2-(4-hydroxybutyl)-6-(2-hydroxypropyl)-4-methylpiperidine, 23

Compound 28 (1 g) was dissolved in absolute ethanol (40 ml) and sodium metal (4 g) was added in large pieces. The mixture was stirred and heated to reflux for two hours, then cooled. Water (20 ml) was added dropwise and the cooled solution was extracted with chloroform (3 x 50 ml). The combined extracts were washed with water until the washings were neutral and the chloroform solution was dried and evaporated to leave a pale yellow oil (780 mg, 77%).

ir$_{(CH_2Cl_2)}$: 3610 (OH), 3250 (NH), 1130, 1120, 1070, 1030 (C-O) cm^{-1}.

The crude material was dissolved in chloroform (10 ml) and stirred vigorously with 10% aqueous HCl (20 ml) for one hour. The aqueous layer was basified with aqueous sodium carbonate, then extracted with chloroform (3 x 25 ml). The combined extracts were dried and evaporated to yield <u>23</u> as a pale yellow oil (558 mg, 75% from <u>28</u>).

ir$_{(CH_2Cl_2)}$: 3610 (OH), 3250 (NH), 1070, 1030 (C-O) cm^{-1}.

The triacetate of this compound was formed by treatment with acetic anhydride in pyridine.

ir$_{(CH_2Cl_2)}$: 1735 (C=O), 1635 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.91 (d, 3, J=6Hz, -C$\underline{H}_3$), 1.24 (d, 3, J=6Hz, -C$\underline{H}_3$), 2.03 (s, 6, C$\underline{H}_3$CO), 2.06 (s, 3, C$\underline{H}_3$CO), 4.02 (t, 2, J=6Hz, -C$\underline{H}_2$OAc), 4.84 (m, 1, C$\underline{H}$OAc).

mass spectrum: $C_{19}H_{35}NO_5$, <u>m/e</u> calcd. 355.2359 meas. 355.2369(2), 280(4), 254(7), 252(4), 240(8), 212(20), 198(24), 182(5), 181(4), 180(8), 154(11), 152(8), 139(8), 137(15), 112(13), 110(9), 97(5), 96(15), 95(7), 94(7), 82(8), 81(9), 70(10), 69(13), 68(7), 67(10), 56(7), 55(15), 44(6), 43(100), 42(7), 41(17).

Anal. Calcd. for $C_{19}H_{35}NO_5$: C, 66.50; H, 9.82; N, 3.53.
Found: C, 66.23; H, 9.95; N, 3.87.

Attempted oxidations of 23

a) Chromium trioxide-pyridine-acetic acid

Piperidine diol 23 (321 mg) was stirred at room temperature with chromium trioxide-pyridine-acetic acid (0.8M, 10.5 ml, 6 equivalents) for one hour. The brown mixture was poured carefully into cold aqueous ammonia (20 ml) and then the mixture diluted to 200 ml with water. The resulting solution was extracted with ether (3 x 20 ml) and the combined extracts washed with water (30 ml) dried and evaporated to give a dark oil (69 mg). This was a mixture of at least three compounds (tlc, alumina, chloroform) and the ir showed a medium intensity band at 1680 cm^{-1} with a shoulder at 1720 cm^{-1}.

b) Collins' reagent

Diol 23 (243 mg) dissolved in methylene chloride (5 ml) was added to a solution of CrO_3-py_2 complex (Collins' reagent) in methylene chloride (5%, 60 ml, 12 equivalents) and the mixture was stirred at room temperature for two hours. The dark mixture was filtered and the filtrate evaporated to give a dark-brown semi-solid. This was partitioned between chloroform and 5% aqueous HCl. The aqueous solution was basified with dilute sodium bicarbonate solution and then extracted with chloroform. The dried extracts were evaporated to give a small amount of dark oil (3 mg).

c) Chromium trioxide-pyridine

Diol 23 (200 mg) dissolved in pyridine (5 ml) was added to a slurry of chromium trioxide (400 mg, 4 equivalents) in pyridine (10 ml) at 0°. The mixture was stirred for two hours at 0°, then poured into ice-cold aqueous ammonia (25 ml). The solution was extracted with chloroform (3 x 50 ml) and the combined extracts washed with water (20 ml), dried and evaporated to give a dark brown semi-solid (99 mg) which was a mixture of four compounds (tlc, alumina, chloroform).

d) Chromium trioxide-pyridine (complex) in methylene chloride (in situ preparation and use of Collin's reagent)

To dry methylene chloride (30 ml) under a nitrogen atmosphere was added dry pyridine (0.96 ml, 0.012 m) followed by chromium trioxide (600 mg, 0.006 m). The mixture was stirred for 15 minutes at room temperature and then diol 23 (317 mg, 0.001 m) in methylene chloride (4 ml) was added in one portion. The mixture was stirred for 15 minutes then poured into water (50 ml). The mixture was extracted with ether (3 x 50 ml) and the combined extracts washed with water (50 ml), dried and evaporated to give a dark oil (106 mg) which was a mixture of at least five compounds (tlc, alumina, chloroform).

e) Silver carbonate-celite, benzene

Silver carbonate-celite (6.0 g) was azeotropically distilled with benzene (90 ml) to remove residual water from the solid and to this mixture was added diol 23 (267 mg) in benzene (10 ml). After one hour the mixture was cooled, filtered and the filtrate evaporated to give a dark oil (206 mg) which was a mixture of at least four compounds (tlc, alumina, chloroform).

2-(2-oxopropyl)-4,6-dimethylpyridine 39

2,4,6-Collidine (24.2 g, 0.2 m) dissolved in anhydrous ether (120 ml) was added dropwise to a solution of n-butyllithium in hexane (135 ml, 0.22 m) under a nitrogen atmosphere. The solution was stirred for 1½ hours at room temperature.

Acetonitrile (12 ml, 9.35 g, 0.23 m) in ether (13 ml) was added dropwise over ½ hour. The mixture was stirred at room temperature for 1½ hours. 6N Sulphuric acid (100 ml) was added dropwise and the resulting mixture stirred overnight. The layers were separated and the aqueous solution basified with aqueous ammonia, then extracted with ether (4 x 100 ml). The combined ethereal solution was dried and evaporated to give a yellow oil. Distillation at 4.5 mm gave a fraction boiling at 35 - 45° (10.2 g) which was identical to starting material. Pyridine-ketone 39 (11.0 g, 58%) was obtained as a yellow oil, b.p. 105 - 109°, 4.5 mm, n_D^{24} 1.5264.

ir$_{(neat)}$: 3400 (-OH intramolecular H-bonded), 1720 (C=O), 1655 (C=C), 1612, 1570 (pyridine) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 2.20 (s, 3, -COC$\underline{H}_3$), 2.27 (s, 3, -C$\underline{H}_3$), 2.48 (s, 3, -C$\underline{H}_3$), 3.83 (s, 2, -C$\underline{H}_2$), 6.87 (s, 2, -Ar$\underline{H}$).

mass spectrum: $C_{10}H_{13}NO$, m/e calcd. 163.0997, meas. 163.1004(24), 148(10), 122(9), 121(100), 120(17), 77(8), 43(10).

m*/e 90 corresponds to 163 ⟶ 121.

2-(2-[2-(5,5-dimethyl-1,3-dioxanyl)]propyl)-4,6-dimethylpyridine, 45

Pyridine-ketone 39 (4.0 g, 0.025 m) was dissolved in benzene (50 ml). 2,2-Dimethyl-1,3-propanediol (2.6 g, 0.025 m) and p-toluenesulphonic acid (4.65, 0.026 m) were added and the resulting solution was stirred and heated to reflux under a Dean-Stark trap for nine hours. Triethylamine (3 ml) was added and the solution washed with aqueous sodium carbonate (2 x 25 ml) and water (25 ml). The solution was dried and evaporated to give a pale-yellow oil (5.60 g, 92%), n_D^{24} 1.4989.

ir$_{(neat)}$: 1612, 1570 (pyridine), 1120, 1080 cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.93 (s, 6, gemdimethyl), 1.37 (s, 3, C$\underline{H}_3$ ketal), 2.26 (s, 3, C$\underline{H}_3$), 2.47 (s, 3, C$\underline{H}_3$), 3.18 (s, 2, C$\underline{H}_2$), 3.58 (s, 4, -C$\underline{H}_2$O-), 6.81 (s, 1, Ar$\underline{H}$), 6.95 (s, 1, Ar$\underline{H}$).

mass spectrum: $C_{15}H_{23}NO_2$, m/e calcd. 249.1720, meas. 249.1730(1), 234(5), 164(7), 130(7), 129(100), 122(5), 121(23), 120(8), 77(6), 69(67), 43(90), 41(10).

Ketal 45 (2.5 g, 0.01 m) in anhydrous ether (10 ml) was added dropwise to a solution of phenyllithium in ether (5 ml, 0.01 m) at room temperature under a nitrogen atmosphere. An aliquot was removed by syringe and plunged into D_2O. The ethereal layer was dried and evaporated.

nmr$_{(\mathrm{CDCl}_3)}$: δ 2.47 (s, 3, C$\underline{\mathrm{H}}_3$), 3.18 (s, 1.1, -C$\underline{\mathrm{H}}$D).

2-(3-iodopropyl)-5,5-dimethyl-1,3-dioxane $\underline{48}$

β-chloropropionaldehyde diethylacetal (16.65 g, 0.1 m) was dissolved in benzene (150 ml) with 2,2-dimethyl-1,3-propanediol (10.4 g, 0.1 m) and p-toluenesulphonic acid (500 mg).

The solution was stirred and distilled. During the distillation benzene was added at a rate sufficient to maintain constant volume. After 200 ml of distillate was collected the solution was cooled, washed with dilute sodium bicarbonate (2 x 25 ml), dried and evaporated to give a colourless oil (18.0 g).

nmr$_{(\mathrm{CDCl}_3)}$: δ 0.73 (s, 3, -C$\underline{\mathrm{H}}_3$), 1.18 (s, 3, -C$\underline{\mathrm{H}}_3$), 3.65 (t, 2, J=6.5Hz, -C$\underline{\mathrm{H}}_2$Cl), 4.62 (t, 1, J=5Hz, -OC$\underline{\mathrm{H}}$O-).

The oil (18.0 g) was dissolved in dry acetone (100 ml) and sodium iodide (30 g) dissolved in acetone (200 ml) was added. The stirred solution was heated to reflux in a dry atmosphere for ten hours. The cooled mixture was filtered and the filtrate evaporated. The residue was partitioned between ether and 1% aqueous sodium bicarbonate. The ether layer was dried and evaporated. The residual oil was distilled to give the iodo-acetal $\underline{48}$, b.p. 78 - 81°, 1.5 mm (20.2 g, 75%).

nmr$_{(CDCl_3)}$: δ 0.75 (s, 3, -C$\underline{H}_3$), 1.18 (s, 3, -C$\underline{H}_3$), 3.25 (t, 2, J=7Hz, C$\underline{H}_2$I), 4.53 (t, 1, J=5Hz, -OC$\underline{H}$O-).

mass spectrum: $C_8H_{15}O_2I$, m/e calcd. 270.0117, meas. 270.0110(3), 269(10), 184(6), 183(5), 155(6), 142(4), 128(4), 116(7), 115(100), 87(4), 69(42), 57(8), 56(53), 45(10), 43(4), 41(30).

2-(4-[2-(5,5-dimethyl-1,3-dioxanyl)]butyl)-4,6-dimethylpyridine, 49

To a solution of n-butyllithium in hexane (1.4M, 18 ml, 0.025 m) in anhydrous ether (25 ml) was added dropwise a solution of 2,4,6-collidine (3.775 g, 0.025 m) in ether (25 ml). The solution was stirred at room temperature for 1½ hours then cooled to 0°. A solution of iodoacetal 48 (6.75 g) in ether (50 ml) was added dropwise and the mixture was stirred for ½ hour at room temperature. Water (50 ml) was added and the mixture worked up as usual. Distillation of the residue gave a colourless oil, b.p. 127 - 128°, 0.4 mm (8.0 g, 97%).

ir$_{(neat)}$: 1610, 1570 (pyridine), 1130, 1090 (CO) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.70 (s, 3, C$\underline{H}_3$), 1.18 (s, 3, C$\underline{H}_3$), 2.23 (s, 3, C$\underline{H}_3$), 2.47 (s, 3, C$\underline{H}_3$), 4.43 (t, 1, C$\underline{H}$ acetal), 6.77 (s, 2, Ar$\underline{H}$).

mass spectrum: m/e 263(7), 178(5), 177(5), 176(4), 148(9), 134(7), 122(11), 121(100), 115(6), 69(9), 41(5).

Anal. calcd. for $C_{16}H_{25}NO_2$: C, 73.00; H. 9.51; N, 5.32.

Found: C, 73.11; H, 9.26; N, 5.56.

Attempted hydrolyses of 49

a) Chloroform-aqueous HCl

Acetal 49 (550 mg) was dissolved in chloroform (10 ml) and 10% aqueous HCl (10 ml) added. The two-phase system was stirred and heated to reflux for 60 hours. The aqueous layer was basified with aqueous ammonia and extracted with chloroform. The extracts were dried and evaporated to give a pale yellow oil (510 mg) which was identical with starting material (tlc, mass spectrometry and ir).

b) Chloral-chloroform-aqueous HCl

Acetal 49 (510 mg) was dissolved in chloroform (10 ml) and 10% aqueous HCl (10 ml) added. To this mixture was added chloral (15 drops) and the mixture was stirred and heated to reflux overnight. The mixture was worked up as above to give an oil (370 mg) which was a mixture of three compounds (tlc). No absorption between 1650 - 1800 cm^{-1} was present in its ir.

c) 100% Sulphuric acid-ether

To a solution of acetal 49 (300 mg) in ether (10 ml) was added 100% sulphuric acid (8.5 ml, from concentrated sulphuric acid and oleum) with cooling. After standing for 1½ hours at 0° the mixture was poured into cold aqueous ammonia containing ice. The mixture was worked up as above to give a dark gum (103 mg).

d) 40% Hydrobromic acid in acetic acid

Acetal 49 (1 g) and 40% hydrobromic acid in acetic acid (10 ml) was heated on a steam bath for 18 hours. The solution was poured into water (10 ml), basified with aqueous ammonia and worked up as before to give a dark solid (400 mg) which was a mixture of four compounds (tlc, alumina, chloroform).

2-(4-[2-(5,5-dimethyl-1,3-dioxanyl)]butyl)-6-(2-oxopropyl)-4-methylpyridine, 50

To a solution of phenyllithium (8.2 g, 0.11 m) in anhydrous ether (300 ml) was added at room temperature under a nitrogen atmosphere pyridine-acetal (26.3 g, 0.1 m) in ether (25 ml). The mixture was stirred for three hours. Acetonitrile (25 g, 0.6 m) in ether (150 ml) was added dropwise and the mixture was stirred for 1½ hours. 6$\underline{N}$ Sulphuric acid (50 ml) was added dropwise and after stirring for 12 hours the mixture was worked up as usual to give a yellow oil (25.1 g) which was a mixture of starting material and product (1:1, nmr).

The crude mixture (5 g), hydroxylamine hydrochloride (2.7 g), and pyridine (5 ml) in 95% ethanol (70 ml) was heated under reflux with stirring for 1½ hours. The ethanol was removed and dilute sodium bicarbonate (100 ml) added. The mixture was extracted with methylene chloride (3 x 100 ml). The combined organic solution was washed with water (100 ml), brine (100 ml), dried and evaporated. The oil so produced was chromatographed over alumina (200 g). Elution with ether gave an oil which was identical in all respects with starting material (1.9 g). Elution with chloroform-methanol (94:6) produced the acetal-oxime $\underline{51}$ as a colourless oil (3.0 g).

ir$_{(\mathrm{CHCl_3})}$: 3580, 3290 (NOH), 1665 (C=N), 1610, 1570 (pyridine), 1130, 1090 (C-O) cm^{-1}.

nmr$_{(\mathrm{CDCl_3})}$: δ 3.67 (s, 1.5, Ar-C$\underline{H}_2$), 3.92 (s, 0.5, ArC$\underline{H}_2$).

The crude oxime $\underline{51}$ was dissolved in acetone-water (2:1, 105 ml) and treated with 20% aqueous titanium trichloride (15 ml, approx. 1.5 equiv.). The solution was stirred at room temperature for three hours then water (50 ml) was added. The mixture was basified with saturated aqueous sodium bicarbonate and extracted with methylene chloride (3 x 50 ml). The extracts were washed with water (50 ml), brine (50 ml) and dried. Distillation of the residue after evaporation of the methylene chloride gave a yellow oil 50, b.p. 150 - 152°; 0.3 mm, (2.26 g, 37%, 57% based on recovered starting material) n_D^{22} 1.5084.

ir$_{(CHCl_3)}$: 1715 (C=O), 1610, 1570 (pyridine), 1130, 1090 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 2.22 (s, 3, C$\underline{H}_3$), 2.30 (s, 3, C$\underline{H}_3$), 3.83 (s, 2, C$\underline{H}_2$).

mass spectrum: $C_{18}H_{27}NO_3$, m/e calcd. 305.1991, meas. 305.2008(41), 304(8), 290(10), 262(6), 220(18), 219(12), 218(57), 190(43), 177(12), 176(23), 164(25), 163(100), 148(9), 147(8), 146(10), 134(8), 121(43), 120(11), 115(27), 69(23), 45(9), 43(12), 41(14).

Anal. calcd. for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59.
Found: C, 70.97; H, 9.19; N, 4.71.

2-(4-[2-(5,5-dimethyl-1,3-dioxanyl)]butyl)-6-(2-[2-(1,3-dioxolanyl)]propyl)-4-methylpyridine, 52

Keto-acetal 50 (2.0 g), ethyleneglycol (2 ml) and p-toluenesulphonic acid (2.0 g) dissolved in benzene (50 ml) were heated to reflux under a Dean-Stark trap for six hours. Triethylamine (3 ml) was added to the cooled solution which was then washed with sodium bicarbonate (25 ml) and water (25 ml). The dried solution was evaporated to give a colourless oil (2.13 g, 93%).

$ir_{(neat)}$: 1610, 1570 (pyridine), 1130, 1090, 1045 (C-O) cm^{-1}.

$nmr_{(CDCl_3)}$: δ 0.72 (s, 3, $C\underline{H}_3$), 1.19 (s, 3, $C\underline{H}_3$), 1.37 (s, 3, $C\underline{H}_3$), 2.28 (s, 3, $C\underline{H}_3$), 3.08 (s, 2, $C\underline{H}_2$), 3.93 (s, 4, $OC\underline{H}_2$-$C\underline{H}_2O$).

In another experiment keto-acetal <u>50</u> (300 mg) was treated with ethyleneglycol (1 ml) and *p*-toluenesulphonic acid (230 mg) in benzene (30 ml).

The resulting product (182 mg) was chromatographed over alumina (6 g). Elution with benzene gave a product identical (nmr, tlc, ir) with the product from the previous reaction (94 mg). Elution with ether gave another fraction, 2-(4-[2-(1,3-dioxolanyl)]butyl)-6-(2-[2-(1,3-dioxoalnyl)]propyl)-4-methylpyridine, <u>53</u> (39 mg) as an oil.

$ir_{(neat)}$: 1610, 1570 (pyridine), 1045 (C-O) cm^{-1}.

$nmr_{(CDCl_3)}$: δ 1.37 (s, 3, $C\underline{H}_3$), 2.28 (s, 3, $C\underline{H}_3$), 3.07 (s, 2, $C\underline{H}_2$), 3.90 (m, 8, -$OC\underline{H}_2C\underline{H}_2O$-).

mass spectrum: <u>m/e</u> 307(1), 222(4), 221(24), 207(9), 178(7), 121(5), 88(9), 87(100), 73(9), 55(4), 45(7), 43(28).

3,3-dimethoxypropyl iodide 54

β-chloropropionaldehyde diethylacetal (10 g) and sodium iodide (30 g) in dry acetone (250 ml), (approximately 0.5 g sodium carbonate was suspended in the solution) was heated under reflux for three hours. The precipitated sodium chloride was removed by filtration and the filtrate evaporated. The residue was partitioned between ether (50 ml) and 5% aqueous sodium bicarbonate (50 ml) and the layers separated. The aqueous solution was extracted with ether (50 ml) and the combined ethereal solution was dried and evaporated.

nmr$_{(CDCl_3)}$: δ 1.22 (t, 6, J=7Hz, $-CH_2\underline{CH_3}$), 3.20 (t, 2, J=7Hz, $I\underline{CH_2}-$), 4.59 (t, 1, J=5.5Hz, $-\underline{CH}(OCH_2CH_3)_2$), 3.6 (m, 4, $-O\underline{CH_2}CH_3$), 2.1 (m, 2, $-CH_2\underline{CH_2}CH-$).

The crude product was dissolved in dry methanol (200 ml) and p-toluenesulphonic acid (250 mg) added. The mixture was stirred at room temperature for two days. 10 g solid sodium carbonate was added and the mixture stirred vigorously for ½ hour. The solid was filtered and the solvent removed from the filtrate by distillation. The residue was worked up as above and the product was distilled, b.p. 82 - 84°, 50 mm.

$\text{nmr}_{(CDCl_3)}$: δ 2.1 (m, 2, $-CH_2C\underline{H}_2CH_2$), 3.17 (t, 2, J=7Hz, $IC\underline{H}_2-$), 3.37 (s, 6, $-OC\underline{H}_3$), 4.45 (t, 1, J=5.5Hz, $-C\underline{H}(OCH_3)_2$).

mass spectrum: $C_5H_{11}O_2I$, m/e calcd. 229.9804, meas. 229.9801(1), 199(6), 75(100), 71(22), 57(6), 47(13), 45(15), 41(11).

2-(4,4-diethoxybutyl)-4,6-dimethylpyridine, 47

To a stirred solution of phenyllithium (6.72 g, 0.08 m) in anhydrous ether (250 ml) under a nitrogen atmosphere at room temperature was added dropwise a solution of 2,4,6-collidine (9.7 g, 0.08 m) in ether (30 ml). The mixture was stirred for two hours at room temperature and to the resulting blood-red solution was added dropwise a solution of β-chloropropionaldehyde diethylacetal (13.3 g, 0.08 m) in ether (30 ml). The mixture was stirred at room temperature overnight and quenched by the dropwise addition of water (100 ml). The layers were separated and the aqueous solution extracted with ether (75 ml). The combined ethereal solution was dried and evaporated. The mixture was distilled to give compound 47 (9.1 g, 45%), b.p. 120 - 124°, 1.2 mm, n_D^{23} 1.4844.

$\text{ir}_{(neat)}$: 1610, 1570 (pyridine), 1125, 1060 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 1.20 (t, 6, J=6.5Hz, -CH$_2$C$\underline{H}_3$), 2.26 (s, 3, -C$\underline{H}_3$), 2.47 (s, 3, -C$\underline{H}_3$), 4.50 (t, 1, J=5Hz, -OC$\underline{H}$O-), 6.77 (s, 2, Ar$\underline{H}$).

mass spectrum: m/e 251(2), 222(17), 207(17), 206(100), 205(28), 178(13), 176(61), 148(32), 121(69), 103(52), 75(25), 47(10).

Anal. calcd. for $C_{15}H_{25}NO_2$: C, 71.71, H, 9.96; N, 5.58.
Found: C, 71.59; H, 9.99; N, 5.65.

A further fraction (3.2 g), b.p. 170 - 174°, 1.2 mm was obtained.

ir$_{(neat)}$: 1610, 1570 (pyridine), 1125, 1060 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 1.17 (t, approx. 3, J=7Hz, -CH$_2$C$\underline{H}_3$), 1.19 (t, approx. 3, J=7Hz, -CH$_2$C$\underline{H}_3$), 2.25 (s, 3.2, -C$\underline{H}_3$), 2.45 (s, 2.8, -C$\underline{H}_3$), 4.42 (t, 1, J=5Hz, -OC$\underline{H}$O), 4.50 (t, 1, J=5Hz, -OC$\underline{H}$O-).

mass spectrum: $C_{22}H_{39}NO_4$, m/e calcd. 381.2879, meas. 381.2884(3), 352(15), 337(15), 336(95), 335(21), 307(7), 306(81), 291(12), 290(48), 262(14), 260(13), 251(12), 232(14), 204(14), 178(12), 176(22), 161(16), 160(10), 158(9), 148(12), 147(15), 146(18), 134(31), 121(23), 103(100), 75(55), 57(28), 47(93).

Anal. calcd. for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67.
Found: C, 69.39; H, 10.55; N, 4.14.

2-(4,4-dimethoxybutyl)-4,6-dimethylpyridine, 55

Diethylacetal 47 (10.28 g) was dissolved in freshly distilled methanol (250 ml) and d-10-camphorsulphonic acid (10.2 g, 10% molar excess) was added. The solution was distilled during which dry methanol was added dropwise to maintain the volume in the flask. This was continued until 100 ml distillate was collected. The solution was cooled, solid sodium carbonate (10 g) was added and the mixture stirred vigorously for 15 minutes. The mixture was filtered and the filtrate evaporated. The residue was partitioned between ether (100 ml) and water (100 ml). The aqueous fraction was extracted with ether (75 ml) and the combined ethereal solution was dried and evaporated. Distillation afforded dimethylacetal 55 (8.3 g, 92%) as a colourless oil, b.p. 94 - 97°, 1 mm, n_D^{22} 1.4904.

ir$_{(neat)}$: 1610, 1570 (pyridine), 1120, 1065 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 1.78 (m, 4, $-CH\underline{H}_2\underline{C}H_2CH-$), 2.28 (s, 3, $-C\underline{H}_3$), 2.51 (s, 3, $-C\underline{H}_3$), 2.77 (m, 2, $ArC\underline{H}_2$), 3.35 (s, 6, $-OC\underline{H}_3$). 4.43 (t, 1, J=5Hz, $-OC\underline{H}O-$), 6.87 (s, 2, $Ar\underline{H}$).

mass spectrum: $C_{13}H_{21}NO_2$, m/e calcd. 223.1572, meas. 223.1566(1), 208(11), 193(15), 192(92), 191(28), 176(35), 148(49), 122(11), 121(100), 75(84), 40(29).

Anal. calcd. for $C_{13}H_{21}NO_2$: C, 69.96; H, 9.42; N. 6.28.

Found: C, 70.16; H, 9.54; N, 6.26.

2-(4,4-dimethoxybutyl)-6-(2-oxopropyl)-4-methylpyridine, 61

To a stirred solution of phenyllithium (4.2 g, 0.05 m) in anhydrous ether (150 ml) under a nitrogen atmosphere was added dropwise a solution of dimethyl acetal 55 (10.98 g, 0.05 m) in ether (50 ml). The mixture was stirred for 1½ hours at room temperature and to the resulting blood-red solution was added dropwise a solution of acetonitrile (10.2 g, 0.25 m) in ether (30 ml). The mixture was stirred for three hours, then 2.5N methanolic HCl (100 ml) was added dropwise and the mixture stirred at room temperature overnight. Triethylamine (20 ml) was added dropwise, the mixture stirred for 15 minutes then poured into saturated aqueous sodium bicarbonate (100 ml). The layers were separated and the aqueous solution extracted with ether (2 x 100 ml). The combined ether solution was washed with water (50 ml), brine (50 ml), dried and evaporated. The residue was distilled and starting material (1.2 g) b.p. 92 - 100°, 0.1 mm was obtained. Crude keto-acetal (4.1 g) was obtained as a yellow oil, b.p. 150 - 157° (0.1 mm). (There was a considerable residue, but this could be greatly reduced by adding a saturated solution of zinc chloride in ether (0.5 molar equivalents) prior to the alkylation with acetonitrile.) $\text{ir}_{(\text{neat})}$: 1720 (C=O), 1655 (C=C(OH)), 1610, 1570 (pyridine), 1120 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 2.20 (s, 3, COC$\underline{H}_3$), 2.28 (s, 3, -C$\underline{H}_3$), 3.83 (s, 2, C$\underline{H}_2$CO).

This spectrum showed that the distillate contained approximately 10% starting material.

mass spectrum: $C_{15}H_{23}NO_3$, m/e calcd. 265.1678, meas. 265.1674.

2-(4-[2-(1,3-dioxolanyl)]butyl)-6-(2-[2-(1,3-dioxolanyl)]propyl)-4-methylpyridine, 53

Crude keto-acetal 61 (3.2 g), ethylene glycol (7 ml (7 ml) and p-toluenesulphonic acid (2.5 g, 10% excess) were dissolved in benzene (150 ml). The mixture was stirred and heated to reflux under a Dean-Stark trap for 18 hours. Triethylamine (5 ml) was added to the cooled mixture which was then stirred for ten minutes at room temperature. The mixture was washed with 5% aqueous sodium bicarbonate (75 ml), water (50 ml) and brine (50 ml), dried and evaporated to give an oil (3.5 g) which was chromatographed over alumina (200 g). Elution with benzene-ether (1:1) gave acetal-ketal 53 (2.5 g, 17% from 55) as a pale yellow oil, b.p. 146 - 149°, 0.08 mm, n_D^{23} 1.5132.

ir$_{(CH_2Cl_2)}$: 1610, 1570 (pyridine), 1045 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 1.36 (s, 3, $-C\underline{H}_3$), 1.82 (m, 4, $-CHC\underline{H}_2C\underline{H}_2CH-$), 2.28 (s, 3, $-C\underline{H}_3$), 2.77 (m, 2, $ArC\underline{H}_2$), 3.05 (s, 2, $ArC\underline{H}_2$), 3.90 (m, 8, $-OC\underline{H}_2C\underline{H}_2O-$), 4.87 (t, 1, J=4Hz, $-OC\underline{H}O-$), 6.85 (s, 1, $Ar\underline{H}$), 6.95 (s, 1, $Ar\underline{H}$).

mass spectrum: $C_{17}H_{25}NO_4$, m/e calcd. 307.1784, meas. 307.1769(1), 222(8), 221(55), 207(16), 204(5), 178(15), 176(4), 148(4), 147(4), 146(5), 134(4), 121(13), 99(5), 88(11), 87(100), 73(12), 45(6), 43(31).

Anal. calcd. for $C_{17}H_{25}NO_4$: C, 66.45; H, 8.14; N, 4.56.

Found: C, 66.58; H, 8.27; N, 4.53.

2-(4-[2-(1,3-dioxolanyl)]butyl)-*cis*-4-methyl-*cis*-6-(2-[2-(1,3-dioxoalnyl)]propyl)-piperidine, 38

Ketal-acetal 53 (2.27 g) was dissolved in freshly distilled *iso*-amyl alcohol (50 ml). The solution was stirred and heated to reflux under a nitrogen atmosphere and sodium metal (4 g in 1 g pieces) was added. The mixture was allowed to reflux until all the sodium had disappeared (2 hours). The solution was cooled and water (50 ml) was added dropwise. The mixture was separated and the aqueous solution extracted with ether (3 x 50 ml), then with brine (50 ml), dried and the ether evaporated. The *iso*-amyl alcohol was removed by simple distillation followed by evacuation at 2 mm overnight. The crude product (2.00 g) was chromatographed over alumina (150 g) and elution with ether gave 38, (1.22 g, 52%) n_D^{20} 1.4784.

ir$_{(neat)}$: 3340 (NH), 1120, 1035 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.90 (d, 3, J=5.5Hz, $-C\underline{H}_3$), 1.35 (s, 3, $-C\underline{H}_3$), 3.95 (m, 8, $OC\underline{H}_2C\underline{H}_2O$), 4.87 (t, 1, J=4Hz, $-C\underline{H}$ acetal).

^{13}cmr$_{(CDCl_3)}$: δ 20.6 (CH_2), 22.3 (CH_3), 24.3 (CH_3), 31.5 (CH), 34.0 (CH_2), 36.9 (CH_2), 41.1 (CH_2), 42.3 (CH_2), 45.3 (CH_2), 53.2 (CH), 56.4 (CH), 64.4 (CH_2), 64.7 (CH_2), 64.8 (2 x CH_2), 104.6 (CH), 110.2 (C).

mass spectrum: $C_{17}H_{31}NO_4$, m/e calcd. 313.2253, meas. 313.2246(1), 212(12), 199(8), 198(100), 155(4), 154(3), 152(4), 140(4), 112(4), 96(7), 87(20), 73(7), 69(6), 57(4), 55(4), 45(5), 43(11), 41(5).

Anal. calcd. for $C_{17}H_{31}NO_4$: C, 65.18; H, 9.90; N, 4.47.

Found: C, 65.39; H, 10.08; N, 4.64.

Elution with pure chloroform gave a pale yellow oil (0.34 g, 15%) which was isomeric with the above material (mass spectrum).

ir$_{(neat)}$: 3340 (NH), 1120, 1035 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.87 (d, 3, J=6Hz, $C\underline{H}_3$), 1.33 (s, 3, $C\underline{H}_3$), 3.97 (m, 8, $OC\underline{H}_2C\underline{H}_2O$), 4.88 (t, 1, J=4Hz, $C\underline{H}$ acetal).

mass spectrum: m/e 212(17), 199(11), 198(100), 155(6), 154(4), 152(7), 150(4), 140(7), 112(5), 110(4), 96(20), 87(25), 69(10), 57(4), 55(5), 45(8), 43(19), 41(8).

2,8-dimethyl 8-hydroxy-3a*cis*-9a*cis*-perhydro-7-oxa-9b-azaphenalene 76

Piperidine ketal-acetal 38 (242 mg) was stirred with 5% aqueous HCl (7 ml) at room temperature overnight. The solution was basified with dilute sodium bicarbonate and extracted with ether (3 x 10 ml). The combined ethereal solution was washed with water (10 ml), brine (10 ml) and dried. Evaporation at room temperature gave a colourless solid (173 mg, 100%).

ir$_{(CH_2Cl_2)}$: 3570 (-OH), 2760, 2730, 2610 (Bohlmann bands), 1060, 1040 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$ δ 0.90 (d, 3, J=6.5Hz, -C$\underline{H}_3$), 1.43 (s, 3, -C$\underline{H}_3$), 4.02 (m, 1, -O-C$\underline{H}$-N-).

mass spectrum: *m/e* 225(8), 224(17), 210(11), 207(20), 168(11), 166(12), 165(8), 164(7), 151(11), 150(100), 108(10), 96(6), 82(6), 55(5), 54(4), 43(11), 41(8).

2-Methyl-8-oxo-3a*cis*-9a*cis*-perhydro-9b-azaphenalene, 81

Hemiketal 76 (45 mg) was dissolved in dry THF (5 ml) and freshly distilled pyrrolidine (17 μl, 1 molar equivalent) and acetic acid (23 μl, 2 equivalents) were added. The solution was stirred and allowed to reflux under a nitrogen atmosphere for 24 hours. The cooled solution was washed with 5% sodium bicarbonate (2 x 5 ml) and the aqueous washings extracted with ether (2 x 5 ml). The combined organic solution was washed with brine (5 ml), dried and evaporated to give ketone 81 as a pale yellow oil (34.5 mg).

ir$_{(CH_2Cl_2)}$: 2780, 2740, 2600 (Bohlmann bands), 1725 (C=O) cm^{-1}.

This material was used immediately in the next step.

2-Methyl-8-hydroxy-3a*cis*-9a*cis*-perhydro-9b-azaphenalene, 83

The oily ketone 81 (34.5 mg) was dissolved in 95% ethanol (3 ml) and sodium borohydride (45 mg) was added. The mixture was stirred at room temperature for ½ hour. Ether (6 ml) and water (6 ml) were added, and after stirring for five minutes the layers were separated. The aqueous solution was extracted with ether (5 ml) and the combined ethereal solution washed with brine (5 ml), dried and evaporated to give a colourless oil (28.8 mg).

ir$_{(neat)}$: 3590 (-OH), 2780, 2740, 2600 (Bohlmann bands) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.88 (d, J=5Hz, C$\underline{H}_3$), 2.90 (m, -NC$\underline{H}$-), 3.61 (m, C$\underline{H}$OH).

mass spectrum: $C_{13}H_{23}NO$, m/e calcd. 209.1780, meas. 209.1792(38), 208(77), 194(11), 192(18), 167(16), 166(18), 164(30), 153(14), 152(12), 151(15), 150(24), 136(12), 122(13), 96(12), 94(10), 82(16), 81(12), 80(10), 79(10), 70(16), 69(21), 68(18), 67(22), 57(11), 56(15), 55(52), 54(31), 53(18), 45(41), 44(13), 43(46), 42(37), 41(100), 39(46).

Synthesis of 83 directly from 76

Hemiketal 76 (107 mg) was dissolved in ethylene glycol (20 ml) and sodium hydroxide (2 g) added. The stirred solution was heated to 150° under a nitrogen atmosphere for 18 hours. The cooled solution was diluted with water (25 ml) and extracted with benzene (3 x 15 ml). The combined benzene solution was washed with water (2 x 15 ml), dried and evaporated to give a pale yellow oil (45 g).

This oil was shown to be identical with alcohol 83 by tlc, ir and mass spectrometry.

2-Methyl-8-methanesulphonoxy-3a*cis*-9a*cis*-perhydro-9b-azaphenalene, 84

The mixture of alcohols 83 (24.0 mg) was dissolved in methylene chloride (0.5 ml) and was treated with triethylamine (40 µl, 1.5 equivalents). The solution was cooled to 0° and treated with methanesulphonyl chloride (15 µl, 1.3 equivalents). A precipitate formed almost immediately and the mixture was stirred for 15 minutes at 0°. 1% aqueous sodium bicarbonate (1 ml) was added, then methylene chloride (2 ml). The layers were separated and the aqueous fraction extracted with methylene chloride (3 x 5 ml). The combined organic solution was dried and evaporated to give an oil (23.0 mg) showing one spot, R_f 0.7 on tlc (alumina, chloroform).

ir$_{(neat)}$: 2780, 2740, 2600 (Bohlmann bands), 1355, 1170 (sulphonate ester) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.87 (d, 3, J=6Hz, $-C\underline{H}_3$), 2.96 (s, 3, $-C\underline{H}_3SO_2-$), 4.78 (m, 1, $-C\underline{H}OS$).

mass spectrum: $C_{14}H_{25}NO_2{}^{32}S$, *m/e* calcd. 287.1555, meas. 287.1567(15), 286(15), 208(10), 192(100), 191(7), 190(20), 176(5), 164(10), 151(12), 150(23), 148(8), 136(5), 134(4), 122(5), 108(8), 106(4), 96(6), 95(5), 94(5), 93(4), 91(4), 82(8), 81(7), 80(7), 79(14), 77(4), 69(10), 68(7), 67(10), 56(5), 55(14), 54(9), 53(7), 43(6), 42(6), 41(26).

2-Methyl-8-p-toluenesulphonoxy-3a*cis*-9a*cis*-perhydro-9b-azaphenalene, 85

The mixture of alcohols 83 (10.5 mg) was dissolved in dry pyridine (0.5 ml) and p-toluenesulphonyl chloride (30 mg, 3 equivalents) was added. The solution was stored at 0° for 24 hours. Water (1 ml) was added and the solution was extracted with ether (3 x 5 ml). The combined extracts were dried and evaporated at room temperature to give an oil (10.7 mg), which was shown to be one compound (tlc, alumina, chloroform, R_f 0.7).

ir$_{(CD_2Cl_2)}$: 2780, 2740, 2600 (Bohlmann bands), 1600 (aromatic), 1355, 1170 (SO_2) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.85 (d, J=6Hz, -C$\underline{H}_3$), 2.44 (s, ArC$\underline{H}_3$), 4.24 (m, C$\underline{H}$OTs), 7.31 (d, J=8Hz, Ar$\underline{H}$), 7.77 (d, J=8Hz, Ar$\underline{H}$).

mass spectrum: $C_{20}H_{29}NO_3{}^{32}S$, *m/e* calcd. 363.1868, meas. 363.1868(14), 363(14), 362(7), 208(7), 194(7), 193(12), 192(100), 190(13), 91(13), 55(9), 41(10).

2-Methyl-8[2-(1,3-dithiolanyl)]-3a*cis*-9a*cis*-perhydro-9b-azaphenalene, 87

Hemiketal 76 (146 mg) was dissolved in dry THF (10 ml) and treated with pyrrolidine (54 μl, 1 equivalent) and acetic acid (73 μl, 2 equivalents). The solution was heated to reflux under a nitrogen atmosphere for 24 hours. The reaction mixture was worked up as before and ketone 81 was isolated as a pale yellow oil (116 mg, 87%). Ir of this material showed no absorption for starting material and was consistent with the tricyclic ketones isolated previously.

The oil was dissolved in ethanedithiol (1 ml) and freshly distilled borontrifluoride-etherate (140 μl, 2 equivalents) was added. The solution was stirred at room temperature for 12 hours. Water (5 ml) and methylene chloride (5 ml) were added. The aqueous layer was extracted with methylene chloride (5 ml) and the combined extracts were washed with 4N aqueous sodium hydroxide (3 x 5 ml), then water (5 ml), brine (5 ml), dried and evaporated to give a pale yellow oil (125.5 mg), which was one diffuse spot, R_f 0.6, on tlc (alumina, chloroform) and was used in the next step.

ir$_{(CD_2Cl_2)}$: no carbonyl peak.

mass spectrum: $C_{15}H_{25}N^{32}S_2$, m/e calcd. 283.1429, meas. 283.1439. 284(M + 1, 6), 283(27), 282(7), 222(10), 190(16), 164(4), 152(16), 151(100), 150(28), 126(9), 109(5), 108(4), 82(4), 55(7), 54(4).

2-Methyl-*cis*,*cis*,*cis*-perhydro-9b-azaphenalene 88a and 2-methyl-*cis*,*trans*,*cis*-perhydro-9b-azaphenalene, 88b

Crude thioketal 87 (250 mg) was dissolved in 95% ethanol (5 ml) and added to a slurry of W-2 Raney Nickel (approx. 2.8 g) in ethanol (30 ml). The mixture was heated to reflux for one hour, the cooled mixture filtered and the filtrate evaporated to give a pale yellow oil (129.4 mg). A further 8.2 mg was obtained by Soxhlet extraction of the nickel with 95% ethanol (40 ml) for 24 hours.

The reduced material consisted mainly of two compounds (tlc, alumina, chloroform of R_f 0.5 and 0.2). These were separated by preparative tlc on alumina with chloroform as eluent.

The less polar fraction (44.3 mg), 88a.

ir [illegible] 2770, 2710, 2600 (Bohlmann bands).

nmr$_{(C[illegible]}$ δ 0.87 (d, 3, J-5Hz, CH$_3$).

mass sp [illegible] m/[illegible] 193([illegible]9), 192(76), 178(14), 176(10), 152(31[illegible] [illegible]50(22), 137(13), 109(13), 96(14), 95(53), 82[illegible] 8[illegible](8[illegible], 7[illegible]7), 77(13), 69(20), 68(28), 67(90), 57(12), [illegible](13), 55(31), 54(89), 53(30), 52(12), 51(10), 44(12), 4[illegible]28), [illegible](12), 41(100).

The more polar fraction (20.2 mg), 88b

ir$_{\text{(neat)}}$: no Bohlmann bands.

nmr$_{(CDCl_3)}$: δ 0.85 (d, 3, J=6Hz, -C$\underline{H}_3$), 2.7 - 3.1 (m, 3, N-C$\underline{H}$).

mass spectrum: $C_{13}H_{23}N$, m/e calcd. 193.1831, meas. 193.1825(41), 192(87), 178(28), 164(43), 152(45), 151(79), 150(67), 137(35), 136(33), 122(23), 110(17), 108(16), 97(16), 96(23), 94(15), 85(37), 84(15), 83(50), 82(24), 81(23), 80(15), 79(16), 70(15), 69(27), 68(23), 67(31), 60(17), 57(20), 56(20), 55(61), 54(32), 53(24), 47(24), 44(49), 43(33), 42(27), 41(100).

2-Methyl-cis,trans,cis-perhydro-9b-azaphenalene N-oxide, 92

Amine (11 mg) was dissolved in chloroform (2 ml) and treated with a solution of 100% m-chloroperbenzoic acid (15 mg, 1.5 equivalents) in chloroform (1 ml). The solution was stirred at room temperature for four hours, then eluted through basic alumina with further chloroform (25 ml). Evaporation gave a pale yellow solid (10.5 mg).

ir$_{(CDCl_3)}$: 3550, 2490 (hydrated form) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.89 (d, J=6Hz, C$\underline{H}_3$), 3.31 (m, $\searrow$-NC$\underline{H}$).

mass spectrum: $C_{13}H_{23}NO$, m/e calcd. 209.1780, meas. 209.1788(16), 194(9), 193(17), 192(100), 176(8), 164(12), 150(14), 96(13), 82(17), 81(16), 79(11), 69(13), 68(15), 67(26), 56(10), 55(47), 54(20), 53(21), 43(10), 42(10), 41(95), 39(38).

2-Methyl-*cis*,*cis*,*cis*-perhydro-9b-azaphenalene N-oxide, 90

Amine 89 was oxidised to the N-oxide in exactly the same manner as described above.

nmr$_{(CDCl_3)}$: δ 0.91 (d, 3, J=6Hz, C$\underline{H}_3$), 2.84 (m, 3, N-C$\underline{H}$).

^{13}cmr$_{(CDCl_3)}$: δ 73.6(1 carbon), 73.3(2), 35.8(2), 35.6(2), 30.1(1), 27.4(2), 23.4(2), 21.4(1).

mass spectrum: $C_{13}H_{23}NO$, *m/e* calcd. 209.1780, meas. 209.1777(14), 208(7), 194(21), 193(13), 192(75), 176(8), 164(6), 152(9), 150(11), 140(9), 100(29), 96(6), 95(6), 84(14), 82(9), 81(12), 80(6), 79(8), 69(13), 68(11), 67(22), 56(20), 55(56), 54(15), 53(17), 43(13), 42(20), 41(100), 39(38).

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II: TOWARDS THE SYNTHESIS OF LUCIDULINE

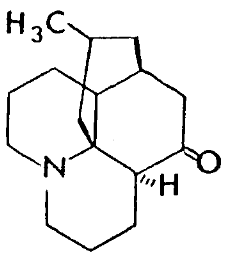
INTRODUCTION

The presence of alkaloids in the genus Lycopodium (family Lycopodiceae) was first observed in 1881 when Bödeker reported the isolation of a base from Lycopodium complanatum L. After five decades of inactivity, research in this area was reported by Achmatowicz and Uzieblo when they isolated and characterized three alkaloids from L. clavatum L. This was followed by a series of publications by Manske and Marion, and then the publication by Weisner and co-workers of the structure of annotinine. Since that time the number of Lycopodium alkaloids isolated and characterized has increased greatly and now at least nine different skeleta are known.

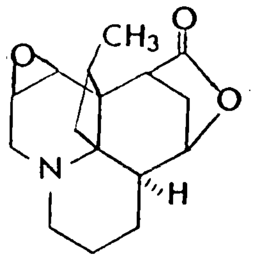
Comprehensive reviews by MacLean[1] and by Ayer[2] give brief descriptions of the work which was carried out on these alkaloids up to 1973.

The alkaloids have been divided into nine groups[2] and a representative of each of these is shown in the following chart.

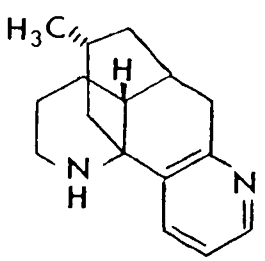
CHART 1



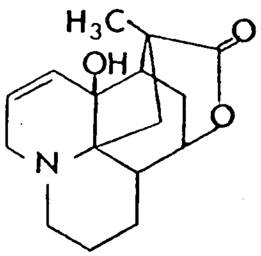
Lycopodine 1



Annotinine 2



Lycodine 3



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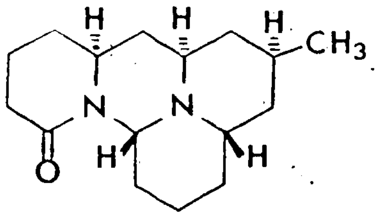
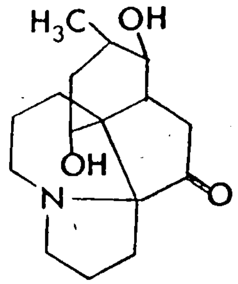
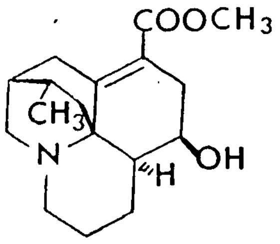


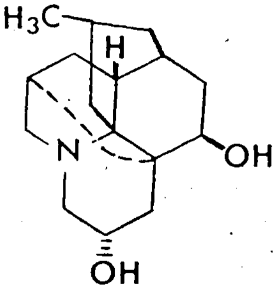
Cernuine 5



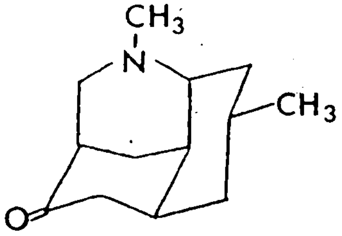
Serratinine 6



Annopodine 7



Debenzoylalopecurine 8

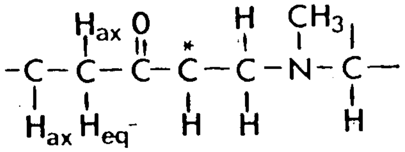


Luciduline 9

At the outset of the work described in this part of the thesis only lycopodine, 1, and annotinine, 2, had been prepared by total synthesis. Since lycodine, 3, has been prepared by transformation of lycopodine, the synthesis of the latter compound represents its (lycodine's) formal synthesis. Dihydrodeoxyepiallocernuine, a degradation product of cernuine has also been synthesised. These syntheses have been reviewed by Ayer[2].

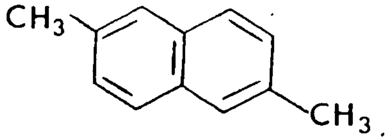
Luciduline, a weakly basic alkaloid isolated from Lycopodium lucidulum, was purified, characterized and its structure elucidated in the 1960's[3]. The alkaloid is a colourless oil which solidifies below room temperature and has empirical formula, $C_{13}H_{21}NO$. Its infrared (ir) spectrum shows absorption bands at 2780 ($N\text{-}CH_3$), 1690 (C=O) and 1400 (methylene adjacent to carbonyl) cm^{-1}. Deuteration ($DCl\text{-}CH_3COOD$, room temperature) leads to luciduline-d_2, which does not show a band at 1400 cm^{-1} in the ir spectrum. Reduction of luciduline with sodium borohydride in methanol gives dihydroluciduline.

A thorough analysis of the nuclear magnetic resonance (nmr) spectra of luciduline, dihydroluciduline, O-acetyldihydroluciduline (prepared by treatment of dihydroluciduline with acetic anhydride-pyridine), luciduline-d_2 and its similar derivatives, enabled the authors to propose part-structure 10 for luciduline[3].



$$-\underset{H_{ax}}{C}-\overset{H_{ax}}{\underset{H_{eq}}{C}}-\overset{O}{\overset{\|}{C}}-\overset{*}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-\overset{CH_3}{N}-\underset{H}{C}-$$

10

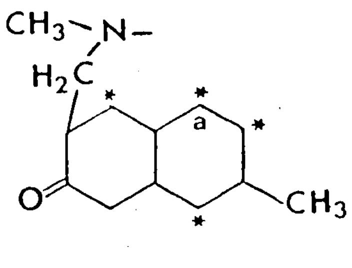


11

The hydrogen at the asterisked carbon is non-enolizable. Further information on the structure of the alkaloid was made available by selenium dehydrogenation of luciduline and dihydroluciduline which both gave, in greater than 30% yield, 2,6-dimethylnaphthalene, 11.

These data coupled with the biogenetic pathway which was then favoured for Lycopodium alkaloids[4,5,6] led to part-structure, 12.

The final bond from the nitrogen must be attached to one of the starred carbons to satisfy the spectral data. Of the starred carbons, only carbon a can be attached to the nitrogen and lead to an essentially strain-free molecule, 13.



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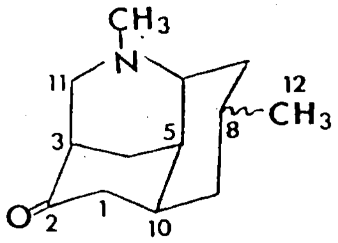
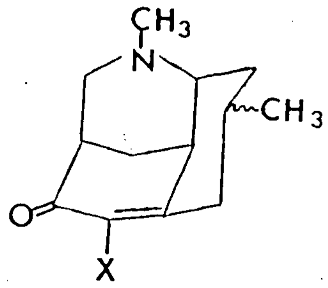


13

Several attempts were made to cleave the ketone-containing ring but all of these were unsuccessful. During this search dehydroluciduline, 14, and bromodehydroluciduline, 15, were prepared.



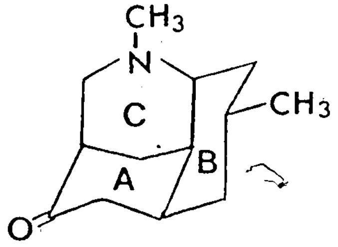
14 X = H
15 X = Br
16 X = OH

The former was obtained when luciduline was oxidized with selenium dioxide in an attempt to prepare the diosphenol 16. Compound 15 resulted when luciduline was treated with two equivalents of bromine in chloroform.

The mass spectra of 14 and 15, along with those of luciduline and dihydroluciduline, were very informative and were completely explainable by fragmentations of structure 13 and its derivatives.

In order to confirm this structure, and to assign the stereochemistry at C-8, p-bromobenzoyldihydroluciduline was prepared, crystallized and subjected to X-ray diffraction. The results of this study verified the proposals and showed that luciduline has the structure and stereochemistry depicted in 9.

As a final chapter to the chemistry of this alkaloid, it was decided to synthesize luciduline in the laboratory. An analysis of the structure shows that there are three types of bicyclic molecules which could act as reasonable synthons.

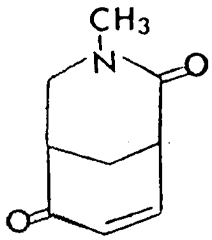


9

Synthesis of a suitably functioned *cis*-decalone corresponding to the A,B rings in 9 and closure of the C-ring is an approach which was originally tested in these laboratories[7,8]. This route was unsuccessful and it was felt that this was due to the conformational mobility of the intermediate *cis*-decalone. An approach *via* the B,C rings with subsequent closure of the A ring also proceeds through a conformationally mobile *cis*-perhydroquinoline derivative.

The remaining approach is *via* a bicyclic compound containing rings A and C. This intermediate would be a functionalized bicyclo[3.3.1]nonane system. Because of its conformational rigidity, and automatic inclusion of the required stereochemistry at the ring junctions, it was decided that this would make an ideal intermediate.

Thus, this part of the thesis describes attempts to synthesize compound 17.

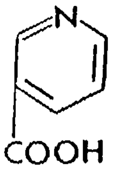


17

It was anticipated that subsequent addition of ring B to this intermediate would lead to luciduline.

DISCUSSION

The starting material for the synthesis of the bicyclic compound 17, was nicotinic acid, 18.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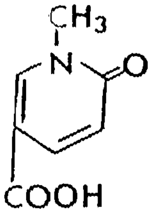
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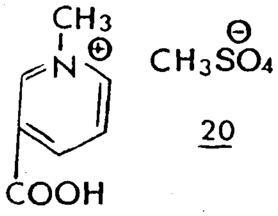
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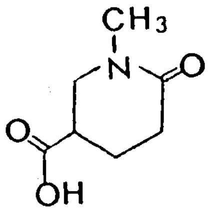
There are two previous reports describing the methylation of this compound to the N-methyl salt and subsequent oxidation to 1-methyl-2(1H)-pyridone-5-carboxylic acid, 19[9]. In both of these methods, acid 18 is treated with dimethyl sulphate to produce the salt 20. The first method of oxidation[9] used 30% aqueous hydrogen peroxide in a solution which was basified by the addition of excess sodium hydroxide. Repetition of the conditions described produced material which from its infrared (ir) spectrum appeared to be inorganic.

The second method described by Bradlow and Vanderwerf[9] uses potassium ferricyanide in basic solution as oxidizing agent. Duplication of these conditions followed by acidification to pH 3.5, using 10% sulphuric acid, precipitated the pyridone-acid, which was isolated by filtration. At this stage the acid was found to be a green-blue colour. This colour, which is presumably due to the presence of ferrous salts formed in the reaction, could not be removed by recrystallization from water. It was found that the best method of purification of the acid was by Soxhlet extraction with diethyl ether. In this way a 59% yield of crystalline acid (m.p. 238 - 239°, Lit.[9] 239.5 - 240.5°) was obtained.

The intermediate required for further elaboration, 1-methyl-2-piperidinone-5-carboxylic acid, <u>21</u>, is available by catalytic hydrogenation of the pyridone-acid. In his book on catalytic hydrogenation[10], Augustine refers to hydrogenation of pyridones and pyridone-acids to the piperidinones making use of platinum oxide in acetic acid at 50 psi[10]. These conditions gave only recovered starting material (ir). Augustine also describes the use of supported rhodium to effect hydrogenation of heteroaromatic molecules[11]. The use of 5% rhodium on charcoal in acetic acid was no more successful than with the platinum catalyst. However, the use of 5% rhodium on alumina (20% by weight of pyridone-acid) in acetic acid at 40 - 50 psi succeeded in the quantitative reduction of <u>19</u> to <u>21</u>. Recrystallization from ethyl acetate-chloroform produced colourless crystals (m.p. 186 - 188°, Lit.[12] 192°).



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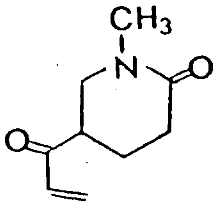

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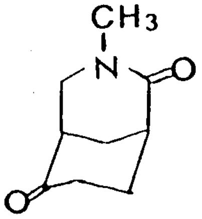

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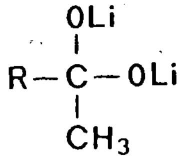


$\mathrm{R{-}\overset{OLi}{\underset{CH_3}{C}}{-}OLi}$

24

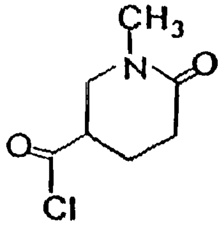
In theory, treatment of compound 22 with a strong base such as sodamide may give the anion at the carbon α to the lactam carbonyl[13]. If this is the case internal Michael-type addition to the vinyl ketone would then produce the bicyclic compound, 23.

Carboxylic acids can be converted into ketones by using organolithium reagents[14]. Thus a synthesis of compound 22 could possibly be performed by reaction of vinyllithium with acid 21. The reaction requires two equivalents of lithium reagent. The first neutralizes the acid to form the lithium salt and the second adds to the carbonyl carbon to produce a dilithiated intermediate such as 24 (if methyllithium is used). It was felt that the second mole of organolithium reagent would not attack the carbonyl carbon of the lactam. This carbon should be a relatively poor electrophile as is generally the case for the carbonyl carbon of amide moieties.

An alternative to the use of two equivalents of organolithium is to preform the lithium carboxylate by addition of an equimolar quantity of lithium hydride to the carboxylic acid[14b]. This is the method which was used here. Following addition of a solution of acid, 21, in anhydrous dioxan to an equivalent of lithium hydride suspended in dioxan and 2½ hours reflux the mixture was cooled to 10°. An equimolar amount of a solution of vinyllithium in tetrahydrofuran (THF) was added and the mixture stirred for two hours. The reaction was quenched with dilute aqueous hydrochloric acid and worked up to give a mixture of an oil and a solid. The solid was shown to be identical with starting acid (ir and mass spectrum). The oil was shown to be mineral oil, originally present in the solution of vinyllithium in THF.

The reaction was repeated, but this time the lithium salt was isolated. The ir spectrum of this solid shows a band due to the lactam carbonyl at 1630 cm^{-1} and a band at 1580 cm^{-1} due to the carboxylate anion. The reaction with vinyllithium was repeated as before to afford two immiscible oils. Mineral oil was isolated by column chromatography over alumina. Elution with chloroform gave a yellow oil, the nuclear magnetic resonance (nmr) spectrum of which shows very little absorption around δ 2.80 for the N-methyl. There are signals attributable to olefinic hydrogens in the region δ 5 - 6. Therefore, it seems that attack by the vinyllithium has occurred at the lactam carbonyl.

The failure of this approach led to an investigation of the possibility of synthesizing 22 from the acid chloride, 25. It is possible to prepare ketones


25

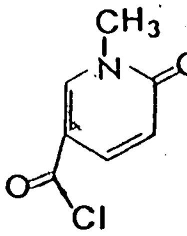
from carboxylic acid halides using organocadmium reagents[15] or organocopperlithium reagents[16]. Unfortunately, it was not possible to find a reliable method to effect the synthesis of the acid chloride. Treatment of a suspension of the acid in dry benzene at 5° with two equivalents of oxalyl chloride[17] gave no reaction, a 90% recovery of starting material being observed. Repetition of the reaction but under reflux conditions gave a 35% recovery of starting material, isolated by filtration of the reaction mixture, together with a dark gum isolated after evaporation of the solvent. The nmr spectrum of this gum in deuteriochloroform had no signal around δ 2.8 for the N-methyl group.

A slight excess of thionyl chloride was added to the acid at room temperature. There was an immediate reaction with evolution of gas and dissolution of the solid. After half an hour the material had solidified and after removal of the remaining thionyl chloride a dark gummy solid was formed. This showed spectral characteristics similar to those observed for the product of the previous reaction. The reaction with thionyl chloride was repeated using methylene chloride as solvent. The gummy solid obtained after work up seemed to contain some acid chloride (ir), but several attempts to form an anilide from this material were unsuccessful.

Perhaps the mildest method for the formation of acid halides is the treatment of the sodium salt of the acid with oxalyl chloride[18]. This method has the advantage that the only by-products are sodium chloride, carbon monoxide and carbon dioxide. The sodium salt was formed by dissolving the acid in water containing an equivalent amount of sodium hydroxide and freeze-drying the solution. Alternatively, the sodium salt could be prepared by treating a solution of the acid in dry diglyme with an equimolar amount of sodium hydride and filtering the precipitated sodium salt. The sodium salt was suspended in dry benzene and treated with a slight excess of oxalyl chloride with a few drops of pyridine added as catalyst. Following work up a dark brown gum was observed. Repeating the reaction with methylene chloride as solvent a yellow solid was obtained and this was shown to be predominantly the acid, 21, (ir, nmr). This result can be explained by formation of the acid chloride and subsequent hydrolysis of this to the acid. Again it proved impossible to form an anilide after repetition of this reaction even when ensuring that anhydrous conditions prevailed until the work up.

These results were very disappointing and frustrating and can possibly be explained by assuming a more basic character for the lactam than was originally suspected. Reaction of the amide nitrogen with acid chloride could then lead to polymeric products which were indeed observed in the majority of cases.

The inability to form the acid chloride resulted in an attempt to functionalize the acid group of the pyridone-acid, 19, prior to reduction of the ring. The first such approach was *via* ketone 27, which could then be hydrogenated and the resulting methyl ketone transformed into the vinyl ketone.



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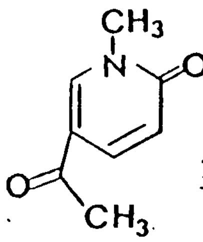
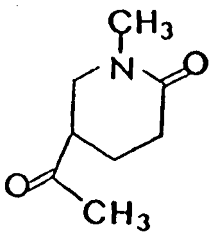


27



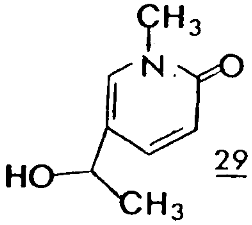
28

Acid chloride, 26, was prepared in quantitative yield by treatment of acid, 19, with thionyl chloride under reflux. The acid chloride displays absorptions at 1760 cm^{-1} for the acid chloride carbonyl and 1680 cm^{-1} for the lactam carbonyl in the ir spectrum. This compound was further characterized by conversion to the anilide. It may be noted that in this case, with the presumably much less basic amide nitrogen, acid chloride formation offers no problem.

As mentioned previously it is possible to convert acid halides to ketones using organometallic reagents[15,16]. An 80% yield of methyl ketone, 27, was obtained when the acid chloride was treated with dimethylcopperlithium in ether at -78°. The nmr spectrum of this ketone displays a 3-proton singlet at δ 2.47 attributed to the methyl ketone and a further singlet at δ 3.65 for the N-methyl group.

Hydrogenation of this methyl ketone over 5%

rhodium on alumina (25% by weight of ketone) in absolute ethanol at 35 psi for four days gave a colourless oil which appeared to be a mixture of two compounds, the alcohol, 30, and ketone, 28, in a ratio of 7:2 (by nmr).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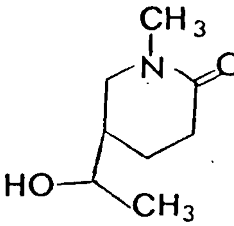
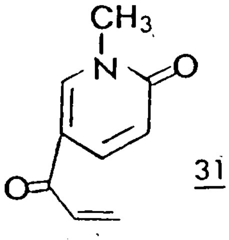

30

The ir spectrum of this mixture displays peaks at 3630 cm^{-1} (OH), 1725 cm^{-1} (C=O), and 1640 cm^{-1} (lactam carbonyl). The spectrum is devoid of peaks at 1700 cm^{-1} and 1675 cm^{-1} attributed to the pyridone-ketone. The nmr spectrum shows a singlet integrating for 3 protons at δ 2.95 (N-C$\underline{H}_3$), a singlet for 2/3 protons at δ 2.22 (CO-C$\underline{H}_3$) and a doublet (J=6Hz) for 2 1/3 protons at δ 1.20. The latter signal appears as two doublets, which can be explained by the formation of the new asymmetric centre at the carbon now bearing hydroxyl thus resulting in two epimers. A shorter period of hydrogenation was found to give a mixture of ketones 27 and 28 accompanied by the alcohols 29 and 30.

The original mixture (i.e., 28 and 30) was treated according to Brown's two-phase oxidation procedure[19] ($Na_2Cr_2O_7$ in H_2SO_4-CH_2Cl_2) and a 25% recovery of a dark oil was obtained. Tlc of this oil (alumina, chloroform) showed a streak along the length of the plate and the oil was not further investigated.

On the assumption that ketone 28 could be prepared satisfactorily it would be necessary to convert this into the vinyl ketone, 22. A short model study was initiated in which attempts were made to synthesize vinyl ketone, 31, from methyl ketone, 29.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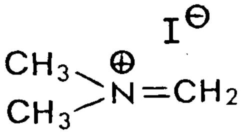
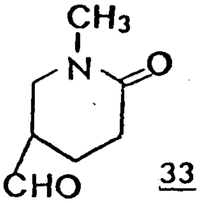

32

In 1971 Eschenmoser described the synthesis of dimethyl(methylene)ammonium iodide, 32[20] and suggested that this reagent could be used in reactions of the Mannich type. Ketone 27 was reacted with 32 using the conditions described[20] and the only compound obtained was found to be identical with starting material (ir and nmr spectra).

Similarly treatment of ketone 29 under Mannich reaction conditions[21] (dimethylamine hydrochloride, paraformaldehyde, ethanolic hydrogen chloride) gave material identical with starting material.

The difficulties which were being observed with this scheme led to consideration of an approach via the aldehyde, 33.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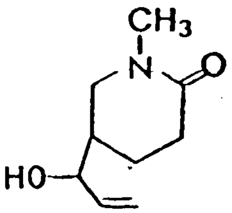
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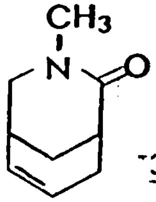
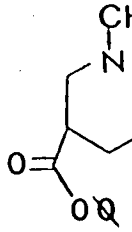

35

Treatment of this aldehyde with vinyllithium should give the allylic alcohol, 34. Conversion of the alcohol to a good leaving group (p-toluenesulphonate for example) followed by treatment with strong base should lead to the bicyclic compound, 35. Alternatively, the alcohol 34, could be oxidized to the vinyl ketone using manganese dioxide and this could be cyclized as suggested previously.

There are two possible routes to 33. Ester derivatives of the piperidinone acid, 21, could be reduced, or the aldehyde grouping could be formed and protected prior to reduction of the pyridone ring. Initially experiments were directed to the first of these possibilities. The piperidinone acid was esterified in 75% yield using absolute ethanol and concentrated sulphuric acid as catalyst. The ethyl ester so produced shows carbonyl absorption in the ir spectrum at 1740 and 1650 cm^{-1}. The nmr spectrum shows a triplet (J=7Hz), integrating for 3 protons at δ 1.28 and a quartet (J=7Hz), 2 protons at δ 4.20 in addition to the singlet for the N-methyl group at δ 2.97. It has been reported[22] that esters can be reduced to aldehydes using diisobutylaluminium hydride in benzene at 5°. Treatment of the ethyl ester with diisobutylaluminium hydride in dry benzene at 5° produced a 40% recovery of a dark brown oil which shows at least four compounds by tlc (alumina, chloroform) and which has an nmr spectrum displaying very little N-methyl at δ 2.95. It appears that the reducing agent has attacked the lactam carbonyl in addition to the ester.

Brown has reported[23] that phenyl esters can be reduced to aldehydes using lithium tri-t-butoxyaluminium hydride (LTBA) in tetrahydrofuran at 0°. Especially he has noted that cyclohexanecarboxaldehyde can be prepared from the corresponding phenyl ester, 37, in 58% yield. Normally phenyl esters can be prepared by proceeding through the acid chloride. However, in the case at hand the acid chloride had been impossible to isolate. Thus a method to form the phenyl ester directly from the acid was required.



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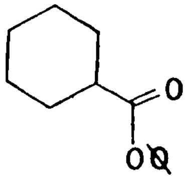
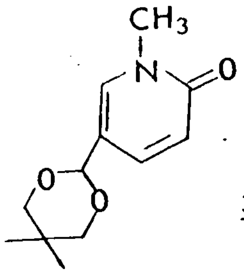


37

A synthesis of the phenyl ester, 36, was realized by heating the acid, 21, phenol and phosphoryl chloride in the ratio 2:2:1 respectively, at 120° for one hour. The phenyl ester was extracted from the residual gum by refluxing with benzene and decanting the resulting solution from the gum containing phosphorus salts. In this manner a 74% yield of phenyl ester was obtained. The ir spectrum of this oil shows carbonyl absorption at 1760 and 1650 cm^{-1}. The phenyl ester was treated with one equivalent of a freshly prepared solution of LTBA in THF at 0° for one hour. The only material obtained from this reaction was an 85% recovery of starting material (ir and tlc). Repetition of the reaction for 24 hours at room temperature was no more successful.

Attempts were then directed to the alternative route, *via* a protected aldehyde such as 38.



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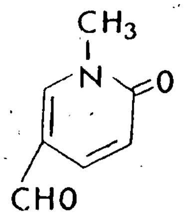
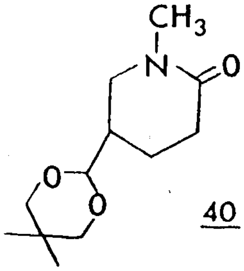


39

The aldehyde, 39, was prepared by Rosenmund reduction of acid chloride, 26[24]. Hydrogen gas was passed through a refluxing solution of the acid chloride in benzene, 5% palladium on barium sulphate being used as catalyst (20% by weight of acid chloride). After four hours there was an approximately 1:1 mixture of acid chloride and desired aldehyde (by nmr). When the reaction was performed in refluxing toluene for four hours it was possible to isolate a 90% yield of the aldehyde, after recrystallization from Skellysolve B-benzene. The nmr spectrum of this aldehyde shows a singlet integrating for one proton at δ 9.63, and the ir spectrum displays a carbonyl peak at 1700 cm^{-1} in addition to that for the lactam carbonyl at 1675 cm^{-1}. Simple acetals of this aldehyde, i.e., ethylene, dimethyl, diethyl, were found to be unstable so it was necessary to use a more stable one, such as that formed from 2,2-dimethyl-1,3-propanediol. This acetal was formed by treatment of equimolar amounts of the aldehyde and the diol with a catalytic amount of p-toluenesulphonic acid in reluxing benzene under a Dean-Stark trap. In a similar fashion 4-methyl-2,4-pentanediol was used and the corresponding acetal isolated.

Hydrogenation of either of these acetals over 5% rhodium on charcoal in ethanol produced the required reduced acetal, 40, for example, but always accompanied by 25 - 50% product of hydrogenolysis.



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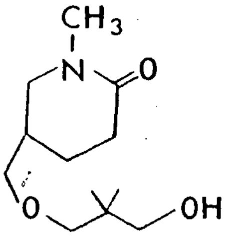


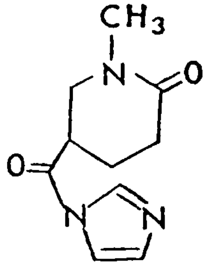
41

The required acetal was purified by chromatography over alumina and elution with benzene. All attempts to isolate the hydrogenolysis product from the column were unsuccessful. The mass spectrum of the crude reaction product, prior to chromatography, displays a peak at m/e 227 for the required product. In addition, there is a peak at m/e 229. The ir spectrum (neat film) of the crude product shows strong absorption at 3420 cm^{-1} attributable to hydroxyl. The nmr spectrum of the purified acetal displays 3-proton singlets at δ 0.73, 1.18 and 2.93 and a one-proton doublet at δ 4.33, J=4.5Hz. The crude product in addition to these peaks has a strong singlet at δ 0.88 and a singlet at δ 3.43 not attributed to the acetal. These spectral characteristics are consistent with structure 41 for the hydrogenolysis product.

Dart and Henbest[25] have reported that hydrogenolysis can be eliminated in the platinum metal hydrogenations by using sodium nitrite as a partial inhibitor. Although no report could be found for the use of this inorganic salt in rhodium metal hydrogenations, it was decided that its effect should be investigated. Sodium nitrite (25% by weight of catalyst) was dissolved in water and added to the hydrogenation mixture. The reaction was much slower (about twice as long was needed before starting material had all disappeared) but the nmr spectrum showed that very little product of hydrogenolysis (less than 2%) was present in the crude reaction mixture. Compound 41 was purified by chromatography.

With the required acetal in hand, conditions for its hydrolysis to the aldehyde were sought. Unfortunately, it appears that both the diols described are far too efficient at protecting aldehydes since under no conditions could hydrolysis of the acetals be achieved. The following methods all led to recovered starting acetal (tlc, ir, nmr): dilute hydrochloric acid in aqueous acetone; aqueous trifluoroacetic acid; 20% aqueous methanolic sulphuric acid; aqueous THF, chloral. Other laboratories report that they have been unable to hydrolyze acetals of 2,2-dimethyl-1,3-propanediol[26].

Staab[27] has reported that imidazolides formed from acids are excellent intermediates for further modification to aldehydes, ketones, etc. They are especially useful when the acid halides are difficult or impossible to prepare. Aldehydes can be formed by reduction of the imidazolide with 0.25 molar equivalents of lithium aluminium hydride.



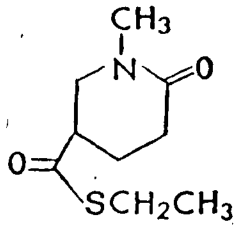
42

Because of the difficulties encountered previously with reduction of the lactam carbonyl, it was expected that lithium aluminium hydride would be too reactive. However, a less reactive hydride such as LTBA should not attack the lactam. In the review, Staab reports that the imidazolides can be prepared from either N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole. The latter reagent is easily prepared *in situ* from thionyl chloride and imidazole so this was the reagent used in this investigation. It is not necessary to isolate the imidazolides; their solutions can be used directly in the following step.

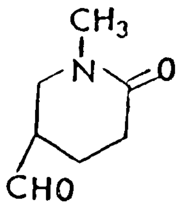
In all cases the imidazolide, 42, was prepared in the following way. Imidazole in dry THF was added to 0.25 molar equivalents of thionyl chloride under nitrogen. To the mixture, now containing N,N'-thionyldiimidazole, was added the acid 21 (equimolar quantity). This mixture was stirred for half an hour then filtered under nitrogen. The solution now containing imidazolide 42 was used in subsequent reactions directly. Treatment with two equivalents of LTBA in THF followed by acid work up gave a yellow solid which was identical with starting acid (ir, nmr).

Treatment of the imidazolide solution with two equivalents of vinyllithium in THF at -78°, followed by acid work up gave a poor yield (approx. 25%) of material showing at least four compounds on tlc (alumina, chloroform). This material was not investigated further.

It has been reported by Spero, McIntosh and Levin[28] that thiolesters can be reduced to aldehydes using partially deactivated Raney Nickel. Although Staab makes no comment on it, it was expected that thiolesters could be synthesized by addition of the sodium salt of the thiol to the imidazolide. Indeed thiolester 43 was prepared in 50% yield by the addition of the sodium salt of ethanethiol to the imidazolide solution. The thiolester has carbonyl absorptions at 1645 cm^{-1} (lactam) and 1680 cm^{-1} (ester) in the ir spectrum.



43



33

Fresh Raney Nickel-W2[29] was deactivated by washing with acetone and then heating to reflux in acetone for two hours. To this mixture was added the thiolester in acetone-water (1:1) and the mixture was refluxed for one hour. Work up of the reaction gave a mixture which showed two spots on tlc (alumina, chloroform). The mixture was separated by chromatography over alumina. Elution with benzene gave the less polar compound which was identical (ir, tlc, nmr) with starting thiolester. The more polar compound was isolated by elution with benzene-ether (1:1). The ir spectrum in chloroform shows a peak at 1640 cm^{-1} for lactam carbonyl and one at 1735 cm^{-1} possibly attributable to aldehyde carbonyl. The mass spectrum has parent at m/e 141, (exact mass $C_7H_{11}NO_2$ calculated 141.0790, observed 141.0788). The nmr spectrum shows a 3-proton singlet at δ 2.97 for the N-methyl and a one-proton singlet at δ 9.70, attributable to an aldehyde proton. Examination of structure 33 predicts that this resonance should be a doublet, but vicinal couplings to aldehydes are small.

At this time it became intriguing to consider whether this aldehyde could be synthesized from the acid *via* the acyl nitrile. In principle, the reduction of acyl nitriles should produce cyanohydrins, which on base hydrolysis would yield aldehydes. Application to the synthesis of aldehyde, 33, would necessitate a synthesis of acyl nitriles from acids which did not proceed *via* the acid halide, since this had been impossible to synthesize.

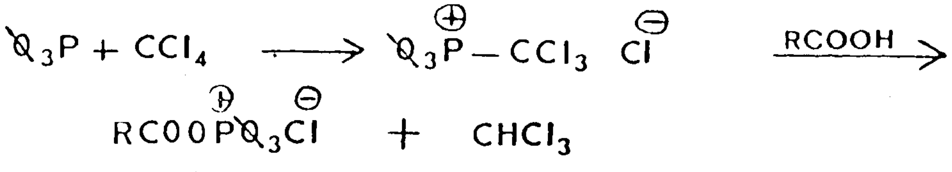
A literature search produced only one method for the synthesis of acyl nitriles - the reaction of acyl halides with inorganic cyanides[31]. The conditions of synthesis are quite drastic since they involve heating the acid halide to its melting point in the presence of cuprous cyanide in the absence of solvent. The acyl cyanide is then distilled from the flask. Apart from the high temperatures employed, of major concern is that acyl chlorides and acyl cyanides have very similar boiling points (for benzoyl chloride and benzoyl cyanide, 195° and 205° respectively[31]).

Ideally, then, a new method for synthesizing acyl cyanides should be much milder than the one already mentioned. Of the common organic solvents, only alcohols are polar enough to dissolve the inorganic cyanides. However, alcohols react with acyl cyanides to form esters and hydrogen cyanide[32]. To enable the use of less polar solvents, to which the acyl cyanides are unreactive, an organic soluble source of cyanide ion is required. Tetraalkylammonium halides are excellent sources of organic soluble halide ion[33], so the ammonium cyanides should have similar properties. This soluble cyanide ion source could then be used to effect nucleophilic substitution on a suitably activated carbonyl group.

A Dowex-1X8 anion exchange column was converted to cyanide ion form by washing the column with aqueous sodium cyanide. Repeated rinsing to remove excess cyanide [illegible] a column suitable for the required transformation. Tetrabutylammonium iodide was dissolved in water and eluted through the column. Evaporation and drying followed by recrystallization from ethyl acetate produced tetrabutylammonium cyanide (Bu_4NCN) as colourless needles. The ir spectrum in chloroform shows absorption at 2080 cm^{-1} attributed to cyanide. In a similar way the tetramethyl and tetraethyl salts were also prepared. The tetramethyl salt does not possess solubility advantages since it is insoluble in such solvents as THF, ether and benzene. The tetrabutyl salt, in contrast, is readily soluble in all of these solvents. However, it is extremely hygroscopic necessitating use of the dry box to facilitate weighing and transfer.

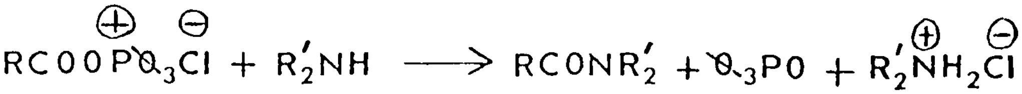
Throughout the work benzoic acid was used as substrate the desired cyanide then being benzoyl cyanide. There is a literature preparation of benzoyl cyanide from benzoyl chloride[31] and this was repeated to enable comparison of crude mixtures with an authentic sample of the required product. Benzoyl cyanide has a very distinctive peak at 1680 cm^{-1} in the ir spectrum and this peak was used as criterion for the presence or absence of benzoyl cyanide in the crude reaction mixtures.

Several methods for activation of carboxylic acids to nucleophilic attack were used and the resulting intermediates treated with one or other of the tetraalkylammonium salts. Barstow and Hruby have published a synthesis of amides from acids <u>via</u> the triphenylphosphonium salt, **44**[34].



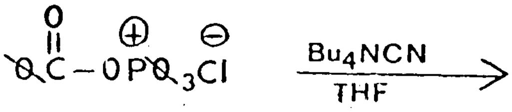
$$\phi_3P + CCl_4 \longrightarrow \phi_3\overset{\oplus}{P}-CCl_3\ \overset{\ominus}{Cl} \xrightarrow{RCOOH} RCOO\overset{\oplus}{P}\phi_3\overset{\ominus}{Cl} + CHCl_3$$

44



$$RCOO\overset{\oplus}{P}\phi_3\overset{\ominus}{Cl} + R'_2NH \longrightarrow RCONR'_2 + \phi_3PO + R'_2\overset{\oplus}{N}H_2\overset{\ominus}{Cl}$$

The intermediate acyloxyphosphonium salt 45, was formed by treatment of triphenylphosphine with carbon tetrachloride in refluxing THF followed by cooling to 0° and addition of an equimolar quantity of benzoic acid.



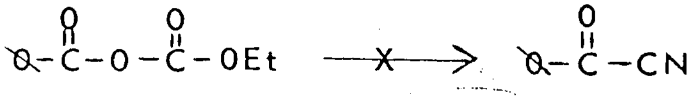
$$\phi\overset{O}{\overset{\|}{C}}-O\overset{\oplus}{P}\phi_3\overset{\ominus}{Cl} \xrightarrow[THF]{Bu_4NCN}$$

45

After stirring for half an hour an equimolar amount of Bu_4NCN in THF was added. The precipitated salt 45 dissolved and a red solution was formed. One hour's reflux followed by evaporation of the solvent gave an olive-green syrup. The ir spectrum (in chloroform) of this material is devoid of absorption around 1680 cm^{-1}. The material was not investigated further.

The remainder of the work towards the synthesis of benzoyl cyanide was directed to methods via anhydrides. In the first such method benzoic acid was treated with p-toluenesulphonyl chloride in acetonitrile containing pyridine. This mixture was refluxed for half an hour then a slurry of two equivalents of tetramethylammonium cyanide (Me_4NCN) in acetonitrile was added. After a further period of reflux the mixture was worked up to produce an oil which shows peaks at 1790 and 1730 cm^{-1}, attributable to benzoic anhydride, in the ir spectrum. In addition there is strong absorption at 1680 cm^{-1} and all the peaks characteristic of the fingerprint region of the spectrum of benzoyl cyanide are present. This reaction presumably takes place via benzoic anhydride[35] so the yield could never be better than 50%. However the promising result suggests that some form of mixed anhydride may serve to activate the acid.

Mixed anhydride, 46, can be synthesized by treatment of benzoic acid with equimolar amounts of ethyl chloroacetate and triethylamine in acetonitrile[36].



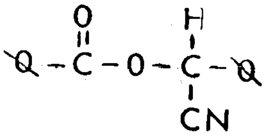
$$\phi-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-OEt \nrightarrow \phi-\overset{O}{\overset{\|}{C}}-CN$$

46

Micucci and co-workers have shown that mixed anhydrides formed from ethyl chloroacetate and the acid can be used for a high yield synthesis of amides[36]. Treatment of the mixed anhydride in acetonitrile with a solution of tetraethylammonium cyanide (Et_4NCN) in acetonitrile gave a product which showed no absorption at 1680 cm^{-1} in the ir spectrum.

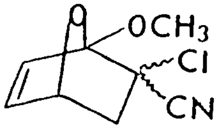
The benzoyl cyanide which had been synthesized earlier allowed experiments to be directed towards the reduction to the cyanohydrin. Addition of a solution of benzoyl cyanide in dimethoxyethane (DME) to a slurry of sodium borohydride in the same solvent resulted in an immediate exothermic reaction. Work up gave a liquid (b.p. 164 - 166°, 1 mm) which crystallized on standing at room temperature. The nmr spectrum of this material displays absorption for ten aromatic protons in addition to a one-proton singlet at δ 6.70. The ir spectrum in chloroform shows a carbonyl peak at 1735 cm^{-1}, but no absorption for cyanide in the 2100 - 2250 cm^{-1} region. The mass spectrum shows a parent peak at <u>m/e</u> 237 with a strong peak at <u>m/e</u> 116 and the base peak at <u>m/e</u> 105.

These spectra are consistent with structure <u>47</u>.



$$\phi-\overset{\overset{O}{\parallel}}{C}-O-\underset{\underset{CN}{|}}{\overset{\overset{H}{|}}{C}}-\phi$$

47



48

This compound contains two electron-withdrawing substituents on the carbon bearing the cyano-group and this could explain the absence of absorption for this functionality in the ir spectrum. Compound 48 prepared in these laboratories[37] is also devoid of absorption in the 2100 - 2250 cm^{-1} region in the ir spectrum and this compound also bears an electron-withdrawing substituent on the α-carbon.

Compound 47 was also obtained when benzoyl cyanide was treated with sodium bis(2-methoxyethoxy)-aluminium hydride (Red-Al) in ether at -78° or with lithium borohydride in THF. Increasing the dilution of the reactants in these reductions and changes in the rate of addition had no effect on the production of this cyanoester.

When 47 was dissolved in THF and treated with 2% aqueous potassium hydroxide for one hour an organic soluble portion and a base soluble portion were isolated. The organic soluble portion shows a carbonyl band at 1705 cm^{-1} and two weak bands at 2820 and 2730 cm^{-1}. These peaks are identical with those observed in the spectrum of benzaldehyde. The base soluble portion, isolated by acidification followed by extraction with ether, gave a colourless solid, the ir spectrum of which was identical with that of benzoic acid. Thus the ester has been hydrolysed to produce the desired aldehyde. However this route can only give, at best, a 50% yield of aldehyde.

Treatment of 47 with a solution of 0.25 equivalents of lithium aluminium hydride in ether at room temperature gave an oil which seems to be a mixture of 47 and benzyl alcohol (ir, nmr). Thus benzaldehyde, formed from 47 must be more readily attacked by the hydride than is 47.

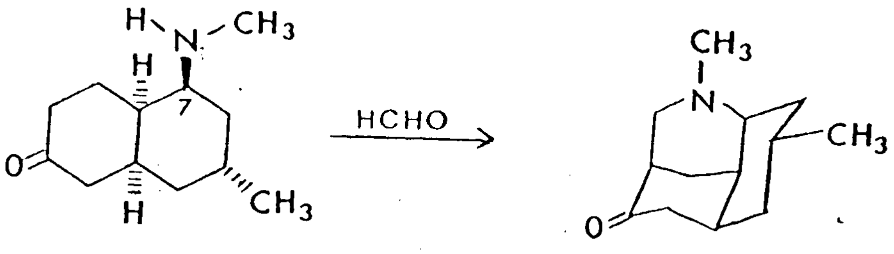
When benzoyl cyanide was treated with Red-Al (0.5 equivalents) in ether at -78° only compound 47 was isolated and this was isolated unchanged when treated with more Red-Al at -78°. When benzoyl cyanide was reacted under the same conditions but at -40° the reduction product showed peaks attributable to benzaldehyde at 2820, 2730 and 1705 cm^{-1} in the ir spectrum (neat film). In addition there is strong absorption at 3400 cm^{-1} possibly due to benzyl alcohol. There are no peaks in the spectrum arising from benzoyl cyanide or 47. Thus it seems 47 is the first reduction product and that this is then further reduced to aldehyde. The complete lack of 47 from the product of the reaction at -40° suggests that this compound is reduced to the aldehyde in preference to reduction of the aldehyde to alcohol. A slight excess of reducing agent must have been present in this reaction and if exactly equivalent amounts of hydride and acyl cyanide are present, then the aldehyde should result as the only product.

Therefore the possibility of both parts of the reduction scheme have been demonstrated, i.e.,

$$\text{R-COOH} \longrightarrow \text{RCOCN} \longrightarrow \text{RCHO}$$

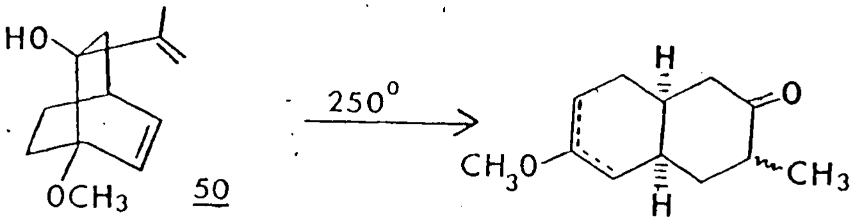
However, further work is necessary before the method could be used for the attempted synthesis of 33.

At this time the total synthesis of (±)-luciduline was reported by Scott and Evans[30]. Their synthesis was completed by forming rings A and B first (structure 9) with final closure of ring C.



49

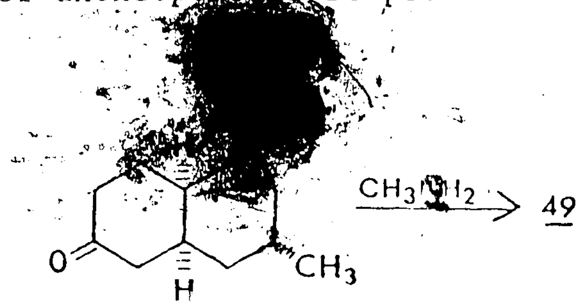
Thus intermediate 49 was refluxed with paraformaldehyde in 3-methylbutan-1-ol for 20 hours to give (±)-luciduline. The key step in this synthesis was the oxy-Cope rearrangement of 50 to 51.



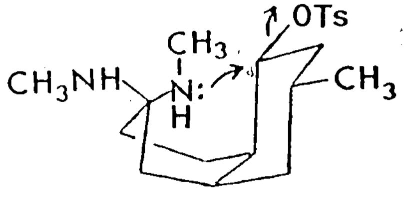
50

51

Thus the cis-decalin system with required functionality was formed. The desired α-methyl epimer of 51 predominated and could be isolated by recrystallization of the mixture from hexane. More of the desired epimer was obtained by re-equilibration-crystallization of the mother liquors. 51 was transformed into 52 in a series of unexceptional steps.



52



53

52 was treated with excess methylamine in benzene in a sealed tube at 75° for 24 hours. It was postulated that this substitution reaction occurred through aminal intermediate 53, thus giving compound 49 with the correct stereochemistry at C-7 (luciduline numbering).

At this point the similarity in structure between cernuine and coccinellin was a great attraction. Since the synthesis of luciduline had been accomplished by Evans, the work lost some of its urgency, and work on this project was suspended until the planned synthetic approach to coccinellin had been investigated. This latter work has required more time than was anticipated and the work on the luciduline synthesis has not been resumed.

EXPERIMENTAL

Solutions were dried over anhydrous magnesium sulphate unless otherwise specified.

R_f value = distance moved by compound/distance moved by solvent.

Melting points were determined on a Fischer-Johns or Leitz-Wetzlar hot-stage melting point apparatus and are uncorrected.

Microanalyses were performed by the Microanalytical Laboratory of this department.

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer, a Unicam SP1000 grating infrared spectrophotometer, or a Perkin-Elmer Model 421 dual grating infrared spectrophotometer.

Nuclear magnetic resonance spectra were measured using a Varian Associates Model A-60 spectrometer or a Varian Model HR-100 spectrometer with tetramethylsilane as internal standard.

Mass spectra were recorded on an A.E.I. Model MS-9 mass spectrometer or an A.E.I. Model GC/MS mass spectrometer with a WB separator.

1-Methyl-2(1H)-pyridone-5-carboxylic acid, 19

Nicotinic acid (50 g) and dimethyl sulphate (80 ml) were heated together at 110° for one hour. The solution was cooled, diluted with water (100 ml) and washed three times with chloroform (20 ml). To the resulting aqueous solution was added 2.5N aqueous sodium hydroxide (1150 m) and, dropwise, 32% aqueous potassium ferricyanide (870 ml). The solution was stirred for 2 hours following addition, then adjusted to pH 3.5 with dilute sulphuric acid. The precipitated acid was filtered and dried, then extracted with ether using a Soxhlet extractor to give a cream crystalline solid (36.4 g, 59%) m.p. 238 - 239° [lit.[9] 239.5 - 240.5°]. nmr$_{(DMSO\text{-}d6)}$: δ 3.53 (s, 3, -C$\underline{H}_3$), 6.42 (d, 1, J=9.5Hz, -N-CO-C$\underline{H}$), 7.78 (dd, 1, J=9.5 Hz, J'=2.5Hz, -N-COCH=C$\underline{H}$-), 8.44 (d, 1, J=2.5Hz, -N-C$\underline{H}$=), 12.65 (br. s, 1, COO$\underline{H}$). mass spectrum: $C_7H_7NO_3$, m/e calcd. 153.0426, meas. 153.0426(100), 125(15), 108(32), 95(10), 44(21), 42(20), 39(17).

1-Methyl-2-piperidinone-5-carboxylic acid, 21

Pyridone acid 19 (10 g) was dissolved in acetic acid (250 ml) and hydrogenated at 50 psi over rhodium on alumina (2 g) at room temperature for three days. The bulk of the catalyst was filtered (a small amount dissolved in the acetic acid) and the solution evaporated. The residue was digested with methanol, the solution filtered and evaporated to give a colourless solid which was recrystallized from ethylacetate-chloroform to give 21 (9.4 g, 91%) m.p. 186 - 188° [lit.[12] 193°].

ir$_{(nujol)}$: 1730 (C=O), 1620 (C=O) cm^{-1}.

nmr$_{(pyr\text{-}d5)}$: δ 2.95 (s, 3, N-C$\underline{H}_3$), 13.22 (s, 1, -COO$\underline{H}$).

mass spectrum: $C_7H_{11}NO_3$, m/e calcd. 157.0739, meas. 157.0735(45), 101(39), 86(14), 76(12), 57(20), 55(25), 44(100), 42(22).

Reaction of lithium 1-methyl-2-piperidinone-5-carboxylate with vinyllithium

a) Lithium hydride (100 mg, 0.0125 m) was suspended in anhydrous dioxan (10 ml). To this suspension under nitrogen was added lactam-acid 21 (1.57 g, 0.01 m). The mixture was heated under reflux for 2½ hours, cooled to 10° and a solution of vinyllithium in THF (4.5 ml, 0.012 m) was added. The mixture was stirred at room temperature for two hours then poured slowly into 5% aqueous HCl (35 ml). The aqueous solution was saturated with sodium chloride and the organic phase separated. The aqueous layer was extracted with ether (3 x 25 ml) and the combined organic layers were dried and evaporated to give a colourless semi-solid (0.94 g). This was digested with ether. The solid which remained was filtered, washed and dried and shown to be identical with starting material (0.23 g). The ether-soluble portion (0.63 g) was shown to be mineral oil (from the vinyllithium solution).

b) Lactam-acid 41 (g) and lithium hydride (65 mg, one equivalent) were heated to reflux in diglyme (40 ml) under nitrogen for 17 hours. The cooled mixture was filtered and the solid washed with ether and dried to give the lithium salt (0.98 g, 97%).

ir$_{\text{(nujol)}}$: 1630 (C=O), 1580 ($-COO^{\ominus}$) cm^{-1}.

The lithium salt (0.98 g) was suspended in THF (20 ml) under an atmosphere of nitrogen. A solution of vinyllithium in THF (3.0 ml, one equivalent) was added and after the exothermic reaction had subsided the mixture was stirred at room temperature for three hours. The mixture was poured into 5% aqueous HCl and worked up as in a) to give two immiscible oils (0.92 g). The oils were separated by chromatography on alumina (30 g). Elution with Skellysolve B produced mineral oil (0.59 g). Elution with chloroform produced a pale yellow oil (0.25 g) which shows two spots on tlc (alumina, chloroform .

ir$_{(CHCl_3)}$: 3630, 3440 (OH), 1735 (C=O), 1640 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: very weak absorption at δ 2.81 for the N-methyl group. Olefinic protons between δ 5 - 6 are present.

Attempted syntheses of 1-methyl-2-piperidinone-5-carboxylic acid chloride, 25

a) Oxalyl chloride in benzene, 5°

Lactam-acid, 21 (628 mg, 0.004 m) was suspended in dry benzene (10 ml) at 5°. Oxalyl chloride (0.7 ml, 0.008 m) dissolved in benzene (5 ml) was added and the solution stirred for one hour at 5°, then five hours at room temperature. The mixture was filtered and the solid obtained washed with benzene and dried (562 mg). This was shown to be identical with acid 21 (ir, mass spectrum).

b) Oxalyl chloride in refluxing benzene

A mixture prepared as above was heated under reflux for four hours, after which time the mixture was deep red. The cooled mixture was filtered and the filtrate evaporated to give a dark gum (743 mg).

ir$_{(neat)}$: 1790, 1745 ($(COCl)_2$), 1670, 1635, 1170, 1000, 865 cm^{-1}.

nmr$_{(CDCl_3)}$: no singlet around δ 2.8 for the N-methyl group.

The [illegible] from the filtration was washed with benzene and dried to give a colourless solid identical with starting material (188 mg, 35%; ir, mass spectrum).

c) Thionyl chloride

Thionyl chloride (0.4 ml, 0.0055 m) was added to acid 21 (628 mg, 0.004 m). There was an immediate reaction and after ½ hour a dark gummy solid had formed. This material had similar spectral characteristics to the gum isolated in b).

d) Thionyl chloride in methylene chloride

Lactam-acid 21 (500 mg) was suspended in methylene chloride (20 ml) and thionyl chloride (0.9 ml, 1.5 equivalents) was added. The mixture was heated under reflux under a nitrogen atmosphere for three hours, then evaporated to give a yellowish solid (511 mg).

ir$_{(CH_2Cl_2)}$: 1795, 1660 cm^{-1}.

This was taken up in ether (10 ml). The solid which would not dissolve was removed by filtration and the filtrate treated with aniline (1 ml) in ether (5 ml). The solution was heated under reflux for ½ hour then washed with water (10 ml), 5% aqueous HCl (10 ml) then water (10 ml), dried and evaporated to give a dark oil (3 mg) which was not investigated further.

e) Treatment of the sodium salt of lactam-acid 21 with oxalyl chloride in benzene

Lactam-acid 21 (471 mg, 0.003 m) was stirred with 2% aqueous sodium hydroxide (0.003 m) for five minutes. The water was evaporated and the residue dried by evaporation at 1 mm. overnight. (Alternatively the sodium salt could be prepared by treating a solution of the acid, in dry diglyme with one molar equivalent of sodium hydride.)

The sodium salt was treated with oxalyl chloride (1 ml) dissolved in dry benzene (15 ml). Pyridine (4 drops) was added and the mixture was stirred at room temperature for 18 hours and the dark solid was removed by filtration. The solution was evaporated to give a gum similar to that observed in b) and c).

1-Methyl-2(1H)-pyridone-5-carboxylic acid chloride, 26

Acid 19 (2 g) was refluxed for three hours with thionyl chloride (5 ml). The excess thionyl chloride was evaporated to leave a colourless solid (2.2 g, 100%). $\mathrm{ir}_{(CH_2Cl_2)}$: 1760 (C=O), 1680 (C=O) cm^{-1}.

250 mg acid chloride 26 was converted into the anilide, which was recrystallized from chloroform,

m.p. 174 - 175.5°.

ir$_{(CHCl_3)}$: 1695 (C=O), 1680 (C=O) cm^{-1}.

nmr$_{(DMSO-d6)}$: δ 3.57 (s, 3, N-C$\underline{H}_3$), 6.37 (d, 1, J=9.5Hz, N-CO-C$\underline{H}$=), 7.0 - 8.0 (m, 5, Ar$\underline{H}$), 8.08 (dd, 1, J=9.5Hz, J'=2.5Hz), 8.53 (d, 1, J=2.5Hz, N-C$\underline{H}$=).

mass spectrum: m/e 228(38), 137(13), 136(100), 108(8), 95(27), 93(12), 80(7), 79(6), 77(6), 68(6), 66(9), 65(9), 51(8), 42(27), 39(17).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26; N, 12.28.
Found: C, 68.54; H, 5.38; N, 12.01.

5-Acetyl-1-methyl-2(1H)-pyridone, 27

Cuprous iodide (1.15 g, 0.006 m) was suspended in dry THF (15 ml) at 0° under a nitrogen atmosphere and a solution of methyllithium in ether (2.2$\underline{M}$, 5 ml, 0.011 m) was added. The dark solution was stirred for 10 minutes and then cooled to -78°. Acid chloride (347 mg, 0.002 m) was dissolved in dry THF (10 ml) and added dropwise to the solution. The mixture was stirred for 30 minutes at -78° and quenched with methanol (5 ml). The mixture was allowed to warm to room temperature and then partitioned between water (20 ml) and chloroform (30 ml). The aqueous layer was extracted with $CHCl_3$ (2 x 15 ml) and the combined organic solution was washed with water (15 ml), dilute sodium bicarbonate (15 ml), water (15 ml), brine (2 x 15 ml) dried and evaporated to give crude solid (240 mg, 80%). This was recrystallized from benzene, m.p. 163.5 - 165°.

ir$_{(CHCl_3)}$: 1700 (C=O), 1675 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 2.47 (s, 3, -C$\underline{H}_3$), 3.65 (s, 3, N-C$\underline{H}_3$), 6.55 (d, 1, J=9.5Hz), 7.88 (dd, 1, J=9.5Hz, J'=2.5Hz), 8.20 (d, 1, J=2.5Hz).

mass spectrum: m/e 151(71), 137(8), 136(100), 108(14), 95(20), 80(7), 43(12), 42(18).

Anal. Calcd. for $C_8H_9NO_2$: C, 63.58; H, 5.96; N, 9.27.

Found: C, 63.59; H, 6.04; N, 9.17.

Reduction of 5-acetyl-1-methyl-2(1H)-pyridone, 27

Keto-lactam 27 (115 mg) was dissolved in absolute ethanol (20 ml) and hydrogenated at 35 psi over Rh-Al_2O_3 (30 mg) for four days. The catalyst was removed by filtration and the ethanol evaporated to give a colourless oil (116 mg).

ir$_{(CHCl_3)}$: 3630 (-OH), 1725 (C=O), 1640 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$ of 28: δ 2.22 (s, 3, -COC$\underline{H}_3$), 2.95 (s, 3, -NC$\underline{H}_3$).

nmr$_{(CDCl_3)}$ of 30: δ 1.20 (d, 3, J=6Hz, CHC$\underline{H}_3$), 2.95 (s, 3, -NC$\underline{H}_3$).

This oil is apparently a 2:7 mixture of 28:30 (by nmr).

Attempted oxidation of 28 and 30

Hydrogenation mixture, 28 and 30, (116 mg) was dissolved in methylene chloride (5 ml) and water (5 ml) added. To this was added a standard solution of sodium dichromate in sulphuric acid (0.39 ml). The two-phase system was stirred at room temperature for two hours. After this time there was no change in colour of the sodium dichromate. The layers were separated, the aqueous phase washed with methylene chloride and the combined organic solution washed with dilute sodium bicarbonate (5 ml), dried and evaporated to give a dark oil (30 mg). Tlc (alumina, chloroform) of this oil shows a streak along the length of plate.

Attempted reaction of 27 with dimethyl(methylene)ammonium iodide[20]

Keto-lactam 27 (100 mg) was dissolved in dry THF (10 ml) and was treated with dimethyl(methylene)ammonium iodide (137 mg) and triethylamine (10 drops). The mixture was stirred at room temperature for 24 hours. The mixture was filtered and the filtrate evaporated to give a solid material (99 mg) identical with 27 (ir, tlc).

Ethyl 1-methyl-2-piperidinone-5-carboxylate

Acid 21 (3.1 g) was dissolved in absolute ethanol (25 ml) and concentrated sulphuric acid (1.5 ml) added. The solution was heated under reflux for ten hours. The cooled solution was partitioned between water (25 ml) and chloroform (25 ml). The aqueous solution was extracted with chloroform (2 x 25 ml) and the combined organic solution washed with dilute sodium bicarbonate solution (25 ml), brine (25 ml) and dried. Evaporation of the solvent gave a colourless oil (2.69 g, 77%) b.p. 193 - 195°, 1 mm.

$\mathrm{ir}_{(\mathrm{neat})}$: 1740 (C=O), 1650 (C=O) cm^{-1}.

$\mathrm{nmr}_{(\mathrm{CDCl_3})}$: δ 1.28 (t, 3, J=7Hz, $OCH_2C\underline{H}_3$), 2.97 (s, 3, N-$C\underline{H}_3$), 4.20 (q, 2, J=7Hz, $C\underline{H}_2CH_3$).

mass spectrum: $C_9H_{15}NO_3$, m/e calcd. 185.1052, meas. 185.1052(51), 140(23), 130(6), 129(76), 128(8), 114(28), 113(8), 112(75), 111(11), 101(10), 86(16), 85(16), 84(58), 83(10), 82(7), 70(12), 68(17), 58(8), 57(70), 56(10), 55(75), 54(9), 53(7), 45(12), 44(100), 43(11), 42(52), 41(18), 39(19).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56.

Found: C, 58.30; H, 8.42; N, 7.60.

Reduction of ethyl 1-methyl-2-piperidinone-5-carboxylate with diisobutylaluminium hydride (DIBAL)

The ester (190 mg) was dissolved in dry benzene (10 ml) under a nitrogen atmosphere and the solution cooled to 5°. To this was added 25% DIBAL in benzene (1 ml, one equivalent) and the solution stirred for one hour. The solution was quenched with saturated aqueous ammonium chloride and the aqueous layer extracted with chloroform (2 x 15 ml). The combined organic solution [illegible] dried and evaporated to give an orange-brown oil (70 mg) showing at least four compounds by tlc (alumina, chloroform). nmr$_{(CDCl_3)}$: very weak singlet at δ 2.95 (the N-methyl group).

Phenyl 1-methyl-2-piperidinone-5-carboxylate, 36

Lactam acid 21 (1.57 g, 0.01 m), phenol (0.94 g, 0.01 m) and phosphoryl chloride (0.46 ml, 0.005 m) were heated on an oil-bath to 120° for one hour[38]. Benzene (20 ml) was added and the mixture stirred and heated under reflux for one hour. The benzene solution was decanted from the dull yellow gum, the gum was washed with more benzene and the combined fractions evaporated to give a colourless oil (1.12 g).

The residual gum was digested with methylene chloride in a similar manner and a further 610 mg oil was obtained, which by tlc (alumina, chloroform) was a single spot identical with the former product. Total yield: 1.72 g, 74%.

$\mathrm{ir}_{(\mathrm{neat})}$: 1760 (C=O), 1650 (C=O) cm^{-1}.

$\mathrm{nmr}_{(\mathrm{CDCl_3})}$: 3.03 (s, 3, $-\mathrm{NC}\underline{\mathrm{H}}_3$), 7.0 - 7.5 (m, 5, Ar$\underline{\mathrm{H}}$).

mass spectrum: $C_{13}H_{15}NO_3$, *m/e* calcd. 233.1052, meas. 233.1061(22), 189(15), 177(6), 149(55), 112(90), 95(7), 94(100), 84(22), 66(10), 65(12), 55(71), 44(95), 42(13), 39(13).

Attempted reduction of 36 with lithium tri-*t*-butoxyaluminium hydride (LTBA)

Phenyl ester 36 (1.11 g) was dissolved in dry THF (8 ml) under nitrogen atmosphere. The solution was cooled to 0° and a solution of LTBA in THF (0.8*M*, 6.3 ml, one molar equivalent) was added dropwise. The solution was stirred for one hour then worked up as previously described[23]. The oil so produced (916 mg) was identical with starting material (ir, tlc).

1-Methyl-2(1H)-pyridone-5-carbaldehyde, 39

Acid chloride 26 (10 g) was dissolved in freshly distilled toluene (500 ml) and 5% palladium on barium sulphate (1.2 g) added. The stirred mixture was heated under reflux, while hydrogen gas was passed through it, for 20 hours. The mixture was filtered and the golden solution was evaporated to give a pale yellow solid (7.2 g, 90%) which was recyrstallized from Skellysolve B-benzene m.p. 123 - 124°.

ir$_{(CH_2Cl_2)}$: 1700 (shoulder C=O), 1675 (C=O), 1630 (C=C) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 3.67 (s, 3, N-C$\underline{H}_3$), 6.58 (d, 1, J=9.5Hz, N-CO-C$\underline{H}$=), 7.80 (dd, 1, J=9.5Hz, J'=2.5Hz, CO-CH=C$\underline{H}$-), 8.03 (d, 1, J=2.5Hz, N-C$\underline{H}$=), 9.63 (s, 1, C$\underline{H}$O).

mass spectrum: $C_7H_7NO_2$, m/e calcd. 137.0477, meas. 137.0478(100), 136(18), 108(37), 95(8), 81(15), 80(21), 42(13), 39(10).

Anal. Calcd. for $C_7H_7NO_2$: C, 61.31; H, 5.11; N, 10.22.

Found: C, 61.43; H, 4.96; N, 10.11.

5-[2-(5,5-dimethyl-1,3-dioxanyl)]-1-methyl-2(1H)-pyridone

Aldehyde 39 (137 mg), 2,2-dimethyl-1,3-propanediol (104 mg) and p-toluenesulphonic acid (20 mg) were dissolved in benzene (20 ml) and allowed to reflux under a Dean-Stark trap for six hours. Solid sodium carbonate was added to the cooled solution and after stirring for five minutes the mixture was filtered and the filtrate evaporated to give a colourless solid (208 mg, 93%) which was recrystallized from Skellysolve B-benzene, m.p. 122 - 123.5°.

ir$_{(CHCl_3)}$: 1680 (C=O), 1620, 1610 (C=C), 1100 (C-O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.78 (s, 3, -C$\underline{H}_3$), [illegible]5 (s, [illegible] C$\underline{H}_3$), 3.51 (s, 3, -NC$\underline{H}_3$), 3.65 (s, 4, -C$\underline{H}_2$O), 5.17 (s, 1, C$\underline{H}$ acetal), 6.50 (d, 1, J=10.5Hz, Ar$\underline{H}$), 7.2[illegible] (m, 2, -Ar$\underline{H}$).

mass spectrum: m/e 223(17), 222(11), 138(13), 137(100), 136(23), 109(10), 108(7), 42(10), 41(11).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.57; H, 7.62; N, 6.28.
Found: C, 64.38; H, 7.81; N, 6.46.

5-[2-(5,5-dimethyl-1,3-dioxanyl)]-1-methyl-2-piperidinone 40

The pyridone-acetal (500 mg) was dissolved in 98% ethanol (25 ml) and sodium nitrite (25 mg) dissolved in water (0.5 ml) was added. The solution was hydrogenated over 5% rhodium on charcoal (100 mg) at 40 psi for 36 hours. The catalyst was removed by filtration and the ethanol evaporated to give a viscous oil (482 mg).

ir$_{(neat)}$: 1650 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 0.73 (s, 3, C$\underline{H}_3$), 1.18 (s, 3, C$\underline{H}_3$), 2.93 (s, 3, -NC$\underline{H}_3$), 4.33 (d, 1, J=4.5Hz, C$\underline{H}$ acetal).

mass spectrum: $C_{12}H_{21}NO_3$, *m/e* calcd. 227.1521, meas. 227.1532(48), 199(9), 171(14), 150(8), 141(8), 140(11), 127(60), 126(8), 124(14), 123(17), 115(20), 86(9), 85(15), 84(9), 69(55), 57(23), 56(20), 55(16), 45(18), 44(100), 43(27), 42(29), 41(32), 39(10).

Attempted reaction of the N-imidazolide of 1-methyl-2-piperidinone-5-carboxylic acid with LTBA

Imidazole (816 mg, 0.012 m) was dissolved in dry THF (10 ml) under nitrogen and thionyl chloride (0.22 ml, 0.003 m) was added. To this mixture was added acid 21 (471 mg, 0.003 m) and the mixture was stirred for ½ hour at room temperature.

The mixture was filtered in a nitrogen atmosphere and a solution of LTBA in THF (0.8*M*, 7 ml, 0.006 m) was added. The solution was stirred for one hour and 40% aqueous HCl (2 ml) was added. The mixture was separated and the aqueous solution extracted with chloroform (2 x 10 ml). The combined organic solution was washed with water (10 ml), dried and evaporated to give a yellow solid (310 mg) which was identical (ir, nmr) with starting acid.

Ethylthio 1-methyl-2-piperidinone-5-carboxylate 43

The imidazolide was prepared from acid 21 (942 mg) as above. The mixture was treated with the sodium salt of ethanethiol (504 mg, 1 equivalent) and the mixture was stirred for one hour then filtered. The filtrate was evaporated to give an oil (1.14 g) which was chromatographed on alumina. Elution with benzene produced a mobile oil (480 mg, 40%), b.p. 248 - 250°, 6 mm.

$\mathrm{ir}_{(\mathrm{neat})}$: 1680 (C=O), 1645 (C=O) cm^{-1}.

$\mathrm{nmr}_{(\mathrm{CDCl}_3)}$: δ 1.27 (t, 3, J=7Hz, $-\mathrm{SCH_2C\underline{H}_3}$), 2.96 (q, 2, J=7Hz, $-\mathrm{SC\underline{H}_2CH_3}$), 2.98 (s, 3, $-\mathrm{NC\underline{H}_3}$).

mass spectrum: $\mathrm{C_9H_{15}NO_2{}^{32}S}$, m/e calcd. 201.0824, meas. 201.0831(10), 172(12), 140(7), 113(9) 112(100), 111(62), 88(8), 85(35), 70(18), 69(7), 68(12), 60(7), 58(8), 57(10), 56(7), 55(72), 54(8), 53(7), 44(90), 45(8), 43(20), 41(15), 40(83), 39(13).

1-Methyl-2-piperidinone-5-carbaldehyde, 33

Raney Nickel W2 (approx. 5 g) was washed five times with acetone (10 ml) and then heated under reflux in acetone (20 ml) for two hours.

Thiolester 43 (500 mg) was dissolved in acetone water (20 ml 1:1) and added to the catalyst. The mixture was heated under reflux for one hour, cooled, and the catalyst removed by filtration. The filtrate was evaporated to approximately 20 ml and this was extracted with chloroform (3 x 15 ml). The combined extracts were dried and evaporated to give an oil (245 mg) which was chromatographed over alumina (20 g). Elution with benzene gave a mobile oil (165 mg) which was identical with starting material (tlc, ir). Elution wi [illegible] nzene-ether (1:3) gave a more polar oil (54 mg).

ir$_{(CHCl_3)}$: 1735 (C=O), 1640 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: δ 2.97 (s, 3, -NC$\underline{H}_3$), 9[illegible] (s, 1, -C$\underline{H}$O).

mass spectrum: $C_7H_{11}NO_2$, m/e calcd. 141.0790, meas. 141.0788(10), 140(7), 113(20), 112(100), 111(65), 98(7), 88(7), 85(45), 84(12), 70(23), 68(15), 59(8), 58(10), 56(10), 55(75), 44(90), 43(17), 42(40), 41(18), 39(16).

Tetrabutylammonium cyanide (Bu$_4$NCN)

A Dowex-1X8 anion exchange column was washed with 15% aqueous sodium cyanide (3 x 200 ml) and then the column was rinsed repeatedly with water until the washings contained no cyanide ion.

Tetrabutylammonium iodide (20 g) was dissolved in water (400 ml) and was eluted through the column, which was then further eluted with water (300 ml). The combined water solution (700 ml) was evaporated to give a semi-solid mass. This was dissolved in acetonitrile and the solution dried and evaporated. The resulting syrup was digested with benzene (100 ml) and then the solvent evaporated. The syrup was evaporated at 1 mm. for 24 hours and a brownish solid was obtained. The solid was recrystallized from ethyl acetate to produce Bu_4NCN (6.5 g) as needles.

$ir_{(CHCl_3)}$: 2080 ($C \equiv N$) cm^{-1}.

Benzoyl cyanide

Benzoyl chloride (24 ml, 0.2 m) and cuprous cyanide (22 g, 0.24 m) were heated on an oil bath at 215° for 1½ hours. At 15 minutes intervals during this time the flask was swirled vigorously. The reaction mixture was distilled at 188 - 195° to give a colourless oil.

$ir_{(neat)}$: 2205 (C=N), 1780 (C=O), 1680 (C=O) cm^{-1}.

The distillate was dissolved in benzene (100 ml) and stirred with 1% aqueous HCl (50 ml) for 24 hours. The benzene solution was dried and evaporated. The residue was distilled at 64 - 72°, 2 mm. to give benzoyl cyanide (11.6 g, 45%).

$ir_{(neat)}$: 2205 (C=N), 1680 (C=O) cm^{-1}.

Attempted syntheses of benzoyl cyanide directly from benzoic acid

a) via an acyloxyphosphonium salt and Bu_4NCN

Triphenylphosphine (1.31 g, 0.005 m) was dissolved in dry THF (15 ml) and carbon tetrachloride (5 ml) and the solution heated under reflux for 30 minutes. The solution was cooled to 0° and benzoic acid (0.56 g, 0.005 m) was added. The solution was allowed to stand for 30 minutes at 0°. Bu_4NCN (1.4 g, 0.005 m) was added and the mixture stirred and heated under reflux in a dry atmosphere for one hour. The resulting solution was evaporated to give an olive-green syrup which was digested for ½ hour with ether. The mixture was filtered and the filtrate evaporated to give a green solid (1.1 g). The ir spectrum of this material (chloroform) shows no absorption at 2205 or 1680 cm^{-1}.

b) via an anhydride and tetramethylammonium cyanide (Me_4NCN)

Benzoic acid (0.56 g, 0.005 m) was dissolved in dry acetonitrile (10 ml) and pyridine (0.4 ml, 0.005 m) was added. The solution was treated with p-toluenesulphonyl chloride (0.96 g, 0.005 m) and heated under reflux in a nitrogen atmosphere for ½ hour. A slurry of Me_4NCN

.0 g, 0.01 m) in acetonitrile (25 ml) was added and the mixture was heated under reflux for 3½ hours. The cooled mixture was poured into water (25 ml) then extracted with ether (2 x 50 ml). The combined organic solution was washed consecutively with water, 10% aqueous HCl, water, dilute sodium bicarbonate, water (25 ml each), dried and evaporated to give a dark oil (412 mg). The ir spectrum (neat) of this oil displays absorption at 2205 and 1680 cm^{-1}.

c) via reaction of a mixed anhydride with tetraethylammonium cyanide (Et_4NCN)

Benzoic acid (0.56 g, 0.005 m) was dissolved in dry acetonitrile (15 ml) and triethylamine (0.7 ml, 0.005 m) was added. This solution was cooled to -5° under nitrogen and ethyl chloroacetate (0.4 ml, 0.005 m) in acetonitrile (5 ml) was added. The mixture was stirred for 15 minutes at -5° then Et_4NCN (0.78 g, 0.005 m) in acetonitrile (20 ml) was added dropwise over ten minutes. The solution was allowed to warm to room temperature and was stirred for 18 hours.

The solution was diluted with 5% aqueous HCl (10 ml) and ether (50 ml). The aqueous fraction was extracted with ether (10 ml) and the combined ethereal solution was washed with dilute sodium bicarbonate (10 ml) and water (10 ml), dried and evaporated to give an oil which displays no absorption at 1680 cm^{-1} in the ir spectrum (chloroform).

α-Cyanobenzyl benzoate, 47

To sodium borohydride (0.095 g, 0.0025m) in dry dimethoxyethane (10 ml) was added a solution of benzoyl cyanide (0.66 g, 0.005 m) in dimethoxyethane (10 ml). The mixture was stirred at room temperature for 15 minutes, then poured into 10% aqueous HCl (30 ml). The aqueous layer was extracted with ether (30 ml) and the combined organic solution was dried and evaporated to give a colourless oil (0.71 g) which was distilled, b.p. 164 - 166°, 1 mm. The distillate crystallized on standing at room temperature.

$ir_{(CHCl_3)}$: 1735 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: δ 6.70 (s, 1, C<u>H</u>), 7.2 - 8.2 (m, 10, Ar<u>H</u>).

mass spectrum: $C_{15}H_{11}NO_2$, <u>m/e</u> calcd. 237.0790, meas. 237.0792(24), 116(26), 115(9), 108(8), 107(7), 106(9), 105(100), 91(8), 89(7), 79(10), 77(25), 51(11).

Reaction of cyanoester 47 with 2% aqueous potassium hydroxide

Cyanoester 47 (307 mg) was dissolved in THF (10 ml) and heated under reflux with 2% aqueous potassium hydroxide for 1½ hours. The aqueous fraction was extracted with ether (10 ml) and the combined organic solution was washed with water (5 ml) and brine (10 ml), dried and evaporated to give an oil (108 mg).

ir$_{\text{(neat)}}$: 2820, 2730 (CHO), 1705 (C=O) cm^{-1}.

The aqueous solution was acidified and extracted as above to give a colourless solid (136 mg).

ir$_{(\text{CHCl}_3)}$: 1700 (C=O) cm^{-1}.

Reaction of benzoyl cyanide with sodium bis(2-methoxyethoxy)-aluminium hydride (Red-Al)

Benzoyl cyanide (330 mg, 0.0025 m) was dissolved in ether (20 ml) and cooled to approximately -40°. A solution of Red-Al (approx. 7% in benzene-ether, 3 ml, 0.00125 m) was added. After stirring for one hour at -40°, 1% aqueous HCl (10 ml) was added and the mixture allowed to warm to room temperature. The aqueous fraction was extracted with ether (2 x 10 ml) and the combined ethereal solution was washed with water (10 ml), dried and evaporated to give a colourless oil (270 mg).

i.r$_{\text{(neat)}}$: 3400 (OH), 2820, 2730 (C$\underline{\text{H}}$O), 1705 (C=O) cm^{-1}.

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