Studies on the chemistry of morphine and Amaryllidaceae alkaloids

This item was submitted to Loughborough University's Institutional Repository by the author.

Additional Information:


Metadata Record: [https://dspace.lboro.ac.uk/2134/34330](https://dspace.lboro.ac.uk/2134/34330)

Publisher: © Serjinder Singh

Rights: This work is made available according to the conditions of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) licence. Full details of this licence are available at: [https://creativecommons.org/licenses/by-nc-nd/4.0/](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Please cite the published version.
STUDIES ON THE CHEMISTRY
OF
MORPHINE AND AMARYLLIDACEAE ALKALOIDS

A Thesis submitted to
Loughborough University of Technology
by
Serjinder Singh
Supervisor: Professor G.W. Kirby

In partial fulfilment of the requirements
for the degree of
DOCTOR OF PHILOSOPHY

Chemistry Department

April, 1972
To my wife

and

to my parents.
ACKNOWLEDGEMENTS

I wish to express my deep and sincere gratitude to Professor G.W. Kirby for the intelligent, friendly and considerate guidance throughout the project.

I wish to express my thanks to the academic and technical staff of the Chemistry Department for their assistance during this work.

I finally acknowledge with gratitude financial assistance from Loughborough University of Technology.
SUMMARY

Nitrosation of thebaine using nitrosyl chloride, pentyl nitrite and nitrosyl sulphuric acid was investigated. Substitution was shown to take place at C-7 of thebaine. The major product of nitrosation was the dimethyl or diethyl ketal of 7-hydroxyiminonepinone depending on whether methanol or ethanol was used as the solvent. The transient 7-nitroso derivatives which tautomerized to these oximes were also found to attack the diene system of another molecule of thebaine, especially when nitrosyl sulphuric acid was used as a nitrosating agent, to give adducts the structures of which were established.

1,4-Cycloadditions of nitrosoarenes to thebaine were investigated to establish the orientation of the cycloaddition and the chemistry of the products studied. The oxime obtained from nitrosation was converted to the parent ketone by further nitrosation with pentyl nitrite and acetic acid.

Attempts were made to synthesise a biogenetic precursor of eurine through diazonium and benzyne intermediates. Cyclisation reactions, involving these intermediates, to yield cyclohexadienones were studied with a variety of model compounds especially those related to belladine. Formation of 7-membered ring systems was however frustrated by competing hydrogen transfer reactions.
CONTENTS

Reactions of Thebaine with Electrophiles and Dienophiles

a. Reactions of Thebaine with Electrophiles 1
b. Reactions of Thebaine with Dienophiles 13

Nitrosation of Thebaine 19

Synthesis of Cyclohexa-2,6-dienones 47

An Approach to the Synthesis of Crinine

The Diazonium Intermediate Approach 69
The Benzyne Intermediate Approach 77

Experimental 84

References 114
The electron rich diene system present in thebaine (1) is of particular interest chemically as a key site for bringing about various structural modifications in the morphine alkaloids. This system has been found\(^{(1)}\) to undergo a wide range of chemical transformations to give new products of both chemical and biological interest. Among the most important reactions of thebaine are the reactions of the electron rich diene towards various electrophiles and dienophiles.

\[ (1) \quad (2) \quad (3) \]

\[ a, X = Br \]
\[ b, X = OH \]
\[ c, X = Cl \]
\[ d, X = NO \]

a. Reactions of Thebaine with Electrophiles.

Normally, electrophilic attack takes place at C-14
of thebaine to give initially a 1:4 adduct of the reagent across the diene system, which then usually undergoes further change to give 14-substituted derivatives of codeinone. Thus, thebaine when treated with bromine\(^{(2)}\) or hydrogen peroxide\(^{(3-7)}\) in glacial acetic acid gives, respectively, 14-bromocodeinone \((3a)\) and 14-hydroxycodeinone \((3b)\). These compounds arise from 1:4 addition of bromine and hydrogen peroxide to the methoxy diene in thebaine to give, respectively, \((2a)\) and \((2b)\), which then lose formally methyl bromide and methanol to give \((3a)\) and \((3b)\). Similarly, 14-chlorocodeinone \((3c)\) is obtained in 80% yield by the action of iodo-benzene dichloride, \(\text{PhICl}_2\), on thebaine. 14-Hydroxycodeinone is also formed when thebaine is oxidised with sodium or potassium \((3-5, 9-10)\) dichromate in aqueous acetic acid or sulphuric acid.

In some cases, only the C-8,C-14 double bond of the diene is involved in reaction with the electrophile.

![Diagram](image_url)
Thus, the oxidation of thebaine with manganic acetate (11) first gives 8-(or 14-)acetyl-8,14-dihydroxy-dihydrothebaine (4), which on hydrolysis by 20% hydrochloric acid at 100° gives 8,14-dihydroxy-dihydrocodeinone (5) after 3 minutes and 14-hydroxycodeinone (3b) after 20 minutes.

In warm 30% hydrogen peroxide, in the absence of acid, thebaine is converted into a normal amine oxide, (12-13) but prolonged action (4) at 100° gives 'dehydrothebaine' C_{19}H_{19}O_{3}N, about which nothing is known beyond the fact that it contains two methoxyl groups.

Bromothebaine and bromothebaine tetrabromide were reported (14) as products when thebaine was treated with bromine in dilute hydrobromic acid. However, hydrobromic acid has recently been shown (15) to undergo electrophilic addition to the diene system in thebaine.

Thus, treatment of thebaine in dichloromethane with a solution of hydrogen bromide in dibutyl ether at 0°, followed by sodium methoxide in methanol, gave 8β-bromo-6-methoxy-6,7,8,14-tetrahydrothebaine (6).
Refluxing (6) in acetone for 2 hr. in the presence of hydrochloric acid and toluene p-sulphonic acid gave codeinone. Similar treatment of (7), obtained by lithium aluminium hydride reduction of (6), gave dihydrocodeinone (8). The reaction of thebaine with hydrogen bromide is believed to proceed through the intermediate (9). Thus, in this case, hydrogen bromide acts as an electrophile in protonating C-7 and C-14, the centres of relatively higher electron density. Attack by bromide anion at C-8 and C-6 then gives (9).
Sodium methoxide replaces the bromine at C-6 selectively to give (6), whereas potassium t-butoxide causes dehydrobromination to regenerate thebaine.

The same workers treated thebaine in methylene chloride with bromine followed, after evaporation of the solvent, by sodium methoxide, to give 14-bromocodeinone dimethylketal (10), thus again showing that the electrophilic addition of bromine takes place only at C-14.

Thebaine base on treatment with bromoacetamide in anhydrous methanol gives \(15,51,52\) 14-bromocodeinone dimethylketal (10). This ketal (10) is so unstable in acid that 14-bromocodeinone salt is obtained when an attempt is made to prepare its salt. Neither (10) nor (3a) can be converted into their quarternary metho salts with methyl iodide or dimethyl sulphate, possibly due to steric hindrance by the bromine at C-14.

Unlike thebaine, thebaine metho methyl sulphate, on treatment with bromoacetamide in anhydrous methanol, yielded the metho salt of the isomeric 7-bromoneopinone dimethyl ketal\(^{54}\) (11). The high resistance of the ketal group in (11) to hydrolysis was supposed to be due to the twofold shielding of the ketal group by the aromatic nucleus on one side of the ring C and the bromine at C-14 on the other.
It was suggested that the formal addition of methyl-hypobromite involved in the preparation of the bromoacetals (10) and (11) is also governed by steric considerations similar to those mentioned above. Thus thebaine methyl sulphate, the onium group, makes access to C-14 difficult for the electrophilic reagent.

Nitration and iodination of thebaine have been recently investigated\(^5\) in these laboratories. Thebaine, when treated with tetrainitromethane in methanol at room temperature for one hr., gave 14-nitrocodeinone dimethyl ketal (12) in 30% yield. The progress of the reaction was indicated
by the precipitation of the nitroform salt of thebaine. Treatment of thebaine with a mixture of silver nitrite and iodine in a 9:1 mixture of chloroform and methanol for 5 hr. at room temperature, gave 7-iodoneopinone dimethyl ketal (13). This reaction also proceeded, though more slowly, in the absence of the silver salt.

Another electrophile which reacts with the diene system of thebaine is diborane. The initial addition of the borane molecule occurs at the nitrogen giving the amino-borane. So, thebaine borane (14) (prepared by the reaction of thebaine with an equivalent amount of pyridine borane or diborane) was used for hydroboration. Reaction of (14) with one molar equivalent of borane, followed by oxidation with alkaline hydrogen peroxide, gave 7α-hydroxyisoneopine methyl ether (15) and 7β-hydroxyneopine methyl ethers (16) in 45.7% and 8.1% yields respectively. Small amounts of isoneopine and a phenolic compound were also isolated. Since (15) and (16) are the main products,
addition of borane to thebaine occurs predominantly from the α-side at C-7 presumably due to steric factors.

The course of the reaction is found to be quite different when (14) is treated with more than one mole of borane. Elimination of alkylborane seems to take place from the intermediate electrophilic addition product (17) in the presence of excess borane, giving an unsubstituted diene system (18). The presence of excess borane would result in a series of reactions giving various mono and dihydroxy derivatives. Thus when (14) is treated with 3 moles of borane for 180 hr., 7α-hydroxy-Δ8-deoxycodine (19) is isolated in 7% yield whereas the yield of (15) is highly diminished (5%). No dihydroxy derivative is however formed in this case. Similarly, treatment of (14) with excess of borane (ca. 7 moles) for a limited period (18 hr.)
gave (19) as the main product (10% yield); (20) and (21) were also isolated in 3.4% and 4.6% yields. Hydroboration of thebaine is quite useful in that the products can be used to make other morphine derivatives. Thus, (15) when oxidised with manganese dioxide, gave salutaridine (22a), while oxidation using acetic anhydride and dimethyl sulfoxide gave the O-acetyl derivative of salutaridine (22b). Since the hydroboration of \( \Delta^8-14 \)-compounds...
takes place mainly from the α-side of the molecule, this behaviour affords an easy method of preparing morphine-like structures having the B and C rings trans-fused unlike the usual cis-fused ring structures.

When thebaine was treated with iron penta-(or dodeca-) carbonyl, the diene was found to form a complex (23) with iron tricarbonyl. It appears that bonding with iron tricarbonyl stabilises the butadiene system during acid-catalysed rearrangements. Thus, whereas thebaine is completely converted into thebenine (26) in boiling dilute hydrochloric acid, the iron tricarbonyl complex of thebaine resisted aromatisation when treated with aqueous fluoroboric acid or acetic anhydride and fluoroboric acid. Instead the fluoroborate salt (24) was obtained. 20

\[
\text{MeO} \quad \text{MeO} \quad \text{MeO} \\
\text{Fe(\text{CO})}_3 \quad \text{MeO} \quad \text{MeO} \\
\text{Fe(\text{CO})}_3 \quad \text{Fe(\text{CO})}_3 \\
\text{NMe} \quad \text{NMe} \quad \text{Me} \\
\]

(23) (24) (25)

\[
R = \text{H or Ac}
\]
Thus, only opening of the ether link took place and complex formation prevented aromatisation of the diene. Rearrangement of the salt (24; R=H) took place in refluxing ethanol to give a new salt (25) in which the diene-iron tricarbonyl system was still present.

Dihydrothebaine (27) reacts with electrophilic reagents by attack at C-7. Thus, methyl hypobromite reacted with (27) to give 7-bromo codeinone dimethyl ketal (28). This reaction has been found useful in preparing the baine specifically labelled at various positions in the ring containing the diene system. Thus methyl hypobromite labelled in the methyl group with $^{14}$C or $^2$H gave the correspondingly labelled ketal (28). The ketal (28) was converted into codeinone dimethyl ketal (29) by treatment with potassium t-pentoxide in t-pentanol.
Phosphorus oxychloride was then used to eliminate the original unlabelled methoxy group as methanol. Deuterium was introduced into thebaine at C-8 via deuteriated dihydro-thebaine prepared by the reduction of thebaine with deuteriated hydrazine hydrate. The stereochemistry of the whole process can be pictured as below:
Elimination of methanol from (29) by base caused the labelled methoxy group to be lost.

So, by choosing the appropriate procedure, the required label can be introduced into thebaine.

b. Reactions of Thebaine with Dienophiles.

The electron rich diene in thebaine readily undergoes cycloaddition with dienophiles. Thus cycloadducts (30 - 32) are easily formed when thebaine is treated with maleic anhydride, p-benzoquinone and 1,4-naphthoquinone. The dienophile adds to the diene from the same side of the diene ring as the ethylamino side chain. The substituents on the dienophile are directed, in the cycloadduct, away from the C-14-etheno bridge thus formed. Thus thebaine, according to Schöpf, gives (30) as the cycloadduct when treated with maleic anhydride in hot benzene solution.
When the dienophile is not symmetrically substituted, the end of the dienophile multiple bond with least electron density attacks C-14 of thebaine. Acrolein gives \(^{(33)}\) and not \(^{(34)}\) when it reacts with thebaine.

Bentley \(^{25,26,27,28,29,30,39,40}\) and his co-workers have prepared a large number of compounds of the general formula \((35)\) (where R is CH\(_3\), Ph, or alkoxy groups) \(^{27}\) and converted these into their biologically active
derivatives by various chemical methods, viz. reduction of the carbonyl group, hydrogenation of 6-14-etheno bridge, replacement of the methyl group on nitrogen by other alkyl groups, and treatment with Grignard reagents.

The behaviour of acrylonitrile towards thebaine is the same as that of acrylaldehyde. Bentley prepared (36) from thebaine and acrylonitrile and prepared a large number of compounds of general formula (37) (where Y is etheno or ethano and R₁ and R₂ are alkyl groups) by base catalysed rearrangement of (36). The mechanism of the rearrangement was suggested to be as follows:
and was confirmed by the isolation of \((\cdot 38\)) and \((\cdot 39\)).

Somewhat similar rearrangement takes place in thebaine quinone, the cycloadduct of thebaine and benzoquinone \((\cdot 31\)).^{22-23} When \((\cdot 31\)) is heated in high boiling solvents, ethanol, aqueous acid or alkali, it is converted to its aromatic form \((\cdot 40\)).^{23} Further treatment of

![Diagram 40](image)

\((\cdot 40\)) with aqueous acid gives flavothebaïne \((\cdot 41\)).

The mechanism has been shown\(^{32-37}\) to involve the protonation of the oxygen bridge and the migration of the phenyl ring from C-6 to C-5 assisted by the methoxy group at C-6 and involving cleavage of the O-C-5 bond. Dihydrothebaine quinone also undergoes this rearrangement \(^{32,33}\) to give the dihydro derivative of \((\cdot 41\)) thus ruling out the involvement of 6,14-etheno double bond in the rearrangement.

Acetylenic dienophiles\(^{38}\) have been reported to undergo cycloaddition with thebaine. Thus, acetylene
dimethyl dicarboxylate adds to thebaine to give (42) $R_1=R_2=\text{COOMe}$ and acetylene ethyl carboxylate gives

![Chemical structure](image)

(42) and (43).

These adducts, when pyrolysed, undergo a retro Diels-Alder reaction to give the corresponding azocine compounds (43).

Attempts to obtain cycloadducts of thebaine with crotonaldehyde, coumarin and trans-$\beta$-nitrostyrene have been unsuccessful.25

The Diels-Alder reaction of thebaine with acrylamides to give (44) has been reported.56 The adducts were compared
with the products which are obtained by reaction of (45) with amines.

Thebaine has been reported to react with one mole alkyl azodicarboxylate to give (46) whereas with two moles (47) is formed.
NITROSATION OF THEBAINE

It was reported earlier\textsuperscript{42} that thebaine undergoes a reaction with nitrosyl chloride, alkyl nitrites and nitrosyl-sulphuric acid when its salts are treated with these reagents in the presence of alcohols, the products being the same (if the same alcohol is used) in the case of all reagents. With thebaine and nitrosyl chloride in methanol or ethanol, two pairs of isomeric substances were reported, one of each pair alkali soluble, and the other alkali insoluble. The compositions of these compounds were reported as $\text{C}_{20}\text{H}_{24}\text{N}_{2}\text{O}_{5}$ and $\text{C}_{22}\text{H}_{28}\text{N}_{2}\text{O}_{5}$ when methanol and ethanol were used respectively. Structures were not assigned to these compounds. It was considered probable that\textsuperscript{42,1} nitrosation of thebaine takes a course similar to that of bromination and hydrogenation with nitrosyl chloride adding to the diene system to give (48).

\begin{align*}
\text{(48)} & \quad \text{(49)} & \quad \text{(50)}
\end{align*}
Replacement of the chlorine by an ethoxy group in ethanol or methoxy group in methanol would give (49, R=Et) or (49, R=Me).

It was argued therefore that the product in ethanol would be C_{21}H_{26}N_{2}O_{5} and not C_{22}H_{28}N_{2}O_{5} as reported and it was suggested that analytical data could not reliably distinguish between the two.

More recently, the reaction of thebaine hydrochloride with pentyl nitrite and hydrochloric acid in ethanol was investigated. Two products apparently identical with those described earlier, were isolated. They had similar melting points, the same analytical data, and both were soluble in acid and alkali. However they had different crystalline forms whether crystallised from alcohol or ethyl acetate. The infrared spectrum of the major product showed the presence of a hydroxy group which, from a negative diazosulphanilic acid test, was shown to be nonphenolic. It was pointed out that the compound (49) would show no i.r., hydroxy absorption; should be readily reduced to a 14-amino-compound with the uptake of 3 moles of hydrogen, and readily hydrolysed to 14-nitrosocodeinone (3, X=NO). From these facts, it was suggested that the products were two isomeric oximes. The possible formulation was as follows:
The two isomers could then be accounted for by postulating syn- and anti- isomerism in the oxime system. However it was thought that the structure (51) should be readily hydrolysed to a diketone that would undergo ready aromatization with loss of the side chain.

We decided to investigate the nitrosation of thebaine and establish structures for the products obtained. We were particularly interested in the suggestion\(^\text{43}\) that nitrosation might involve electrophilic attack at C-7 instead of the usual attack at C-14. We believed this reaction could thus provide a potential route to morphine derivatives, for example, salutaridine\(^\text{45}\) with a functional group at C-7.

The reinvestigation was begun in these laboratories by Mr. A. P. Price who isolated crystalline products from the reaction in methanol, and in ethanol and who obtained full spectroscopic data. Chemical degradation to confirm these structures and all studies on the "dimeric" reaction products were carried out by the present author.

Thebaine hydrochloride in methanol was treated with an excess of nitrosyl chloride. An alkali soluble compound was isolated in 16.7% yield along with a 5.9% yield of an alkali insoluble compound. The alkali soluble compound m.p. 247\(^\circ\), could be precipitated by adding carbon dioxide to its solution in sodium hydroxide. This behaviour, coupled with its hydroxylic absorption (in CHCl\(_3\)) at \(\nu_{\text{max}}\) 3600 cm\(^{-1}\) in the i.r., suggested that it might be a phenol, but unlike phenols, it did not give a colour with ferric chloride.

21.
As suggested earlier, it was next considered that the compound might be an oxime formed by tautomerization of a 7-nitroso-derivative, the latter having been formed by nitrosation of thebaine at C-7. The alkali solubility could thus be explained by ionization of the oxime hydroxyl group. The anion thus resulting would be stabilized by α-β unsaturation. If this were the case, the u.v. absorption should show a red shift on the addition of alkali. This was found indeed to be so. The compound in ethanol absorbed at $\lambda_{\text{max}}. 234$ nm (ε 22,100) and the absorption band shifted to $\lambda_{\text{max}}. 273$ (ε 17,150) upon addition of sodium ethoxide. To further confirm this behaviour, cholest-4-ene-3-one oxime was chosen as the model. The syn-isomer of this oxime absorbed at $\lambda_{\text{max}}. 241$ nm (ε 23,050) in ethanol and at $\lambda_{\text{max}}. 262$ nm (ε 22,480) on addition of sodium ethoxide.

The n.m.r. spectrum of this oxime in CDCl$_3$, showed three O-methyl singlets at $\tau$ 6.12, 6.45 and 7.07, and an N-methyl singlet at $\tau$ 7.56. The singlet at $\tau$ 6.12 corresponds to the aromatic methoxyl group, whereas the other two at $\tau$ 6.45 and 7.07, can be accounted for by postulating a dimethoxy-ketal function at C-6 in the molecule. The ketal (52) could arise from the nitrosation as shown below:

22.
Further evidence for the ketal function at C-6 is provided by comparison with the chemical shifts, $\tau$ 6.45 and 7.07, of the methoxy groups of the ketal $^{21}$ (28). One of the ketal methyl groups absorbs at high field presumably through shielding by the aromatic ring.

When thebaine hydrochloride was treated in ethanol with an excess of nitrosyl chloride, a similar oxime (53) was obtained in ca. 60% yield. This oxime, m.p. 245-7$^\circ$, $\lambda_{\text{max}}$ 234 nm ($\epsilon$ 22,600), $\lambda_{\text{max}}$ 3600 cm$^{-1}$, 3270 cm$^{-1}$, also showed a red shift to $\lambda_{\text{max}}$ 273 nm($\epsilon$6,900) upon addition of sodium ethoxide. The ketal group can be easily
hydrolyzed by aqueous acid and (52) was converted into (53) by treatment of the former at room temperature with ethanolic hydrogen chloride for 30 mins. This further confirms the presence of a ketal function in these oximes.

The oximino hydroxy-group is believed to be syn- to the C-8, C-14 double bond. This followed from the low-field position (δ 3.56) of the C-8 proton singlet. The proton at C-5 gave a singlet at δ 5.25. In hexadeuteriodimethyl sulfoxide, the oximino hydroxy group gave an n.m.r. signal at δ -1.47.

The structure (52) accords well with the analytical (C_{20}H_{24}N_{2}O_{5} M^{+}, m/e 372) and spectroscopic data. Further chemical degradation of the dimethoxy oxime was carried out to confirm the structure (52).

The fact that the oxime ionizes easily in alkali led us to believe that the methiodide would undergo a rapid Hofmann degradation.
It was hoped that the oxime methiodide (54) in alkali should ionize to give the anion (55). The anion should rapidly give the methine (57) via its intermediate nitroso tautomer (56). As the methine (57) has a long conjugated chromophore in its structure, a significant change in the u.v. spectrum of the reaction mixture was expected as the reaction proceeded.

Thus, the thebaine methiodide (54), m.p. 231°, was prepared. It absorbed at $\lambda_{\text{max}} = 230$ nm ($\in 35,545$) in ethanol. Addition of sodium ethoxide to the solution caused a shift in the absorption to $\lambda_{\text{max}} = 285$ nm ($\in 19,125$). After about one hour, a new absorption at $\lambda_{\text{max}} = 350$ nm began to appear with the proportionate disappearance of the band at $\lambda_{\text{max}} = 285$ nm. However, the reaction proceeded very slowly, taking nearly 22 hr. for completion. Since the ionization of the oximino hydroxy group of the methiodide is almost instantaneous, the slow rate of reaction was thought to be perhaps due to the solvation of the anion by ethanol. The use of some aprotic solvent instead of ethanol therefore was considered. Thus, when the methiodide was treated with potassium t-butoxide in dimethyl formamide, the reaction was complete within half an hour. It was noted that in the u.v. spectrum of the reaction mixture, no band at $\lambda_{\text{max}} = 285$ nm, corresponding to the anion, appeared. Only the band $\lambda_{\text{max}} = 350$ nm, corresponding to the methine (57), showed increasing intensity with time.
The methine (57), m.p. 223-4°, was obtained in 54% yield. The extended chromophore is apparent from the high wavelength u.v. absorption, \( \lambda_{\text{max}} \), 257 nm (\( \varepsilon \) 18,000) and 350 nm (\( \varepsilon \) 12,650). The n.m.r. spectrum (in CDCl\(_3\)) also shows the olefinic signals, \( \gamma \) 3.57 (singlet), 3.44 and 3.78 (doublets, J 9.7 Hz). The oximino-hydroxy group absorbed at \( \gamma \) -1.8 in (CD\(_3\))\(_2\)SO.

With the structure of the oxime established as (52), its conversion into some known compound was envisaged. Salutaridine (22a) seemed to be the most suitable.

The route considered was first, conversion of the oxime into the parent enone (58) and then reduction to salutaridine. The method most commonly employed for the conversion of oximes and similar derivatives to ketones is aqueous acid hydrolysis. However, the sensitivity of the ketal function to acid makes acid hydrolysis unsuitable for this purpose. Pyruvic acid treatment is the alternative \(^8^4\) for acid sensitive compounds, but only oxime instead of the enone, was recovered from this treatment. The oxime was also treated with aqueous sodium 26.
Although the products showed carbonyl absorption in the i.r., no compound could be isolated from the complex mixture. All these methods involve the hydrolysis of the oxime to the parent ketone and hydroxylamine. To prevent the hydroxylamine from recombining with the ketone, these reagents either remove the hydroxylamine from the reaction by combining with it, or form an adduct with the ketone themselves.

In view of the difficulty with the above reagents, oxime cleavage by nitrosating agents was considered. Obviously, the oxime should not react with nitrosyl chloride, as the former is itself the product of a nitrosyl chloride reaction. The reason for the stability of the oxime towards nitrosation was believed to be the protonation of the oxime group in the acidic reaction mixture. That oximes of this type are protonated by mineral acids, was shown by the u.v. spectrum of the above oxime and cholest-4-ene-3-one oxime in the presence of acid. A larger red shift takes place with acid than with base. Thus, for cholestenone oxime, absorption in base was at $\lambda_{\text{max.}}$ 262 nm, and in acid it was at $\lambda_{\text{max.}}$ 269 nm.

This view was further confirmed by the fact that on treatment with pentyl nitrite in methanolic hydrogen chloride, the oxime (52) was unchanged even after 16 hr. at 60°. Hence, the use of acetic acid with pentyl nitrite or sodium nitrite was considered. When the oxime was treated with sodium nitrite in acetic acid, the t.l.c. of the reaction
mixture showed the formation of a new compound. The $R_f$ of this compound was far greater than that of the oxime indicating the conversion of the oxime into some less polar compound. But after some time, the reaction slowed down with the appearance of a crystalline precipitate of sodium acetate. The slowing of the reaction was believed to be due to the suppression of nitrous acid formation by the presence of an excess acetate in acetic acid. An attempt was made to complete the reaction by filtering off the sodium acetate and adding more sodium nitrite and acetic acid but again after some time, the precipitate reappeared and the reaction stopped. Therefore the reaction mixture was worked up and the i.r. of the total mixture, in CHCl$_3$, showed the formation of a compound with carbonyl absorption at $\lambda_{\text{max.}}$ 1694 cm$^{-1}$. It also showed a large proportion of unreacted oxime as indicated by the strong oximinohydroxy absorption at $\lambda_{\text{max.}}$ 3590 and 3250 cm$^{-1}$. The oxime was removed from the mixture by extraction with aqueous sodium hydroxide. The enone could not be crystallised even after purification by column chromatography. The t.l.c. of the enone fractions showed a cluster of three partially overlapping spots. The n.m.r. spectra of these fractions resembled that of the oxime but the C-8 proton singlet had moved upfield from $\gamma$ 3.56 in the oxime to $\gamma$ 4.1. This shift in absorption indicated the disappearance of the syn-oximino hydroxy group.

28.
To avoid the problem of sodium acetate formation, the oxime was treated with pentyl nitrite in glacial acetic acid. The reaction, although slow at room temperature, was complete within 2 hr. at 60°. The reaction was worked up as before. The t.l.c. of the product showed three major products, two of these were very fast moving and the third had the same \( R_f \) value as the enone... mentioned above. Column chromatography of this mixture on alumina separated the enone from the fast moving compounds. The enone-rich fractions gave a gum as before which could not be crystallized. The fractions containing the fast moving compounds gave two crystalline compounds. The major of these was obtained in 8% yield, m.p. 181°, \( \lambda_{\text{max}} \) 1700 cm\(^{-1}\). The n.m.r. spectrum showed the absence of an \( N \)-methyl singlet. The molecule seemed to have the ketal function still intact. However, the signal at \( \gamma \) 7.02, due to ketal methyl shielded by the aromatic ring, appeared as a finely split doublet. Similarly split was the C-5 proton signal at \( \gamma \) 5.1 and the olefinic signal also appeared as a pair of singlets at \( \gamma \) 3.9 and 4.07 instead of as a singlet. This suggested a mixture of two isomers. However, the absence of the \( N \)-methyl signal suggested \( N \)-nitrosation of the enone to give an \( N \)-nitroso-norderivative, possibly (59). In this \( N \)-nitroso compound slow rotation, on the n.m.r. time scale, about the \( N\text{-NO} \) bond might lead to the observed duplication of signals. Model compounds like the \( N \)-nitrosonorcodeine\(^{48}\), and \( N \)-nitrosonorcodeinone were prepared to see if these also
exhibited similar effects. However, the insolubility of these compounds in suitable solvents rendered it impossible to compare their n.m.r. spectra with that of the compound in hand.

\[ \text{Diagram not legible} \]

The structure (59) was further confirmed by accurate mass measurements of its molecular ion. The measured mass was 372.1321, identical with that required for \( \text{C}_{19}\text{H}_{20}\text{N}_{2}\text{O}_{6} \) corresponding to (59). The minor compound, m.p. 215°, \( \nu_{\text{max}} \) 1685 cm\(^{-1} \), was obtained in 1% yield. The n.m.r. spectrum showed an \( N \)-methyl singlet and the usual three \( O \)-methyl singlets indicating the presence of a ketal function. The chemical shifts of various signals, however, were quite different. Thus, the ketal methoxy singlets appeared at \( \tau \) 6.87, and \( \tau \) 6.12. Also the olefinic and C-5 singlets were lowfield at \( \tau \) 3.81 and 4.46 respectively. Because of the low yield of this compound, further investigations were not carried out.

The gummy enone was further purified by p.l.c. on alumina. The major enone band was accompanied by two very close bands.
of two other fast running impurities. However, careful scraping of the major enone band ($R_f 0.65$ in the 5% MeOH-EtOAc system) gave pure enone. This was recrystallized from a mixture of diethyl ether and light petroleum (b.p. 40-60°).

Due to shortage of time, reduction of the enone to salutaridine was not investigated. It was believed by analogy with the work on steroids, that the most suitable reagent for this purpose might be chromous acetate.

Nitrosation of thebaine with nitrosylsulphuric acid was also investigated. Treatment of thebaine hydrochloride with nitrosylsulphuric acid (5 moles) in methanol at room temperature gave a compound, $C_{38}H_{43}N_3O_8$, insoluble in cold alkali, m.p. 189-90°, in 20% yield, identical with the minor product obtained when nitrosyl chloride was used. The oxime (52) was also isolated in some cases, though in very small yields (~0%).

The n.m.r. spectrum (in CDCl$_3$) of this alkali insoluble compound showed two aromatic $\alpha$-methyl singlets at $\gamma$ 6.16 and 6.24, two other $\alpha$-methyl singlets at $\gamma$ 6.48 and 7.18, and two $N$-methyl singlets at $\gamma$ 7.52 and 7.60. In addition, a five proton band at $\gamma$ 3.4 was observed in the aromatic region of the spectrum.

When ethanol was used as the solvent and nitrosyl-sulphuric acid as the nitrosating agent, an alkali insoluble compound, m.p. 189-90°, similar to the one obtained with
methanol, was obtained in 20% yield. The n.m.r. spectrum (in CDCl$_3$) of this compound (obtained when EtOH was used) was almost identical with that of its methoxy analogue, except that the former had two methyl triplets at $\delta$ 8.96 and 9.42 in place of the two $\delta$-methyl singlets at $\delta$ 6.48 and 7.18 of the latter. This clearly indicated that the two compounds differ in the same way as the methoxy and the ethoxy oximes described above. Thus both these compounds appeared to possess a ketal function. This was also confirmed by a difference of 28 mass units in the molecular ion peak (m/e 669 and 697) in the mass spectrum of these two compounds. Moreover, the positions of the ketal alkoxy groups in these compounds appeared to resemble those in the oximes as shown by the high chemical shifts of the methyl groups in the ketal functions due to shielding by the aromatic nuclei. In order to distinguish between the two compounds, they will be called the methoxy and ethoxy compounds.

From the n.m.r. spectra of these compounds it appeared that they were formed somehow by combination of two thebaine units. This was further confirmed by the microanalysis and accurate mass measurements on the methoxy compound which showed it to be a di-ethanol solvate of C$_{38}$H$_{43}$N$_3$O$_8$. The molecular ion fragmented to give an ion of C$_{20}$H$_{24}$N$_2$O$_5$, the same as that of the oxime (52) or some nitroso isomer (60 or 61).
This further led us to believe that the methoxy compound consisted of two thebaine skeletons, joined somehow by a single nitroso unit.

It was possible that the oxime might be a precursor for this "methoxy dimer", since both the oxime and the 'dimer', in different proportions, were isolated from all nitrosation reactions. To verify this, the oxime was treated with nitrosyl sulphuric acid (5 moles) in methanol. Unreacted oxime was recovered quantitatively, thus disproving the above idea. It was certain that the formation of the dimer involves nitrosation of thebaine as the first step. This was apparent from the presence of a ketal function in the molecule and the fragmentation of the molecular ion to the ion of composition $C_{20}H_{24}N_2O_5$. Since formation of the oxime involved attack at C-7 of thebaine, it was thought that perhaps attack at C-14 would give the 14-nitrosocodeinone ketal (61) which could not tautomerise to an oxime and might instead dimerise or react with another molecule of thebaine. The presence of only three nitrogen atoms in
the molecule indicates that it is not a dimerised nitroso compound but its formation could involve a second molecule of thebaine. The most likely manner in which a nitroso compound and a molecule of thebaine can react is by a Diels-Alder reaction. The electron rich diene in thebaine should undergo easy cycloaddition with the nitroso group. The reaction was formulated as follows:

\[ \text{MeO} \quad \text{MeO} \quad \text{HeO} + .~N--O \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \]

\[ \text{(62)} \quad \text{(63)} \]

To decide whether addition took place to give (62) or (63), degradation of the molecule was considered.

Careful reduction of the 'dimer' with zinc in acetic acid was carried out. To our surprise, the dimethoxy oxime (52) was isolated in 36% yield. This could be formed only if (60) instead of (61) had reacted with thebaine. Thus, the initial adducts must have been (64) or (65).
From electronic considerations, the formation of (64) would seem more likely. The slightly electrophilic nitrogen atom would attach itself to the nucleophilic C-14 instead of C-6.

Nitroso compounds have been shown to undergo cycloaddition to various dienes. No report of a similar reaction with thebaine, however, was found in the literature. To see whether nitroso compounds really can undergo cycloaddition with thebaine, it was decided to carry out some model experiments with thebaine. Nitrosobenzene was the most easily available nitroso compound. On treatment of thebaine with nitrobenzene in chloroform at room temperature, a beautiful crystalline compound, m.p. 120° (decomp.) was formed. The n.m.r. spectrum of this compound showed it to be a cycloadduct. It dissociated rapidly to give a small concentration of thebaine.
and nitrosobenzene in all solvents tested.

Although this demonstrated the possibility of cycloaddition of nitrosocompounds to thebaine, it gave no information as to which way the nitroso group adds to thebaine. That is to say, whether (66) or (67) is formed. Thebaine was mostly recovered when attempts were made to degrade this adduct by methanolysis, reduction etc. However, P. Horsewood, during his project work in this Department, trituated the adduct with 1N-hydrochloric acid and obtained a hydrolysis product as a dihydrochloride. The free base, m.p. 127-128°C was regenerated using sodium bicarbonate solution. From the i.r. spectrum in CHCl₃ (ν max. 3540, 1687 cm⁻¹) the free base appeared to be an enone. The n.m.r. spectrum in CDCl₃ showed the olefinic protons of the enone as doublets (J 10 Hz) at γ 3.71 and 4.08. The C-5 proton absorbed as a singlet at γ 5.12. The acid hydrolysis product of the adduct could be either (68) or (69) depending on whether
the structure of the adduct itself is (66) or (67).

\[ \text{Acetylation (Ac}_2\text{O, pyridine) was carried out at room temperature. An acetate, m.p. 157-158^\circ, was obtained. The i.r. spectrum in CHCl}_3, \nu_{\text{max.}} \text{ 1773, 1688 cm}^{-1}, \text{ showed it to be an O-acetate. Thus (66) was the structure of the adduct and (68) that of its hydrolysis product. The mode of attachment of the phenylhydroxlamino-residue at C-14 in the adduct hydrolysate was further confirmed to be as in (68) by its catalytic (Pd/C) hydrogenation.}
\]

The product of hydrogenation was shown to be 14-phenylaminodihydrocodeinone (70), m.p. 189-190^\circ; \nu_{\text{max.}} \text{(CHCl}_3) \text{ 1721 cm}^{-1}; \gamma \text{(CDCl}_3) \text{ 5.33 (s, 5-H).}
These experiments indicated that during the formation of the "methoxy dimer", (64) should have been the initial cycloadduct. The i.r. absorption of the "methoxy dimer" in CHCl\textsubscript{3} at $\nu_{\text{max.}}$ 3555, 1682 cm\textsuperscript{-1} showed it to be an enone containing a hydroxy group. This immediately tempted us to believe that the "methoxy dimer" is merely a hydrolysis product of the adduct (64). Thus, the structure of the 'methoxy dimer' was believed to be (71).

![Diagram](image)

That the 'dimer' contains a hydroxylic group was shown by acetylation (Ac\textsubscript{2}O, pyridine). A monoacetyl derivative, m.p. 246\degree C, $\nu_{\text{max.}}$(CHCl\textsubscript{3}) 1772 cm\textsuperscript{-1}; singlet at $\gamma$ 7.65 (CDCl\textsubscript{3}) was obtained. The i.r. spectrum shows it clearly to be an O-acetate.

The structure (71) for the 'dimer' explained most of the chemical and spectroscopic data. Still some important observations remained to be explained. The u.v. spectrum of the 'dimer' in ethanol showed absorption at $\lambda_{\text{max.}}$ 215 nm ($\varepsilon$ 34,100), 287 nm ($\varepsilon$ 4680), and 360 nm.
On addition of sodium ethoxide, the absorption showed a red shift to $\lambda_{max}$ 223 (€ 49.500), 292 nm (€ 6.980), 360 nm (€ 1.610). The structure (71) has no feature consistent with this behaviour. The presence of a phenolic hydroxyl group is more likely to be in accordance with the above observation than the hydroxylamino group in (71). By analogy to the formation of (68), it was believed that (71) is formed, though transiently. Rearrangement of (71) could then be postulated to give a phenol (72) on the same lines as formation of flavothebaone (41). The "dimer" (72) was recovered after treatment with methanolic sodium methoxide and must therefore have been in the phenolic form before this treatment with alkali.

Thus, if (72) represented the structure of the "dimer", the red shift with alkali could be due to its being a phenol. The weak, long wave-length absorption could be ascribed to the enone function.
This weak absorption disappears when dimer is reduced with sodium borohydride. The alcohol (73) thus formed, m.p. 180-2\(^{\circ}\), showed hydroxylic absorption in the i.r. at \(\nu_{\text{max.}}\) (CHCl\(_3\)) \(3645, 3540\) cm\(^{-1}\). Whereas the 'dimer' is a pale yellow compound, the alcohol is colourless, thus suggesting that the pale yellow colour and the long wave-length absorption at \(\lambda_{\text{max.}}\) 360 nm is due to the enone. The alcohol showed no absorption at this wavelength.

As we have seen earlier, (68) has been shown to possess a hydroxylamino group in its structure. This compound was investigated further by the present author. Unlike the dimer which seems to behave as a phenol, (68) was expected to be insoluble in alkali. It was found to be insoluble in cold aqueous alkali but, surprisingly, on warming, the compound dissolved to give a yellow solution. Addition of carbon dioxide to this solution gave a precipitate. This could be explained only by assuming that (68) rearranged in
the presence of alkali to a new compound, probably a phenol. This was also indicated by the u.v. absorption behaviour of (68). In ethanol, it absorbed at $\lambda_{\text{max.}}$ 240 ($\epsilon$ 9,230), 280 ($\epsilon$ 2,510), 350 nm (sh, $\epsilon$ 636). Addition of sodium ethoxide immediately changed the absorption pattern to $\lambda_{\text{max.}}$ 254, 298, 361 nm. Consequently (68) was treated with ethoxide in ethanol. Ethanol was evaporated and to the aqueous solution of the residue, carbon dioxide added. The precipitate on recrystallization gave a new compound, m.p. 197°, as a hemiethanolate. Spectroscopic data, $\lambda_{\text{max.}}$ (CHC\textsubscript{3}Cl) 3510, 1685 cm\textsuperscript{-1}; $\lambda_{\text{max.}}$ (EtOH) 235 ($\epsilon$ 10,600), 317 (1220), 361 nm (8 72); $\lambda_{\text{max.}}$ (EtOH/EtONa) 254 ($\epsilon$ 12,200), 298 (4370), 361 nm (1480); $\Gamma$ (CDCl\textsubscript{3}) 3.92 (vinyl protons not separated at 60 MHz) and analytical data suggested it to be the phenol (74). This would arise by base catalysed rearrangement of (59) analogous to the formation of the 'dimer' (63) from (62).
The phenol (74) can be seen to be a reasonably close model of the dimer (72). Thus, both show similar absorption behaviour in u.v., both are pale yellow compounds and have similar enone and hydroxylic absorption in the i.r.

Acetylation (Ac₂O, pyridine) of the phenol (74) gave a monoacetyl derivative, m.p. 221-3⁰, \( \nu_{\text{max.}} \text{(CHCl₃)} 1772 \text{ cm}^{-1} \), no hydroxylic absorption. The overall pattern of the i.r. spectrum of the acetate was very similar to that of the Q-acetyl methoxy dimer. The n.m.r. spectral data of two acetates and the parent phenols were also compared. The n.m.r. spectra of both the acetates were virtually identical with those of the parent phenols except for aromatic, methoxy (aryl), and C-5 proton signals. In the phenols, the aromatic protons appeared as a closely spaced AB quartet, but a widely spaced multiplet appeared in both the acetates. Since acetylation caused a shift of aromatic proton signals it appears that the hydroxyl group which was acetylated was phenolic. The C-3 aryl methoxy group, ortho to the Q-acetyl group also shows a change in the chemical shift to higher field of about 3 Hz (at 60 MHz) in both the acetates. The carbonyl group of the acetyl group clearly causes this anisotropic shielding. This shielding is even more striking for the C-5 protons. In both the acetates, the C-5 proton signal is almost 20 Hz higher field than in the parent phenols. These observations in addition to confirming the structural similarity between the two phenols (72) and (74) also confirm the structure of both 42.
these compounds.

So far we have seen that nitrosation of thebaine takes place only at C-7. The products of nitrosation in methanol are the oxime (52) and the 'dimeric phenol' (72). The oxime is the major product when nitrosyl chloride is the reagent and the 'dimer' when nitrosylsulphuric acid is used. A mixture of two other minor products was, however, obtained when nitrosyl chloride was used. The $R_f$ of these two compounds was more than that of thebaine on alumina plates in an ethyl acetate- methanol system. Although it was not possible to crystallize the major of these two, the i.r. spectrum in CHCl₃ had an enone absorption $\nu_{\text{max.}}$(CHCl₃) 1690 cm⁻¹, and a pair of doublets at $\gamma$ 3.89 and 3.09 (10 Hz), characteristic of enones. The C-5 proton gave a singlet at $\gamma$ 5.28. Although it could not be confirmed, it appears to be a compound similar to 14-substituted codeinones, perhaps 14-nitrosocodeinone. The latter could possibly arise as a result of cycloaddition of nitrosyl chloride to the thebaine and then opening up of the adduct with loss of chloride.

\[ \begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\text{ONCl} & \quad \text{ONCl} \\
\text{NMe} & \quad \text{NMe} \\
\end{align*} \]
Nitrosation of thebaine hydrochloride in methanol using pentyl nitrite and methanolic HCl gave the oxime (52) in 40% yield. The "methoxy dimer" (72) was also obtained in 10% yield. Similar yields of 'ethoxy dimer' and ethoxy oxime were obtained when ethanol was used instead of methanol. However, when the same volume of a 50% mixture of ethanol and chloroform was used, a new oxime in addition to (52) was obtained. This oxime, m.p. 234-8°C, appeared from the n.m.r. spectrum to be a mixture of the two epimeric ketal (51). This may possibly be the other "isomer" of the diethoxy oxime reported by earlier workers.

\[ \text{Diagram of molecule (51)} \]

The fact that an intermediate 7-nitrosoneopinone ketal undergoes cycloaddition with thebaine, tempted us to add other dienes to the reaction mixture to see if a new cycloadduct with these dienes could be isolated. Only the dimer was formed when furan or butadiene was added to the reaction mixture of thebaine and nitrosyl.
sulphuric acid in methanol. Attempts were also made to observe reaction of thebaine with tertiary nitroso compounds. Thebaine was recovered unreacted when treated with 2-chloro-2-nitroso propane (75), 2-methyl-2-nitrosopropane (76) or p-nitroso-NN-dimethyl-aniline (77) in chloroform solutions.

Reduction of the methoxy oxime (52) using zinc in acetic acid was carried out. Although no pure compound could be isolated, it appeared from the i.r. and n.m.r. spectra of the gummy products that, in addition to reduction of the oxime to an amine, the C-8, C-14 double bond was also reduced. Catalytic and lithium aluminium hydride reduction of the 'dimer' gave only complex mixtures of products. No pure compound could be isolated.

Long range coupling (ca. 1.8 Hz) between C-5 and the α-olefinic proton of the enone in (72) was shown to take
place by spin decoupling experiments. Similar coupling is known between C-5 and C-18 in (78).
Many important groups of organic compounds contain examples of the cyclohexa-2,5-dienone ring system. The chemistry of such compounds has been extensively reviewed time and again.\textsuperscript{57-60} Since phenols can be easily converted into cyclohexadienones, many natural products biogenetically derived from aromatic precursors have this structural feature. Thus many alkaloids, antibiotics, steroids and other metabolites are known to be cyclohexadienone derivatives. During the biosynthesis of these natural products, it is believed\textsuperscript{61-64} that aryloxy radical coupling takes place to give the dienone system. Examples of dienone alkaloids are, salutaridine (22a), orientalinone (80), amurine (81), flavinanthine (82), isosalutaridine (79), and mecaminine (83). Several of these have been shown\textsuperscript{65} to be converted biosynthetically into other morphine and aporphine alkaloids. These dienone alkaloids are all formed by the intramolecular oxidative radical coupling\textsuperscript{61} of the phenols like (84).
These dienones undergo further reduction and rearrangement to give many other alkaloids occurring in the same plants.

In the biosynthesis of certain groups of alkaloids, the dienone intermediate, rapidly and irreversibly undergoes further change to give new compounds and in these cases no dienone alkaloid has been isolated. Thus most of the Amaryllidaceae alkaloids are derived biogenetically.
from the 2-methylnorbelladine (85). The three dienone intermediates possible believed to be (86), (87) and (88).

These dienones have structures such that the nitrogen atom in (86) and (87) and the phenolic oxygen in (88) attack the dienone ring to give the enones (89), (90) and (91).
The enone (91; R=Me) is a known alkaloid (narwedine) and is obtained chemically by oxidation of galanthamine. These enones are the precursors of many other Amaryllidaceae alkaloids.

Non-alkaloidal natural product dienones are also formed by phenoxy radical coupling. For instance, dehydrogriseofulvin (92) is formed by oxidative coupling of griseophenone (93).

The fungal metabolites geodin (94a) and erdin (94b) provide similar examples.

The earlier predictions that umic acid (95) is derived biogenetically from methylphloroacetophenone (96) has been verified. Many more natural product dienones are biologically derived by alkylation of phenols. Thus in the biosynthesis of tasmanone (97), methylation on carbon...
and oxygen, by $[^{14}\text{C}]$methionine, has been observed.\textsuperscript{75}

Many hop resin constituents have aroused interest\textsuperscript{76} for many years as antibiotics and tuberculostatic agents.\textsuperscript{77,78} The general formulae of these compounds are (98) and (99) where $R$ is usually an isopropyl, isobutyl or isopentyl group.

Similarly, the male fern resins are also dienones formally derived from phloroglucinol. Flavaspidic acid\textsuperscript{79} (100a) and aspidine\textsuperscript{80,81} (100b) have been synthesised.

The chemistry of many steroidal cyclohexa-1,4-diene-3-ones and their bicyclic analogues has been thoroughly investigated.\textsuperscript{82,59,60}

The synthesis of cyclohexadienones is based, in general, on two ideas. One involves the synthesis of the ring from carbonyl derivatives, whereas the other involves the conversion of phenolic ring systems into cyclohexadienones.

Preparation of cyclohexadienones by annelation methods are of two types. The first employs a double aldol condensation of...
aliphatic ketones with 2-alkyl-2-formyl-cyclohexanones; the second
is a modification of Robinson's ring-extension procedure in which
the anion derived from a 2-alkylcyclohexanone is added to an
alkyl vinyl ketone followed by aldol condensation. 87

Wild and Djerassi 88 obtained the chrysene derivative
(101; R,R'=1,2-fused naphthalene, R''=H) from 2-formyl-2-
methyl-1-keto-1,2,3,4-tetrahydrophenanthrene (102; R,R'=1,
fused naphthalene) and acetone via (103)

![Chemical structure](image1)

which was cyclized without isolation. The analogues (101,
R=R'=R''=H) 89 and (101, R=R''=H, R'=Me) 90 have been prepared
similarly.

Various modifications of the Robinson synthesis of
cyclohexadienones have been used. The anion (104) was added
to various α,β-unsaturated ketones such as methyl ethynyl
ketone or (105, where X=Cl, MeO, or C,H₅NC and R''=H,CH₃)
to give (106) which was cyclised to (101) using sulphuric acid. 91
The santonin derivative (108) was obtained from (107) and ethyl ethynyl ketone.92

Many cyclohex-2-enones are available from conventional Robinson reactions and can be easily converted into cyclohexadienones using such methods as halogenation and dehydrohalogenation, dehydrogenation, and oxidation. Recent examples93,94 involve Michael addition of α-aryl aldehydes to methyl vinyl ketone, in the presence of Triton B, and condensation to cyclohexenones. Selenium dioxide oxidation then gives cyclohexadienones. The common halogenating agents employed are bromine in acetic acid,95 ether96 or carbon tetrachloride;97-99 N-bromosuccinimide,99 or sulphuryl chloride.101 Dehalogenation is carried out using lithium102-105 or other102,104 salts or with sodium bromide and dimethylaniline,106,107 in dimethylformamide or dimethylacetamide. 2,4-Dinitrophenylhydrazine in boiling acetic acid108 gives the dienones as their 2,4-dinitrophenylhydrazones but the hydrolysis to the free dienone by pyruvic acid is not always successful.98 Trimethylbenzyl-ammonium mesitoate in acetone109 converts a 2-halo-ketone into the corresponding diene, although quinoline110 has also been used but it was suggested that the low yields may be caused by interfering Favorokii-type reactions.
Dehydrogenation of cyclohexenones is another useful method of preparing cyclohexadienones. Selenium dioxide\textsuperscript{93,94,99} and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)\textsuperscript{111} are particularly useful dehydrogenating agents. The latter is more specific and most of the other functions are unaffected by it. Microbiological dehydrogenation\textsuperscript{112} has also been used but appears specific for steroids.

Phenols are valuable starting materials\textsuperscript{58} for the preparation of cyclohexadienones because of their availability and the simplicity of the procedures involved. It is well known that ambident anions such as phenoxides or the enol anion of ethyl acetoacetate can undergo alkylation at oxygen or carbon, depending upon the alkylation agent and the conditions used. In an extensive study Claisen et al.\textsuperscript{113} obtained ortho-substituted phenols from the anions of phenol, 4-methylphenol, and 1- and 2-naphthol with allyl and benzyl halides in benzene or toluene. Alkylations in alcoholic media gave only the phenolic ethers. Various cyclohexadienones of the type (109) and (110) along with the phenol ethers (111) have been prepared\textsuperscript{114} from

\begin{align*}
\text{(109)} & \quad \begin{array}{c}
\text{R} \\
\text{R'} \\
\text{R''}
\end{array} \\
\text{(110)} & \quad \begin{array}{c}
\text{R} \\
\text{R'} \\
\text{R''}
\end{array} \\
\text{(111)} & \quad \begin{array}{c}
\text{R} \\
\text{R'} \\
\text{OR''}
\end{array}
\end{align*}
sodium phenoxides and allyl bromides in benzene solution, using conditions similar to those of Claisen. Tosylates and brosylates were unsuitable alkylating agents for preparing dienones. Alkylation was also possible in aqueous solution in the presence of an equivalent of silver nitrate or carbonate to prepare 4-allyl-4-methylcyclohexa-2,5-dienone (110, R=H, R′=Me, R″=allyl) in 25% yield. The mechanism of alkylation of ambident nucleophiles has been studied in detail, although the picture has not yet been completely clarified. Significant work has been reported and rationalised by Curtin, Kornblum, and Barner. The subject has been reviewed by Compper.

Many intramolecular alkylations involving neighbouring group participation by a phenyl group have been used to prepare santonin derivatives and 4,4-spiro-substituted cyclohexadienones. Winstein and Baird were the pioneers in isolating spirodienones of the general structure (112, n = 2 to 5) which had been postulated as the unstable intermediates in the methanolysis of (113). Dilute solutions of the brosyltates or bromides with a slight excess of potassium t-butoxide in t-butanol were used; otherwise dimeric or polymeric ethers were formed by intermolecular displacements. To overcome this difficulty Dorling and Harley-Mason used the phenol (114) in which the chlorine atom is
sterically hindered at the rear and is inert to $S_N^2$ displacement; treatment with $t$-butoxide in $t$-butanol at 180° gave the spiro-
cyclohexadienone (115) which was hydrolysed to (116).

The spirodienones (117) and (118) have been prepared from
the appropriate substituted tetrahydronaphthol and cyclohexyl-
phenol.

Hey et al. for the first time reported the formation
of the cyclohexadienone derivatives (119) in an attempted
Pschorr synthesis of the phenanthridones (120). Thermal
decomposition of the diazonium salts derived from (121) gave
the spiro-dienones (119) as the major products along with a
small amount of the corresponding phenol (e.g. 122).
Similarly, the dienone (123) was obtained by the thermal
decomposition of the diazonium salt derived from (124).
Decomposition of the diazonium sulphates (125a),
(125b), (125c), and (125d) followed a closely similar pattern.
All gave the corresponding phenanthridones (126) though in very small yields (1-2%). These result from electrophilic
attack by the diazonium ion on the 6'-carbon meta to the activating alkoxy-group. Much more important in all cases was attack ortho to this substituent, at the 1'-carbon, as shown in (127), to give the spirodienones (128) in yields of 20-25%.

The other major reaction in these decompositions led to a common product from (125a) and (125b), and to another from (125c) and (125d). Thus again the Q-alkyl group had been lost, suggesting the oxazepinone structures (129; R'=Me) and (129; R'=Et) respectively. It is interesting to note that no spirodienone (130) or oxazapinone (129; R=Me) was isolated from the decomposition of the diazonium sulphate from 2'-amino-2-methoxy-N-methylbenzanilide (131).

The major portion of the products (88%) was alkali-soluble and gave, after chromatography and vacuum sublimation, 2'-hydroxy-2-methoxy-N-methylbenzanilide (132).

Formation of the spirodienones (119) (47 and 51%) was favoured over normal ring-closure to the phenanthridones (120) (6.4 and 6.2%). The yields of cross-conjugated
dienones (119) formed in these decompositions were double those of the linearly-conjugated dienones (128) described above. That the former process is favoured over the latter was clearly shown in the decomposition of N-ethyl-2,4-dimethoxy-benzanilide-2-diazonium sulphate (133) in which the cross-conjugated dienone (134) was the major product (47%) and none of the linearly-conjugated isomer (135) could be isolated.

\[ (133) \quad (134) \quad (135) \]

No dienone was formed in the decomposition of (136). A methoxyphenanthridone (137) was formed in much higher
yields (21%) than in the above decompositions. The preferential formation of this, slightly more hindered, isomer (137) over (138) could result from dipolar attraction between the methoxy oxygen and the diazonium ion.

The formation of various products in the above thermal decompositions of diazonium salts, by analogy with earlier observations, was explained by an ionic mechanism. Thus a phenyl cation is formed which reacts intramolecularly with various nucleophilic centres in the molecule. If it is a 2'- or 4'-alkoxy-benzanilide, a spirodienone is formed by reaction at the 1'-carbon by the phenyl cation, whereas, if it is a 3'-alkoxy benzanilide, a phenanthridone results by attack ortho to the alkoxy group by the phenyl cation. Interaction of the alkoxy oxygen atom gives oxazapinones by the loss of alkyl group as an alcohol. Reaction with the solvent gives the corresponding phenols.

On the other hand a free radical mechanism was proposed for the copper catalysed decompositions of diazonium fluoroborates derived from alkoxy-N-alkyl-2-aminobenzanilides. In the catalysed decomposition of (139), in addition to the major product, the dienone (119a), the

\[
\begin{align*}
\text{MeO} & \quad \text{BF}_4^- \quad \text{NET} \\
\text{N}_2 & \quad \text{CO} \\
\text{MeO} & \quad \text{Et}
\end{align*}
\]

(139)

\[
\begin{align*}
\text{CO} & \quad \text{N} \\
\text{Et} & \quad \text{OMe} \\
\text{Et} & \quad \text{OMe}
\end{align*}
\]

(140)
phenanthridone (120a) was formed in a higher yield (17%) than in the uncatalysed decomposition, at the expense of the dienone. A dimeric product (140) was also isolated in small yield (2%). The homolytic pathway in the formation of this dimer is obvious.

The catalysed decomposition of N-ethyl-3'-methoxybenzanilide-2-diazonium fluoroborate (141) gave predominantly 10-ethyl-4'-methoxyphenanthridone (137) (22%) as in the thermal reaction, and again none of the 2-methoxy-isomer (138) was isolated. Two interesting minor products were also isolated. One was 3'-methoxybenzanilide (142), the product of deamination and dealkylation, a process resulting from 1,5-hydrogen atom transfer to the phenyl radical and then loss of the N-ethyl group as acetaldehyde on hydrolysis. The other minor product was a dimer which was assigned structure (143) on the basis of chemical and spectroscopic evidence. Clearly, a radical like (144) must be involved in the formation of (143). That this is so was also supported by the observation that unlike the thermal decomposition, the
catalysed decomposition of the diazonium fluoroborate (1.45) gave, in addition to other products, the dienone (1.46) and the dienol (1.47).

Whereas the formation of (1.43) can be explained by the coupling of the radical (1.44), (1.46) and (1.47) were formed, it was suggested, as a result of reaction of radical (1.48) with molecular oxygen. The hydroperoxide (1.49) thus formed, would give the dienone (1.46) and the dienol (1.47).
The above investigations provided a novel synthetic method for the preparation of spiro-cyclohexadienones where one of the spiro-substituents was an aromatic ring. This led to the synthesis of various alkaloidal diene systems.

Gregson-Alcott and Osbond were the first to report the exploitation of the above idea for the synthesis of iminoethanophenanthrene-2-ones, the ring system present in alkaloids like amurine (150).

\[
\begin{align*}
\text{(150)} & : \\
\text{(151)} & : R^1 \quad R^2 \\
& a; \text{OMe} \quad \text{H} \\
& b; \text{H} \quad \text{H} \\
& c; \text{H} \quad \text{OMe} \\
& d; \text{OMe} \quad \text{OMe} \\
\text{(152)} & : \\
\end{align*}
\]

Thus the copper catalysed decomposition of the diazonium salts derived from (151a) gave a mixture of 6 bases, of which (152a) was the major product. Other products were the dimeric diazo compound (153, (154a) and (155a)).
Decomposition of (151b) gave (154b) and (155a) in addition to the dienone (152b). Similarly, (151c) gave [\(^t\)]-laudanosine (154c) and [\(^s\)]-glaucine (155b). The dienone (152c) thus obtained had spectral data which was well in agreement with that of amurine (150), the methylenedioxy analogue of (152c).

Later many dienone alkaloids were synthesised by Kametani and co-workers employing diazonium salts as intermediates. The dienone (175), related to androcymbine (156), was synthesised by the decomposition of the diazonium salt derived from (158).
At the same time Battersby and co-workers also reported a similar diene synthesis. The diazonium sulphates derived from the bases (159) were catalytically decomposed with copper.

\[
\text{OR} \quad \text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{OH} \\
(159) \quad \text{R} = \text{H, Me}
\]

The diene (160; R=H) was isolated as a gum which was converted into its crystalline methyl ether (160; R=Me) by methylation. The latter was also obtained from (159; R=Me). The diene (160; R=Me) was reduced to the dienol (161) which, after acid catalysed rearrangement and reduction was converted into protostephanine (162).

\[
\text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{OH} \\
(162) \quad \text{R} = \text{Me or Et}
\]

\[
\text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{MeO} \\
(163) \quad \text{R} = \text{Me or Et}
\]

\[
\text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{OMe} \\
(164)
\]
Q-Methylflavinanthine (164) was synthesised by Kametani et al. via the diazonium salts derived from (163). Similarly, (\(\pm\))-amurine (150) was synthesised\(^{128}\) from (165). In addition to the dienone alkaloid, a small amount of epidicentrine (166) was also formed. Decomposition of the diazonium salt from (167) gave\(^{129}\) a dienone (168), isomeric with flavinanthine (173).

Some (\(\pm\)) dicentrine (169) was also formed along with the deamination product (170; R=Me). Synthesis of flavinanthine
(173) was achieved by diazotizing, (171) and decomposing the diazonium salt, and then debenzylating the dienone (172) with methanolic hydrogen bromide. The deamination product (170; R=CH₂Ph) was also isolated.

Recently Kametani et al. reported the synthesis of salutaridine (79) in very low yield (1.1%) by the decomposition of the diazonium salt derived from (174).

The deaminated and debenzylated compound (175) was also isolated along with benzaldehyde. Hey et al. also developed another method for the synthesis of cyclohexadienones, involving the formation of an aryne intermediate. The method involves the
intramolecular addition of a carbon atom para to, and activated by, a phenolic hydroxy group and bearing the side chain. The addition of a nucleophile on a side chain to the aryne structure to bring about ring closure was first suggested by Bunnett and Hrutfiord\textsuperscript{133}. In their preparation of the spirodienone \textit{(119b)} Hey et al. treated the bromophenol \textit{(176)} with potassium amide (5 moles) in liquid ammonia. The aryne structure in intermediate \textit{(177)} was attacked by the 1-carbon atom of the other ring to give the dienone \textit{(119b)}. The yield of the dienone was very good (40\%) compared with diazonium salt decomposition methods. No side reaction was noticed.
An Approach to the Synthesis of Crinine

The Amaryllidaceae alkaloids possessing the 5-10b ethano-phenanthridine skeleton have been the focus of a considerable amount of synthetic work recently.\textsuperscript{134-137} Crinine\textsuperscript{138} (180), the representative alkaloid of this group has been synthesised.\textsuperscript{134,135} Although quite different synthetic procedures were adopted by each group, the basic synthetic plan was to some extent the same in all cases. That is, starting from piperonaldehyde, ring C was synthesised, followed by construction of the nitrogen-carrying side chain in all cases. The basic synthetic ideas involved are outlined in the following schemes (1-4):

\textbf{Scheme 1}  
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=\textwidth]{scheme1.png}};
\end{tikzpicture}  

\textbf{Muxfeldt et al.}\textsuperscript{134}
It must be noted however that all the procedures involve many stages and yields are often not very satisfactory. These methods therefore, are of little practical importance.

We decided to investigate other possible synthetic methods for this group of alkaloids which follow from the knowledge of their biosynthesis. Thus, it has been shown that the ring C of these alkaloids is biogenetically derived from the phenolic ring of an O-methylnorbelladine. It was thought therefore that it should be possible to synthesise these alkaloids from appropriate O-methylnorbelladines instead of synthesising the ring C first as in the methods described above. Oxidative coupling of O-methylnorbelladines in vitro has been shown to give very poor results. Since it was known that the compounds such as (178) and (179) undergo rapid cyclisation, the synthesis of dienones

---

Scheme 4

Hendrickson et al.136
such as (87) was planned,

which on cyclisation would give the enone (181).

Among the numerous methods available for the synthesis of dienones, those involving cyclisation of diazonium and aryne intermediates are more in line with the biosynthetic route and are shorter. The enone (181; $R_1=\text{OMe}$, $R_2=\text{H}$) was believed to be an important intermediate in the biosynthesis of the crinine group of Amaryllidaceae alkaloids and for that reason was needed in connection with some biosynthetic investigations in these laboratories. We therefore decided to synthesise this enone (181; $R_1=\text{OMe}$, $R_2=\text{H}$) first and then apply the same method to crininone (181; $R_1R_2=\text{CH}_2$).
The Diazonium Intermediate Approach

It was decided to carry out Pschorr cyclisation of the diazonium salt derived from the amine (182). Similar compounds are known to give dienones with the loss of a methyl group. The amine (182), it was thought, could be prepared by catalytic reduction of the nitro-Schiff's base (183). The latter could be synthesised from O-methyltyramine (184) and 6-nitro-O-benzylisovanillin (185).

6-Nitroisovanillin was prepared by the method of Pschorr and Stoherer\textsuperscript{140} and purified by precipitation from alkaline solution with carbon dioxide. O-Methyltyramine was prepared by lithium aluminium hydride reduction of \( p \)-methoxy-\( \alpha \)-nitrostyrene which in turn was obtained from anisaldehyde and nitromethane.\textsuperscript{141} 6-Nitroisovanillin was benzylated by Hey and Lobs\textsuperscript{142} method. However, an attempt was also made to obtain 6-nitro-\( O \)-benzylisovanillin more directly by nitration of \( O \)-benzylisovanillin. It was found difficult to separate the 2- and 6-nitro derivatives although the desired 6-nitro compound was the major product. However, crystallization of
the mixture of Schiff's bases obtained from the above mixture of aldehydes with \( O \)-methyltyramine, gave the pure \( 6 \)-nitroimino compound (183), m.p. 153\(^\circ\). This was identical with the compound made by the alternative route.

To obtain the amino-phenolic secondary amine (182) from the imine (183), three functional groups, imino, nitro, and \( O \)-benzyl, have to be reduced. Catalytic hydrogenation seemed to be the best method.\(^{143, 144}\) As the imino function is relatively easily reduced, it was thought of interest to stop hydrogenation after the absorption of one mole of hydrogen and to isolate the nitrobenzyloxy secondary amine (186).

In fact, the compound obtained, m.p. 112\(^\circ\), after one mole of hydrogen had been absorbed, though containing a nitro group\(^{145}\) (\( \lambda_{\text{max}} \) 345 nm, \( \epsilon \) 1,778) and the benzyloxy group (benzylic methylene at \( \tau \) 5.0) did not show any n.m.r. signal corresponding to \( NH \) (no change on addition of \( D_2O \)). Moreover, the attempted acylation of this compound instead of giving the \( N \)-acetyl derivative of (186) gave a compound, m.p. 163\(^\circ\), the spectral properties of which suggested it might be (187).
Further investigations on this unidentified compound were not carried out. Instead, sodium borohydride was used to reduce the imine to give (186), m.p. 94°, hydrochloride m.p. 190°. Reduction of the nitro group and hydrogenolysis of the benzylxy group of (186) was done in one step by catalytic reduction (Pd/C) to give the diaminophenol (182). This could not be crystallized and was therefore converted into its hydrochloride which, although a solid, m.p. 110-165°, could not be purified further. However, the n.m.r. spectrum of the uncrystallized free base was quite satisfactory and showed it to be free from gross impurities.

The above aminophenol was diazotized, and decomposition of the diazonium compound was carried out by heating at 70°. The i.r. spectrum of the mixture of products obtained had absorption in the region 1690-1710 cm\(^{-1}\), but the latter disappeared when the mixture was chromatographed on alumina or silica t.l.c. plates. It is possible that this absorption was due to some aromatic aldehyde formed during the course of the reaction as suggested by a weak absorption in the i.r. spectrum at \( \gamma_{\text{max}} = 2720 \text{ cm}^{-1} \) attributable to the C-H vibration of the aromatic aldehyde group.

The same approach was carried out on the compound having a methylenedioxy group instead of the methoxy and phenolic groups in an effort to obtain crininone. Moreover, less polar and cleaner products were expected from a non-phenolic starting material. In order to avoid side-reactions the catalytic method
of decomposition using copper powder was employed at a temperature below 5°. This would also discourage dienone-phenol rearrangements which might occur at higher temperatures in the presence of acid. No carbonyl compound was formed however but a benzotriazine derivative, m.p. 131° was isolated by elution of the products with a benzene-ethyl acetate mixture from alumina. The structure (188) was assigned on the basis of its n.m.r. spectrum and microanalysis. Similar results were reported by Hendrickson et al.\(^{146}\) who obtained the benzotriazinone (189) in an attempt to synthesise lycorine (190) from diazonium compound (191).
The Benzyne Intermediate Approach

At this point, attention was turned to the second route which should be free from the various competing reactions indicated above. 6-Bromopiperonal was condensed with tyramine in methanol to give the corresponding imine, (192), m.p. 159-61°. Treatment of the imine with sodium borohydride gave the amine (193), m.p. 140°.

\[
\begin{align*}
\text{(192)} & \quad \text{OH} \\
\text{Br} & \quad \text{N} \\
\text{(193)} & \quad \text{OH} \\
\text{Br} & \quad \text{NH}
\end{align*}
\]

The amine (193) was treated with potassamide (3 mols) in liquid ammonia for 8 hours. The reaction products were taken up in water and the pH adjusted to 8. The aqueous mixture was extracted with ether and the ethereal extract was washed with aqueous 2N sodium hydroxide to remove the starting material and phenolic products if any. Evaporation of the ether gave no residue, indicating thereby that none of the desired compound was formed.

Since the desired reaction might depend critically on the structure of the starting material and the reaction conditions, it was decided to investigate some simple model compounds. The amine (193) and the compound studied by Hey et al.\textsuperscript{119} differ in several respects. These are:-
(a) The presence in (193) of a methylenedioxy group on the aromatic ring bearing the halogen atom;
(b) The absence in (193) of an alkyl group on the nitrogen atom;
(c) The absence of a carbonyl group in the amine (193);
(d) The presence of a two carbon atom chain in between the nitrogen and the phenolic aromatic ring in (193).

Therefore, to pinpoint the real cause of difficulty of this reaction, it was decided to prepare compounds having structural features with gradual transition from the compound (176) used by Hey et al. to the compound (193) and then try the cyclization reaction on all of them thus checking the effect of each structural feature on the course of reaction. The following sequence of compounds (194-196) was envisaged.

At first, difficulty was found in repeating the known cyclization of the compound (176). However, using liquid ammonia freshly distilled off sodium, a yield of 35\% was observed (all yields quoted are based on starting material consumed).

78.
The compound (194), m.p. 209-10°, though not previously known was readily prepared by standard methods and treated with potassamide (3 mols) in liquid ammonia. The reaction was found to give a 74% yield of the cyclic compound (197), m.p. 246° thus proving that the methylenedioxy group does not inhibit the cyclization. This is supported by a somewhat similar observation by Gibson et al. 147

The compound (195), m.p. 166°, was prepared by treatment of 6-bromopiperonyl bromide (198) with N-methyl-d-aminophenol in acetone in the presence of anhydrous potassium carbonate. Treatment of (195) with potassamide (4 moles) in liquid ammonia for 8 hrs. gave the diene (199) m.p. 189-90° in 16% yield.
This suggested the benzylic methylene group to be an unfavourable structural feature for cyclization, unlike the carbonyl group in (176). Compound (201), m.p. 180-2°C, was prepared by the sodium borohydride reduction of the Schiff's base (200), m.p. 175-176°C, derived from 6-bromopiperonal and p-aminophenol.

\[
\begin{array}{c}
\text{HO} \\
\text{Br} \\
\text{N} \\
\text{O} \\
\text{O}
\end{array}
\quad
\begin{array}{c}
\text{HO} \\
\text{Br} \\
\text{NH} \\
\text{O} \\
\text{O}
\end{array}
\]

(200) \quad (201)

The compound (201) was also treated with potassamide (4 moles) in liquid ammonia. The products obtained showed no carbonyl absorption in the i.r. and no definite compound could be isolated from the complex mixture of products. This shows that, in addition to the presence of an amide carbonyl group, the N-alkyl group is also desirable for cyclization. Possibly, the -NH group ionized in liquid ammonia thus preventing cyclization. Therefore, it was decided to prepare the compound (202) which had a amide carbonyl group and also an N-methyl and was expected to undergo cyclization to give (203). It was thought that the dienone (203) could be converted into the known 138 methine (204) thus establishing a new synthetic route to orinine derivatives.
Q-Benzyl-\(N\)-methyltyramine (205) was prepared by basic hydrolysis of Q-benzyl-\(N\)-methyl-\(N\)-trifluoroacetyltyramine (206). The latter compound was prepared by the methylation of Q-benzyl-\(N\)-trifluoroacetyltyramine (207) in acetone with methyl iodide in the presence of potassium hydroxide.

Hydrogenolysis of Q-benzyl-\(N\)-methylyramine with 10% palladium on charcoal at atmospheric pressure gave \(N\)-methylyramine. Treatment of \(N\)-methylyramine with 6-bromopiperonyl chloride...
in the presence of pyridine in ether gave the amide (202), m.p. 170-2°.

The amide (202) was treated with potassamide (5 moles) in liquid ammonia for 8 hrs. A mixture of four compounds was obtained. The major compound was isolated by preparative t.l.c. on alumina. This compound, m.p. 167°, was shown, from its i.r. and mass spectra, and by accurate mass measurement to be identical with piperonylamide m.p. 167° (lit., m.p. 169°) prepared by standard methods. The above observation points a side reaction responsible for the failure of cyclization in compounds with an ethano chain in between the nitrogen and the phenolic ring. A 1,5-hydride transfer seems to be taking place in the aryne intermediate as shown in the following scheme:
This is further supported by a similar observation in the attempted cyclization\textsuperscript{149} of the compound (208) via an aryne intermediate. Benzoic acid was isolated instead of the desired

\[
\begin{align*}
\text{Br} & \quad \text{N} \\
\begin{array}{c}
\text{O} \\
\end{array} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{COOH} & \quad \text{COOH}
\end{align*}
\]

cyclized product. Formation of benzoic acid was explained in terms of a 1,5-hydride transfer to the aryne followed by hydrolysis of the imidium intermediate.

The present investigations have helped to define the scope and limitations of the diazonium and aryne routes to dienones. It seemed unlikely that a high yield route to the crinine alkaloids could be developed using this approach and further studies were therefore not pursued.
Experimental

M.P. s were measured on a Reichert Kofler block. The i.r. spectra were taken on a Perkin Elmer 257 grating spectrophotograph, n.m.r. spectra on a Perkin Elmer R10 spectrometer, and u.v. spectra on a Unicam SP800 spectrometer.

Nitrosation of Thebaine with Nitrosyl Chloride in Methanol.

Thebaine (2.5 g.) was converted into the hydrochloride by treatment with 0.3N methanolic hydrogen chloride (27 ml.). The hydrochloride was dissolved in dry methanol (50 ml.) and nitrosyl chloride\textsuperscript{150} gas was passed through this solution for one hour. The solvent was evaporated and the residue dissolved in sodium bicarbonate solution. Extraction with chloroform, followed by drying (Na\textsubscript{2}SO\textsubscript{4}) and evaporation gave a gum (1.42 g.). Chromatography of this gum was carried out on neutral alumina (grade V) (50 g.). Elution with chloroform (60 ml.) gave a gummy mixture of two fast running products (\( R_f \approx 0.65 \) and 0.70 on alumina plates in ethyl acetate) (133 mg.), \( \gamma \) max. (CHCl\textsubscript{3}) 1690 cm.\textsuperscript{-1}, \( \gamma \) (CDCl\textsubscript{3}) 3.09 and 3.89 (d, J 10 Hz.), 5.28 (s), 6.22 (s), and 7.51 (s).

Further elution with chloroform (30 ml.) gave the 'methoxy dimer' (72) (130 mg.), m.p. 188-90\textdegree (\( R_f \approx 0.15 \)). The 'methoxy oxime' (52) (420 mg.) (\( R_f \approx 0.05 \)) was obtained by eluting the column further with chloroform (300 ml.). The oxime dissolved sparingly in aqueous sodium hydroxide and was reprecipitated by carbon dioxide but did not give a colour with ferric chloride. It crystallized from ethanol as colourless needles, m.p. 247\textdegree (Found: C, 64.77; H, 6.70;
N, 7.31. \( \text{C}_{20\text{H}_{24}\text{N}_{2}O_{5}} \) requires C, 64.5; H, 6.5; N, 7.5%.

\( \lambda_{\text{max.}} 234 \text{ nm} (\varepsilon 22,100) \) in EtOH, 273 nm (\( \varepsilon 17,150 \)) in EtOH-EtONa; \( \gamma (\text{CDCl}_{3}) 3.56 \) and 5.25 (s), 6.12, 6.45 and 7.07 (s, MeO) and 7.56 (s, MeN), -1.47 \( ((\text{CD}_{3})_{2}) \text{SO} \) (s, oximinohydroxy); \( \gamma_{\text{max.}} (\text{CHCl}_{3}) 3600 \text{ cm}^{-1} \).

Quantitative u.v. Studies on Cholest-4-en-3-one Oxime

Cholestenone oxime \( 46 \) (m.p. 152°) (2.088 mg.) was dissolved in ethanol (10 ml.). This solution (1.5 ml.) was further diluted to 10 ml. This diluted solution (5.0 ml.) was placed in a u.v. cell of 1 cm. path length being compensated by a matched cell containing only the solvent. Absorption was observed at \( \lambda_{\text{max.}} 241 \text{ nm} (\varepsilon 23,050) \) which changed to 262 nm (\( \varepsilon 22,480 \)) upon adding sodium ethoxide. Acidification of the above solution to pH 2 caused an even greater change to \( \lambda_{\text{max.}} 269 \text{ nm} \) (the extinction coefficient could not be determined accurately due to turbidity in the solution.

Conversion of the Methoxy Oxime (52) into its Ethoxy Analogue (53). The methoxy oxime (52) was dissolved in 2.7N ethanolic hydrogen chloride (10 ml.). The solution was left for one hour after which the solvent was evaporated and the residue taken up in sodium bicarbonate solution and extracted with chloroform. The extract was dried (Na₂SO₄) and the solution evaporated. The residual gum crystallized from ethanol to give (53) (70 mg.) as needles, m.p. 245-7°, \( \lambda_{\text{max.}} 234 \text{ nm} (\varepsilon 22,600), \gamma_{\text{max.}} 3600, 3270 \text{ cm}^{-1}, \gamma (\text{CDCl}_{3}) 3.35 \text{ (q, J 8 Hz., aromatic), } 3.56 \text{ (s, } 8\text{-H), } 5.25 \text{ (s, } 5\text{-H),} \)
6.12 (s, methoxy-aryl), 7.56 (s, MeN), 8.74 and 9.29 (t, J 8 Hz., methyls in ketal ethoxy groups), -0.8 (broad band, oximinoxydroxy).

**Hofmann Degradation of the Methoxy Oxime (52)**

The methoxy oxime (52) (1.31 g.) in methanol (35 ml.) was treated overnight with methyl iodide (5 ml.) at room temperature. Evaporation of the solvent and recrystallization gave the methiodide (54) (1.3 g.), m.p. 231° (decomp.), \( \lambda_{\text{max.}} \) 230 nm (\( \epsilon \) 35,545) in EtOH and 285 nm (\( \epsilon \) 19,125) in EtOH-EtONa. The methiodide (54) (860 mg.) in dimethylformamide (75 ml.) was treated at room temperature with potassium t-butoxide (230 mg.) for 0.5 hr. The solvent was evaporated and the residue dissolved in water. Extraction with chloroform, drying (\( \text{Na}_2\text{SO}_4 \)) and evaporation of the solvent gave on recrystallization from methanol the methine (57) (330 mg.) as plates, m.p. 223-4°, \( \lambda_{\text{max.}} \) 257 nm (\( \epsilon \) 18,000) and 350 nm (\( \epsilon \) 12,650), \( \delta^1 \) (CDCl\(_3\)) 3.57 (s), 3.44 and 3.78 (d, J 9.7 Hz.), - 1.8 [s, oximinoxydroxy in (CD\(_3\))\(_2\)SO]. (Found: C, 65.12; H, 6.99; N, 7.45. \( \text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5 \) requires C, 65.27; H, 6.78; N, 7.25%).

**Cleavage of the Oxime Group in (52)**

(1) **Pyruvic acid method**

The oxime (52) (100 mg.) in glacial acetic acid (0.3 ml.) in the presence of sodium acetate (32 mg.) and water (0.2 ml.) was treated overnight at room temperature with pyruvic acid (0.03 ml.). Neutralization of the mixture with sodium bicarbonate solution and extraction with chloroform.

86.
gave only the unreacted oxime (52) (60 mg.).

(ii) Sodium bisulphite method

The oxime (208 mg.) was refluxed in 50% aqueous methanol (20 ml.) for 8 hrs. with a large excess of sodium bisulphite. Methanol was evaporated and the aqueous solution was mixed with chloroform and an excess of dilute hydrochloric acid. Separation of the organic layer after further extraction with chloroform, drying (Na$_2$SO$_4$) and evaporation of the solvent gave a gum (91 mg.), $\nu_{\text{max.}}$ 1700 cm.$^{-1}$. No definite product could be isolated from this gummy mixture.

(iii) Nitrosation method

(a) Pentyl Nitrite and Methanolic Hydrogen Chloride

The oxime (53 mg.) in methanol (3 ml.) was treated with n-pentyl nitrite (0.3 ml.) in the presence of 1.4N methanolic hydrogen chloride (0.6 ml.). The reaction was followed by t.l.c.. No reaction took place even after 16 hrs. treatment at 60°.

(b) Pentyl Nitrite and Acetic Acid

The oxime (790 mg.) in glacial acetic acid (25 ml.) was treated with n-pentyl nitrite (25 ml.) at 50°-60° for 30 mins. and left overnight at room temperature. The reaction mixture was evaporated first on a rotary evaporator and then with an oil pump for 2 hrs. to give a gummy residue (700 mg.). This residue was chromatographed on neutral alumina (grade III) (50 g.). Elution with 50% benzene-ethyl acetate mixture gave a gum (400 mg.). This gum was purified by p.l.c. on alumina
GF<sub>254</sub> in a 5% methanol-ethyl acetate system. The major compound (R<sub>f</sub> 0.65) was separated and recrystallized from ether-pet. ether (b.p. 40<sup>0</sup>-60<sup>0</sup>) mixture to give the enone (58) (100 mg.) as rectangular plates m.p. 137-8<sup>0</sup>, <i>ν<sub>max</sub></i> 1694 cm.<sup>-1</sup>, γ<sub>1</sub> (CDCl<sub>3</sub>) 3.30 (q, J 9 Hz.), 4.12 (s), 5.18 (s), 6.1 (s, methoxy aryl), 6.46 and 7.0 (s, ketal methyls) and 7.5 (s, MeN) (Found: m/e 357.1573, calculated for C<sub>20</sub>H<sub>23</sub>N<sub>0</sub>5, 357.1576). Elution of the column with 10% ethyl acetate-90% benzene gave (59) (63 mg.), m.p. 181<sup>0</sup>, <i>ν<sub>max</sub></i> 1700 cm.<sup>-1</sup>, γ<sub>1</sub> (CDCl<sub>3</sub>) (q, J 9 Hz.), 3.92 (s), 4.10 (s), 5.12 (d), 6.10 (s, MeO aryl), 6.43 (s, Ketal methyl) and 7.03 (d, ketal methyl shielded) (Found: m/e 372.1321, calculated for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>0<sub>6</sub>, 372.1321). Another compound (45 mg.) was also eluted along with (59). This recrystallization from ether gave crystals, m.p. 215<sup>0</sup>, <i>ν<sub>max</sub></i> 1685 cm.<sup>-1</sup>, γ<sub>1</sub> (CDCl<sub>3</sub>) 3.29 (q, J 9 Hz.), 3.81 (s), 4.46 (s), 6.09 (s), 6.12 (s), 6.87 (s).

(c) Sodium Nitrite and Acetic Acid

To the methoxy oxime (52) (313 mg.) in glacial acetic acid (10 ml.) sodium nitrite (690 mg.) was added. The t.l.c. of the reaction mixture after 30 min. indicated the formation of (58) but soon a crystalline precipitate of sodium acetate appeared which slowed down the reaction (no change on t.l.c.). The precipitate was therefore filtered off and more acetic acid (10 ml.) and sodium nitrite (300 mg.) added to the filtrate. But the precipitate reappeared. This was again filtered off and more acetic acid (10 ml.) and sodium nitrite (300 mg.) was
added and the mixture left overnight. T.l.c. examination of the product, however, indicated the reaction to be still incomplete. The reaction mixture was neutralized with sodium bicarbonate and extracted with chloroform to give a gummy residue (272 mg.) which absorbed in the i.r. at \( \nu_{\text{max.}} 3590, 3250, 1694 \text{ cm}^{-1} \). The residue was dissolved in benzene and washed with aqueous 2N sodium hydroxide. The benzene solution, on drying and evaporation, gave a gum (195 mg.). The gum was not further purified.

**Nitrosation of Thebaine with Nitrosyl Sulphuric Acid**

Thebaine (1.038 g.) was treated with 2.75N methanolic hydrogen chloride (1.4 ml.) and anhydrous methanol (20 ml.) was added. Nitrosyl sulphuric acid\(^{150}\) (2.2 g.) (5 moles) was added to this solution. The pale yellow solution soon turned red. The solvent was evaporated after 4 hr. and the red gum was dissolved in water. A precipitate appeared on neutralizing the solution with sodium bicarbonate. The precipitate was filtered off, dissolved in chloroform and washed with water. The organic layer was dried (\( \text{Na}_2\text{SO}_4 \)) and evaporated. The residue when recrystallized from ethanol gave the methoxy dimer (72) as the diethanolate (210 mg.), m.p. 189-90°, \( \nu_{\text{max.}} (\text{CHCl}_3) 3555, 1682 \text{ cm}^{-1} \), \( \lambda_{\text{max.}} 215 \text{ nm (} \varepsilon 34,100) \), 287 nm (\( \varepsilon 4,680 \)) and 360 nm (\( \varepsilon 1,060 \)) in ethanol and \( \lambda_{\text{max.}} 223 \text{ nm (} \varepsilon 49,500) \), 292 nm (\( \varepsilon 6,980 \)) and 360 nm (\( \varepsilon 1,610 \)) in EtOH-EtONa, \( ^{1}H (\text{CDCl}_3) 3.34 \text{ (m), } 3.84 \text{ (q, } J 10, 1.8 \text{ Hz., H-7), } 4.43 \text{ (d, } J 6 \text{ Hz., H-8}' \), 4.63
(s, H-5'), 5.10 (s, H-5), 6.13 and 6.21 (s, aryl methoxyls), 6.41 and 7.15 (s, ketal methoxyls), 7.51 and 7.58 (s, NMe) (Found: m/e 669.3020, calculated for C_{38}H_{43}N_{3}O_{8}, 669.3050) (Found: C, 66.39; H, 7.20; N, 5.57, C_{38}H_{43}N_{3}O_{8}, 2C_{2}H_{5}OH requires C, 66.40; H, 7.20; N, 5.50%)

When ethanol was used as the solvent the work up as above gave the ethoxy analogue of (72) in 20% yield, m.p. 189-90°, \( \delta \text{(CDCl}_3 \text{)} \) 8.76 and 9.42 (t, J 7 Hz.), m/e 697.

**Zinc-Acetic Acid Reduction of Methoxy Dimer (72)**

The methoxy dimer (72) (148 mg.) and zinc dust (152 mg.) in glacial acetic acid (5 ml.) were heated for a few minutes on a heating mantle till the colour of the solution changed to reddish brown. The reaction mixture was poured into saturated sodium bicarbonate solution. The basic solution was extracted with chloroform and the extract dried (Na$_2$SO$_4$) and evaporated. The residue was chromatographed on neutral alumina (grade III). Elution with ethyl acetate gave, in addition to a small amount of a complex mixture of fast running compounds, the unreacted dimer (72) (16 mg.) and the methoxy oxime (52) (35 mg.).

**Diels-Alder Adduct from Thebaine and Nitrosobenzene**

Thebaine (5.0 g.) and nitrosobenzene (1.75 g.) were dissolved in chloroform (25 ml.). The solution was left overnight at room temperature. The solvent was evaporated and the solid residue recrystallized from methanol to give the adduct (68) (5.02 g.), m.p. 120° (decomp.); \( \delta \text{(CDCl}_3 \text{)} \) (q, J 1.9 Hz., 7-H), 4.64 (d, J 9 Hz., 8-H), 5.25
Acetylation of the Methoxy Dimer (72)

The methoxy dimer (72) (328 mg.) in pyridine (15 ml.) was treated with acetic anhydride (3 ml.). The mixture was left overnight at room temperature. The solvent was evaporated on a rotary evaporator and saturated sodium bicarbonate solution added. The aqueous mixture was extracted with chloroform and the extract dried (Na₂SO₄). The solvent was evaporated and the residue was kept in vacuo (oil pump) to remove traces of pyridine. The foamy residue (334 mg.) was dissolved in the minimum of ethanol. After a few minutes crystals began to appear to give the dimer acetate (224 mg.), m.p. 246°; \( \nu_{\text{max.}} \) (CHCl₃) 1772 cm.⁻¹, \( \tau \) (CDCl₃) 2.96 (d, \( J \) 10 Hz., 8-H), 3.19 (s, 1-H), 3.35 (m, 2,2' and 3'-H), 3.82 (q, \( J \) 10, 1.8 Hz., 8-H), 4.48 (d, \( J \) 6 Hz., 8'-H), 4.7 (s, 5'-H), 5.43 (d, \( J \) 1.8 Hz., 5-H), 6.12, 6.26, and 7.14 (s, MeO), 7.50 and 7.58 (s, MeN), 7.64 (s, MeCO) (Found: C, 67.19; H, 6.45; N, 5.97. \( C_{40}H_{45}N_3O_9 \) requires C, 67.48; H, 6.34; N, 5.90%).

Alkali Treatment of the Methoxy Dimer

The methoxy dimer (25 mg.) was added to aqueous 2N NaOH (1 ml.). The solid did not dissolve even on vigorous shaking. The suspension was warmed on a flame to give a yellow solution. Addition of carbon dioxide to the solution gave a precipitate.
which, on filtration and recrystallization, gave a compound, m.p. 189-90°, which was identical in every respect with the methoxy dimer (72). The same procedure using sodium methoxide in methanol, gave the same results.

Rearrangement of 14-Phenylhydroxylaminocodeinone (68)

The compound (68) (60 mg.) was dissolved in ethanol (10 ml.) and 2N ethanolic sodium ethoxide (0.5 ml.) added. The solution was kept at room temperature for 20 min. Solvent was evaporated and water (10 ml.) added. To this solution carbon dioxide was added and the precipitate after filtration and crystallization from ethanol, gave the phenol (74) (35 mg.) m.p. 197° (CHCl₃) 3510, 1695 cm.⁻¹; \( \lambda_{\text{max.}} \) (EtOH) 235 (ε 10,600), 317 (1220), 361 nm. (872); \( \lambda_{\text{max.}} \) (EtOH/EtONa) 254 (ε 12,200), 298 (4,370), 361 nm. (1480); \( \gamma \) (CDCl₃) 2.88 (m, Ph), 3.39 (s, 1,2-H), 3.9 (s, 7,8-H), 4.83 (s, 5-H), 6.22 (s, OMe), 7.46 (s, MeN) (Found: C, 70.52; H, 6.20; N, 6.82. C₂₄H₂₄N₂O₄·1/₂C₂H₅OH requires C, 70.20; H, 6.30; N, 6.60%).

Acetylation of the Phenol (74)

The phenol (74) (100 mg.) in pyridine (3 ml.) was treated with acetic anhydride (1.5 ml.). The reaction mixture was left overnight. The solvent was evaporated and the residue dissolved in aqueous sodium bicarbonate. The aqueous mixture was extracted with chloroform. The extract was dried (Na₂SO₄), evaporated, and the residue recrystallized from ethanol gave the acetate (60 mg.), 92.
m.p. 221-3°; γ (CDCl₃) 2.72 (d, J 9 Hz., 1-H), 2.92 (m, phenyl), 3.29 (d, J 9 Hz., 2-H), 3.95 (s, 7,8-H), 5.20 (s, 5-H), 6.31 (s, MeO), 7.50 (s, MeN), 7.68 (s, MeO);

γ max. (CHCl₃) 1772 cm⁻¹ (Found: C, 70.03; H, 5.52; N, 6.43. C₂₆H₂₆N₂O₅ requires C, 69.94; H, 5.87; N, 6.27%).

Borohydride Reduction of Methoxy Dimer (72)

The methoxy dimer (72) (432 mg.) was dissolved in methanol (100 ml.) and sodium borohydride (635 mg.) was added in small portions with stirring. The reaction mixture was left overnight. The solvent was evaporated and the residue dissolved in water. The aqueous mixture was extracted with chloroform. The extract was dried (Na₂SO₄) and the solvent evaporated to give a colourless crystalline residue (300 mg.). This was chromatographed on alumina (grade V). Elution with chloroform-benzene (9:1) gave the unreacted dimer (58 mg.) and with chloroform-methanol (9:1) the alcohol (73) (210 mg.), m.p. 181-2° after crystallization from ethanol; γ max. (CHCl₃) 3645, 3540 cm⁻¹; γ (CDCl₃) 3.3 (m, aromatic), 4.2 (s, 7,8-H), 4.32 (d, J 6 Hz., 8-H), 4.65 (s, 5'-H), 5.2 (s, 5-H), 6.13 and 6.21 (s, MeO aryl), 6.5 and 7.13 (s, MeO ketal) 7.46 and 7.61 (s, MeN).

Nitrosation of Thebaine with Pentyl Nitrite

a. In the presence of methanol

Thebaine (2.5 g.) was dissolved in a 1:1 mixture (25 ml.) of methanol and chloroform and 1.4 N methanolic hydrogen chloride (27.5 ml.) added. To this solution pentyl nitrite (3.75 ml.) was added and the solution left overnight in a
refrigerator. The solvent was evaporated and the gummy residue dissolved in aqueous 2N sodium hydroxide (17 ml.). A precipitate appeared which was filtered off and washed with water. The washings were combined with the alkaline filtrate. The precipitate on recrystallization from ethanol gave the methoxy dimer (72) (250 mg.). The alkaline solution when neutralized with carbon dioxide gave a precipitate which was collected, washed with water and recrystallized to give the methoxy oxime (58) (1.1 g.).

b. In the presence of ethanol

Thebaine (5.25 g.) was dissolved in 1:1 mixture (22.5 ml.) of chloroform and ethanol and 2.75 N ethanolic hydrogen chloride (11.3 ml.) was added. The solution was cooled in ice and pentyl nitrite (1.8 ml.) was added. The mixture was left in a refrigerator overnight. Addition of ether (25 ml.) gave a white precipitate which redissolved on adding water (25 ml.). The ethereal layer was separated and the aqueous layer was shaken with aqueous 2N sodium hydroxide (37.5 ml.) and left in the refrigerator for 2 hr. The crystals that appeared were filtered off and the filtrate neutralized with carbon dioxide to give a precipitate which, when washed with water and recrystallized, gave the ethoxy oxime (53) (800 mg.). The crystals were dissolved in water and any unreacted thebaine filtered from this aqueous solution. This solution on neutralization with carbon dioxide gave a white precipitate which was filtered and recrystallized to give a compound (1.16 g.), m.p. 234-8°. The n.m.r. spectrum of this compound had the features of the methoxy as well as 94.
the ethoxy oximes except for the absence of a shielded methoxy signal at τ 7.07. The methoxy signal at τ 6.45 and the methyl triplet signal at τ 8.74 had intensities less than those required for three protons each. However the combined intensities of both the signals were equivalent to a three proton signal thus each complementing the other.

Nitration of Isovanillin

Isovanillin (10.4 g.) in acetone (50 ml.) was cooled to 0° and fuming nitric acid (12 ml.) was added dropwise while keeping the temperature of the reaction mixture below 10°. After the addition was complete, the reaction mixture was quickly transferred to a beaker containing water (100 ml.). The solid was filtered off and dissolved in aqueous 0.5N sodium hydroxide. Solid carbon dioxide was added until a solid precipitated. More carbon dioxide was added to complete the precipitation. Filtration of the solid and recrystallization from ethanol gave 6-nitroisovanillin (1.25 g.), m.p. 189° (lit. 140° 189°). The filtrate on acification with dilute hydrochloric acid gave a precipitate which was collected and recrystallized to give 2-nitroisovanillin (4.0 g.), m.p. 148° (lit. 140° 148-9°).

0-Benzyl-6-nitroisovanillin

A mixture of 6-nitroisovanillin (0.79 g.), ethanol (5 ml.), water (7 ml.), anhydrous sodium carbonate (1.1 g.) and benzyl chloride (5.0 g.) was refluxed for 4 hr. Water (10 ml.) was added and the excess of benzyl chloride was
removed by steam distillation. The residual oil solidified to give yellow needles. Recrystallization from ethanol gave \(O\)-benzyl-6-nitroisovanillin (0.87 g.), yellow needles, m.p. 133.5-4° (lit. 134°).

**p-Methoxy-\(\alpha\)-nitrostyrene**

To anisaldehyde (50 ml.) in nitromethane (250 ml.) was added ammonium acetate (2 g.). The mixture was refluxed for one hour, cooled and evaporated to dryness. The solid was dissolved in water and extracted with benzene. The extract was dried (\(Na_2SO_4\)) and then evaporated to give a yellow solid which was recrystallized from benzene to give \(p\)-methoxy-\(\alpha\)-nitrostyrene (50 g.), m.p. 88° (lit. 86-87°).

**O-Methyltyramine**

The nitrostyrene (1.2 g.) prepared above was extracted (soxhlet) into a refluxing suspension of lithium aluminium hydride (2 g.) in sodium-dried ether (70 ml.). The excess of the reagent was destroyed with ethyl acetate and water. The ether layer was separated and the pasty aqueous layer further extracted with ether. Evaporation of the dried (\(MgSO_4\)) ethereal solutions gave an oil which was converted into \(O\)-methyltyramine hydrochloride (50%) m.p. 205-206°. The free base was regenerated with aqueous ammonium hydroxide to give a colourless oil, b.p. 125-6°/8 mm (lit. 153° 129-30°/12 mm.).
Nitration of O-Benzylisovanillin

O-Benzylisovanillin (10 g.) in glacial acetic acid (35 ml.) was added dropwise with constant stirring to fuming nitric acid (35 ml.). The mixture was stirred for another 2 hr. then poured into cold water (100 ml.) and the resulting precipitate filtered off. The solid on recrystallization from ethanol gave yellow needles (7 g.), m.p. 120-121°.

Preparation of Schiff's Base (183)

O-Benzyl-6-nitroisovanillin (226 mg.) and O-methyltyramine (196 mg.) were dissolved in benzene (25 ml.). The solution was refluxed for 1 hr. and the solvent evaporated to give a yellow solid. The solid when recrystallized from benzene gave the compound (183) (362 mg.), m.p. 153°, \( \gamma (\text{C}_{6}\text{H}_{5}\text{COOH}) 0.9 \text{ (d, } J 15.5 \text{ Hz.}), 2.02 \text{ (s), 2.53 \text{ (s, phenyl), 2.75 \text{ (q, } J 10, 7 \text{ Hz.}), 4.68 \text{ (s, benzylic CH}_2\text{), 5.65 \text{ (m), 5.65 and 5.89 \text{ (s, MeO)}}, 6.75 \text{ (t, } J 7 \text{ Hz.}), \) (Found: C, 69.0; H, 5.6; N, 6.6. \( \text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_5 \) requires C, 68.9; H, 5.75; N, 6.7%).

Catalytic Hydrogenation of (183)

The imine (218 mg.) was dissolved in sulphur free benzene and the catalyst (10% Pd/C) (25 mg.) was added. Hydrogenation slowed down after 41 ml. of hydrogen absorption. The catalyst was filtered off and the solvent evaporated. Crystallization of the gummy mass from methanol-ether gave a pale yellow crystalline compound (27 mg.), m.p. 112°; \( \gamma_{\text{max.}} 3420, 1628 \text{ cm}^{-1}, \lambda_{\text{max.}} \) (EtOH) 275 (\( \varepsilon \) 2,630) and
345 nm (ε 1,778); τ (CDCl₃) 1.9 (s), 2.62 (s, phenyl), 3.0 (q, J 9, 10 Hz.), 3.28 and 3.82 (s, aromatic), 5.0 (s, CH₂-O⁻, 6.18 and 6.24 (s, MeO), 6.25 (m, CH₂) and 7.12 (s, CH₂N).

**Acetylation of Hydrogenation Product**

The above compound (73 mg.) was dissolved in the minimum quantity of acetic anhydride. After a few minutes at room temperature water was added and the mixture evaporated to dryness. The residue crystallized from ethanol to give a substance, m.p. 163°; τ (CDCl₃) 0.31 (s), 1.5 (s), 2.6 (s, phenyl), 2.92 (s), 4.85 (s, CH₂), 6.0 (s, MeO), 7.78 (s, CH₂CO).

**Borohydride Reduction of (183)**

The imine (183) (1.67 g.) was suspended in methanol (50 ml.). Sodium borohydride (0.32 g.) was added in small portions to the stirred suspension. Stirring was continued for half an hour, the solvent evaporated to one-third its volume, and water added with continuous swirling until precipitation was complete. The precipitate was collected and recrystallized to give (186) as yellow crystals (1.56 g.), m.p. 94° (hydrochloride m.p. 190°); τ (CDCl₃) 2.35 (s), 2.60 (s, phenyl), 2.81 (s), 3.01 (q, J 10, 9 Hz.), 4.81 (s, CH₂Ph), 5.99 (s, CH₂-PhNO₂), 6.10 and 6.28 (s, MeO), 7.26 (s, -CH₃-CH₃-), 8.2 (s, NH) (Found: C, 68.29; H, 6.03; N, 6.68. C₂₄H₂₆N₂O₅ requires C, 68.23; H, 6.20; N, 6.63%).

98.
Preparation of the Aminophenol (182)

The above nitroamine (1.45 g.) was dissolved in methanol (100 ml.) and conc. hydrochloric acid (0.45 ml.) was added. The catalyst (10% Pd/C) (143 mg.) was added carefully to the solution and hydrogenation carried out at atmospheric pressure till no more hydrogen was absorbed. The catalyst was filtered off and solvent evaporated to give the aminophenol (182) hydrochloride (0.88 g.), m.p. 110-165°C. The hydrochloride was dissolved in water and saturated sodium bicarbonate added to give a greenish precipitate. The precipitate was extracted with chloroform and the extract dried (Na2SO4). Evaporation of the solvent gave an uncrystallizable substance, \( \delta \) (CDCl3) 3.01 (q, \( J = 10.9 \) Hz.), 3.38 and 3.75 (s,), 6.19 and 6.21 (s, MeO), 6.31 (s, CH2), 6.55 (s, broad band NH, NH2), 7.21 (t, CH2-CH2).

Thermal Decomposition of Diazonium Salt of (182)

The hydrochloride (95 mg.) of the aminophenol (182) was dissolved in 12% hydrochloric acid (50 ml.). While stirring the solution at 0°C, 8% sodium nitrite solution (5 ml.) was added. Stirring was continued for one hour. The solution was gradually warmed to 70°C and was kept at this temperature for one hour. The solution was neutralized with sodium bicarbonate and extracted with chloroform. The extract was dried (MgSO4) and the solvent evaporated to give a gummy material (40 g.), \( \nu_{\text{max.}} \) 2720, 1710, 1680 cm\(^{-1}\). The t.l.c. of the gum showed it to be a mixture of several compounds. The separation of the mixture on t.l.c. silica
gel plates gave fractions none of which had any carbonyl absorption in the i.r.

**Nitration of Piperonal**

Piperonal (30 g.) in carbon tetrachloride (100 ml.) was stirred at 0° and fuming nitric acid (85 ml.) was carefully added so that the temperature did not rise above 20°. After the addition was complete, water (50 ml.) was added and the mixture filtered. The precipitate was washed with water and recrystallized from methanol to give 6-nitropiperonal (31.5 g.) as yellow crystals, m.p. 84–5° (lit. 153 m.p. 85°); \( \gamma \) (CF\(_3\)COOH) - 0.4 (s, CHO), 2.35, 2.54 and 3.71 (s). The filtrate separated into two layers. The organic layer on evaporation and recrystallisation gave a substance, m.p. 146–47°, as yellow needles (2.65 g.); \( \gamma \) (CF\(_3\)COOH) 1.97 (q, \( \delta \) 9, 2.5 Hz.), 2.28 (d, \( \delta \) 2.5 Hz.), 3.06 (d, \( \delta \) 9 Hz.), 3.84 (s). The n.m.r. spectrum suggests it to be 3,4-methylenedioxy-nitrobenzene (lit. 154 m.p. 147°).

**Preparation of the Schiff's Base from 6-Nitropiperonal and O-Methyltyramine**

6-Nitropiperonal (1.97 g.) and O-methyltyramine (1.51 g.) were dissolved in methanol (100 ml.) and the solution refluxed for 15 min. Evaporation of the solvent and recrystallization of the crystalline residue gave the imine (2.51 g.) as yellow needles, m.p. 88°; \( \gamma \) (CDCl\(_3\)) 1.42 (s), 2.56 (s), 3.01 (q, \( \delta \) 10.9 Hz.), 3.9 (s), 6.11 (t, \( \delta \) 7 Hz.), 6.23 (s, MeO), 7.05 (t, \( \delta \) 7 Hz.) (Found: C, 62.02; H, 4.87; N, 8.4. C\(_{17}\)H\(_{16}\)N\(_2\)O\(_5\) requires C, 62.19; H, 4.91; N, 8.53%).
Preparation of \( N-(6-\text{Nitropiperonyl})-O\text{-methyltyramine} \)

The above imine (1.85 g.) in methanol (100 ml.) was cooled and sodium borohydride (1.0 g.) was added portionwise with stirring. Stirring was continued for half an hour. The solvent was evaporated and the residue recrystallized from methanol to give the desired amine (1.4 g.), m.p. 130°C; hydrochloride, m.p. 200°C. The free amine had

\[
\begin{align*}
\tau (\text{CDCl}_3) & \quad 2.55 (s), \quad 2.95 (s), \quad 3.02 (q, J 9 \text{ Hz.}), \quad 3.98 (s), \quad 6.03 (s), \quad 6.26 (s, \text{MeO}), \quad 7.22 (t, J 3 \text{ Hz.}) \quad \text{and} \quad 8.36 (s, \text{NH}) \quad \text{(Found: C, 61.76; H, 5.44; N, 8.36. \quad C_{17}H_{18}N_{2}O_{5} \quad \text{requires} \quad C, 61.81; H, 5.49; N, 8.48%).}
\end{align*}
\]

Preparation of \( N-(6-\text{Aminopiperonyl})-O\text{-methyltyramine} \)

The above amine (0.7 g.) was hydrogenated in methanol (50 ml.) using 10% Pd/C catalyst (0.1 g.). The catalyst was filtered off and the solvent evaporated. The oily residue was dissolved in ethanol (5 ml.) and 25% sulphuric acid added till the mixture became acidic. The amine sulphate crystallized out. The mixture was heated on the water bath for a few minutes and the pinkish crystals (0.5 g.) collected; m.p. 140°C; \( \tau (\text{CF}_3\text{COOH}) 2.79 (\text{AB quartet}, J 9 \text{ Hz.}), \quad 2.85 (s), \quad 2.95 \quad \text{and} \quad 3.88 (s), \quad 5.45 (m), \quad 6.0 (s, \text{MeO}), \quad 6.35 \quad \text{and} \quad 6.8 (m). \)

Decomposition of Diazonium salt from \( N-(6-\text{Aminopiperonyl})-O\text{-methyltyramine} \)

The above amine sulphate (1.1 g.) was suspended in 2N sulphuric acid (30 ml.) and cooled to -6°C. 30% Aqueous
sodium nitrite solution (3 ml.) was added over 15 min.

Acetone (25 ml.), cooled to -15°, was added to the solution followed by copper powder (1 g.). The mixture was stirred for 2 hr. and then basified with sodium bicarbonate and filtered. Acetone was evaporated from the filtrate and the resulting suspension extracted with chloroform (3 x 50 ml.). The extract was dried (Na₂SO₄) and evaporated to give a gum (0.5 g.). The t.l.c. of the gum indicated it to be a complex mixture of many compounds. One major, fast running component was separated on alumina (grade I). Elution with benzene-ethyl acetate (2:1) gave the major compound benzotriazine (188) (40 mg.), m.p. 136° (ex. benzene); \[ \delta (\text{CDCl}_3) \]

- 2.99 (q, J 9 Hz.), 3.06 (s), 3.70 (s), 4.05 (s), 5.8 (s),
- 6.0 (t, J 7 Hz.), 6.01 (s, MeO), 7.02 (t, J 1 Hz.) (Found:
  - C, 65.50; H, 5.52; N, 13.24. C₁₇H₁₇N₂O₃ requires C, 65.58; H, 5.50; N, 13.50%).

**Bromination of Piperonal**

To piperonal (100 g.) in glacial acetic acid (200 ml.) was added bromine (40 ml.) in acetic acid (100 ml.) drop-wise with constant stirring. Stirring was continued for 48 hr. then the reaction mixture was poured into water (2 l.). The resulting precipitate was collected and washed with carbon tetrachloride. Recrystallization from ethanol gave 6-bromopiperonal (75 g.), m.p. 128° (lit. 155° 127-85°); \[ \delta (\text{CDCl}_3) \]

- 0.42 (s, CHO), 2.62 and 2.92 (s) and 3.90 (s, methylenedioxy).
Decarboxylation of Tyrosine

Tyrosine (16 g.) was mixed with diphenylamine (100 g.) and the mixture heated on a Wood's metal bath to 260°. The mixture was kept at this temperature till the evolution of carbon dioxide ceased. The liquid mixture was poured into a 600 ml. beaker, cooled to 80° and petroleum ether (60°-80°) (100 ml.) added with constant stirring. The mixture while still a semi-solid, was poured into Soxhlet thimbles, which were then extracted with light petroleum (40°-60°) till no more diphenylamine was extracted. The residue was sublimed at 180° under reduced pressure (1 mm. Hg) to give tyramine (10 g.), m.p. 164° (lit. 156-165°).

Preparation of the Amine (193) and the Imine (192)

6-Bromopiperonal (1.05 g.) and tyramine (0.54 g.) were dissolved in methanol (100 ml.) and the mixture stirred for 4 hr. Sodium borohydride (250 mg.) was added to the above solution portionwise and stirring continued further for 2 hr. The solvent was evaporated, the residue treated with water and extracted with chloroform. The extract was dried (Na₂SO₄) and the solvent evaporated. The residue recrystallized from ethanol to give the amine (193) (1.25 g.), m.p. 140°; 140°; T (CDCl₃) 2.96 and 3.3 (d, J 8 Hz.), 3.02 and 3.19 (s), 4.08 (s), 6.22 (s, CH₂) (6.30 (broad singlet, NH), 7.20 (t, J 3 Hz.), (Found: C, 55.20; H, 4.53; Br, 23.17. C₁₆H₁₆BrN₃O₂ requires C, 54.80; H, 4.57; Br, 22.80%).

The intermediate imine (192) was also isolated in some cases by evaporation of methanol to give colourless crystals,
m.p. 159°-61°; \( \gamma (\text{CF}_3\text{COOH}) \) 1.60 (d, \( J \approx 17 \text{ Hz.} \)), 2.87 (m), 3.77 (s), 5.77 (q, \( J \approx 7.5 \text{ Hz.} \)), 6.82 (t, \( J \approx 5 \text{ Hz.} \))

(Found: C, 55.17; H, 4.02; N, 4.02. \( \text{C}_{16}\text{H}_{14}\text{BrNO}_{3} \) requires C, 55.28; H, 4.29; N, 3.95%).

Procedure for the Potassium Treatment of Bromophenols

Liquid ammonia (50 ml.) was distilled over sodium into a Quickfit Dewar flask (100 ml.). Small pieces of potassium were added with stirring until a permanent blue colour was observed. A single crystal of ferric nitrate was added, followed by the required amount of potassium. When the initial blue colour had faded to grey (ca. 10 min.) the dry, finely powdered phenol was added in small portions. Any reactant adhering to the neck of the flask was washed down with a small quantity of dry ether. After the required reaction time an excess of ammonium chloride was added. The mixture was diluted with ether (100 ml.) and the ammonia allowed to evaporate off overnight.

Potassium Treatment of (193) in Liquid Ammonia

The bromophenol (193) (326 mg.) was treated in liquid ammonia (50 ml.) with potassamide prepared from potassium (214 mg.). The ethereal extract was washed first with aqueous 2N sodium hydroxide and then with water, dried \( \text{(Na}_2\text{SO}_4) \) and evaporated to give a gum (44 mg.) which exhibited no absorption in the carbonyl region of the i.r.

T.l.c. examination indicated it to be a mixture of several components. Acidification of the alkaline washings gave the bromophenol (110 mg.).
Preparation of 6-Bromopiperononic Acid

6-Bromopiperonal (5.7 g.) was dissolved in acetone (25 ml.) and to this solution, potassium permanganate (15 g.) dissolved in 50% aqueous acetone (300 ml.) was added with constant stirring. The mixture was stirred for one hr. at room temperature and then refluxed for one hr. The reaction mixture was cooled and sulphur dioxide gas passed through the mixture till all the manganese dioxide dissolved. Acetone was evaporated and the precipitate filtered. The precipitate was dissolved in 2N sodium hydroxide (25 ml.) and the solution acidified. The resulting precipitate was filtered off, washed with water, dried, and sublimed under reduced pressure to give 6-bromopiperononic acid (3 g.), m.p. 209° (Found: C, 39.18; H, 2.04 C₈H₅BrO₄ requires C, 39.32; H, 2.24%).

Preparation of the Bromophenol (194)

6-Bromopiperonoyl chloride (1.023 g.), prepared by refluxing 6-bromopiperononic acid with thionyl chloride, was added to a suspension of p-hydroxy-N-methyl aniline sulphate (Metol) (184 mg.) in a 50% pyridine-ether mixture (50 ml.). The mixture was stirred for 4 hr. till a gum separated out. The mixture was poured into dilute hydrochloric acid and extracted with methylene dichloride. The solvent was evaporated and the residue refluxed with 2N sodium hydroxide (50 ml.) for one hr. The aqueous solution was acidified and extracted with ether. The ethereal extract
was washed first with saturated aqueous sodium bicarbonate and then with 10% aqueous sodium hydroxide. Acidification of the sodium bicarbonate washings gave bromopiperonylic acid (0.708 g.) while acidification of the sodium hydroxide washings gave a precipitate of the bromophenol (194) which crystallized from ethanol (0.233 g.), m.p. 209-10°C (Found: C, 51.30; H, 3.22; N, 4.21; Br, 22.45. C_{15}H_{12}BrNO_{4} requires C, 51.42; H, 3.42; N, 4.00; Br, 22.85%).

Preparation of the Dienone (197)

The bromophenol (194) (198 mg.) was treated in liquid ammonia (50 ml.) with potassium (4.5 moles) from potassium metal (100 mg.). Treatment was continued for 8 hr. after which an excess of ammonium chloride was added to the reaction mixture. Ether (100 ml.) was added and the ammonia allowed to evaporate overnight. The ethereal solution was extracted with 2N sodium hydroxide. Acidification of the alkaline extract gave no starting material. The ether layer was washed with water and dried (Na_{2}SO_{4}). Evaporation of the solvent and recrystallization of the crystalline residue from ethanol gave the dienone (197) (114 mg.), m.p. 246°C, as pale yellow needles; $\nu_{\text{max.}}$ (CHCl$_3$) 1669 cm.$^{-1}$; $\gamma$(CDCl$_3$) 2.70 (s), 3.33 (s), 3.50 (s, vinyl protons), 3.90 (s, methylenedioxy) and 7.02 (s, MeN) (Found: C, 67.05; H, 3.92; N, 5.37. C$_{15}$H$_{11}$NO$_4$ requires C, 66.91; H, 4.12; N, 5.20%).

Borohydride Reduction of 6-Bromopiperonal

To 6-bromopiperonal (10 g.) in methanol (100 ml.) was
added sodium borohydride (1.0 g.) in small portions with constant stirring. Stirring was continued for one hr. The solution was evaporated to half its volume and water (50 ml.) was added. The product was collected and recrystallized from methanol to give 6-bromopiperonyl alcohol (8 g.), m.p. 90° (lit. 157° 90°); \( \gamma \) (CDCl\textsubscript{3}) 3.02 (s, aromatic), 4.03 (s, methylenedioxy), 5.39 (d, \( J \) 6 Hz. benzylic), 7.65 (t, \( J \) 6 Hz., OH).

**Preparation of 6-Bromopiperonyl Bromide (198)**

6-Bromopiperonyl alcohol (4.6 g.) was dissolved in benzene (100 ml.). Hydrobromic acid (48%, 6 ml.) was added and the reaction mixture stirred for two hr. The reaction mixture was dried (Na\textsubscript{2}SO\textsubscript{4}) and the solvent evaporated. Recrystallization of the residue from methanol gave 6-bromopiperonyl bromide (198) (3.5 g.), m.p. 91° (lit. 158° 94°); \( \gamma \) (CDCl\textsubscript{3}) 2.92 and 3.01 (d, \( J \) 2 Hz.), 3.93 and 5.38 (s).

**Preparation of N-(6-Bromopiperonyl)-N-methyl-p-aminophenol (195)**

6-Bromopiperonyl bromide (2.34 g.) and N-methyl-p-aminophenol (0.98 g.) in acetone (100 ml.) were refluxed in the presence of anhydrous potassium carbonate (1.0 g.) for 4 hr. The reaction mixture was filtered and the filtrate evaporated. The residue on recrystallization from ethyl acetate gave the bromophenol (195) (550 mg.), m.p. 166° (Found: C, 53.32; H, 4.31; N, 3.95; Br, 24.01. \( \text{C}_{15}\text{H}_{14}\text{BrNO}_{3} \) requires C, 53.57; H, 4.16; N, 4.16; Br, 23.81%)
(CF₃COOH) 2.45 and 2.87 (d, J 11 Hz.), 2.78 (s), 3.68 and 3.98 (s), 4.60 (d, J 6 Hz.), 7.59 (s).

Preparation of the Dienone (199)

The bromophenol (195) (326 mg.) in liquid ammonia (50 ml.) was treated with potassamide, prepared from potassium metal (154 mg., 4 moles), for 8 hr. Ammonium chloride (1 g.) and ether (100 ml.) were added and the mixture left overnight. The ethereal solution was washed with 2N sodium hydroxide and the ether evaporated. The residue (57 mg.) was chromatographed on neutral alumina (grade I). Elution with benzene-ethylacetate (9:1) gave the dienone (199) (34 mg.), m.p. 189-90°C; \( \nu_{\text{max.}} ^{(\text{CHCl}_3)} 1699 \text{ cm}^{-1} \); \( \nu_{\text{max.}} ^{(\text{CDCl}_3)} 3.12 \) and 3.62 (d, J 10 Hz.), 3.20, 4.02, 5.85 and 7.51 (s) (Found: C, 70.31; H, 5.39; C₁₅H₁₃NO₃ requires C, 70.58; H, 5.13%).

Preparation of the Imine (200)

p-Aminophenol (1 g.) and 6-bromopiperonal (2.2 g.) in methanol (100 ml.) were stirred for 4 hr. Evaporation of the solvent and recrystallization from methanol gave the imine (200) (1.8 g.), m.p. 175-76°C (Found: C, 52.71; H, 3.34; N, 4.27. C₁₄H₁₆BrNO₃ requires C, 52.50; H, 3.12; N, 4.37%).

Reduction of the Imine (200)

The imine (1.5 g.) in methanol (50 ml.) was treated with sodium borohydride (8 moles) in small portions. Reaction was continued for 4 hr. The solvent was evaporated and the residue treated with water. The aqueous mixture was
extracted with benzene, the extract dried (Na$_2$SO$_4$) and benzene evaporated. The residue when recrystallized from ethanol gave the aminophenol (201) (1.2 g.), m.p. 182°; $\delta$(CDCl$_3$) 2.95 and 3.25 (s), 3.25 and 3.52 (d, $\delta$ 9 Hz.), 4.06 (s), 5.32 (s, NH) and 5.52 (s).

Potassiumamide Treatment of the Bromophenol (201)

The bromophenol (201) (0.5 g.) was treated with potassiumamide (4 moles) in liquid ammonia (50 ml.) for 22 hr. Ammonium chloride (1 g.) and ether (100 ml.) were added and the reaction mixture left overnight. The ethereal solution was extracted with 2N sodium hydroxide and the extract acidified to give the starting material (30 mg.). The ethereal layer was evaporated to give a residue (112 mg.). This gummy residue showed no carbonyl absorption in the i.r. and no definite compound could be isolated by chromatography on alumina.

p-Benzylhydroxybenzaldehyde

p-Hydroxybenzaldehyde (25 g.) was refluxed for 4 hr. with 50% aqueous ethanol (200 ml.) in the presence of benzyl chloride (100 ml.) and anhydrous sodium carbonate (30 g.). The excess of benzyl chloride was steam distilled out and the solidified benzyl ether filtered off, washed with water and recrystallized from aqueous ethanol to give p-benzylhydroxybenzaldehyde (40.3 g.), m.p. 70-72° (lit. 159 m.p. 72°)

p-Benzylhydroxybenzaldehyde (40 g.) in glacial acetic acid (100 ml.) was refluxed with nitromethane (30 ml.) in the
presence of ammonium acetate (10 g.) for 4 hr. The excess of nitromethane and some acetic acid was evaporated off and the remaining solution poured onto crushed ice (150 g.). The resulting greenish solid was collected and recrystallized from ethanol to give p-benzyloxy-ω-nitrostyrene (27 g.), m.p. 121-122° (lit. 160 120°).

O-Benzyltyramine

p-Benzylloxy-ω-nitrostyrene (27 g.) was extracted from a soxhlet thimble into dry ether (800 ml.) containing lithium aluminium hydride (15 g.) during 24 hr. The excess of lithium aluminium hydride was decomposed with ethyl acetate and water was added. The ethereal layer was decanted off and the residual white paste further shaken twice with ether (500 ml.). The ethereal solutions were combined and washed first with sodium hydroxide solution and then with water. The ethereal solution was dried (Na₂SO₄) and evaporated to give an oil which was distilled to give O-benzyltyramine (23 g.), b.p. 129°/9 mm (lit. 161 130°/12 mm).

N-Trifluoroacetyl-O-benzyltyramine (207)

To O-benzyltyramine (550 mg.) was added trifluoroacetic anhydride (1.5 ml.) and the mixture stirred overnight. Water (5 ml.) was added and the crystalline precipitate filtered off and recrystallized from aqueous ethanol to give the desired amide (207) (547 mg.), m.p. 135-37° (Found: C, 62.96; H, 5.44 C₁₇H₁₆F₃NO₂ requires C, 63.15; H, 4.95%).
N-Trifluoroacetyl-N-methyl-O-benzyltyramine (206)

To O-benzyl-N-trifluoroacetyltyramine (1.2 g.) in dry acetone (12 ml.) was added methyl iodide (1 ml.). The mixture was warmed and freshly powdered potassium hydroxide (800 mg.) was added. The mixture was refluxed for 10 min. The excess of methyl iodide and acetone were evaporated on a rotary evaporator and the final traces removed using an oil pump. Water (20 ml.) was added to the residue and dilute hydrochloric acid added till the mixture became acidic. The suspension was repeatedly extracted with ether (20 x 10 ml.) and the yellow ethereal solution dried (Na₂SO₄) and evaporated. The residue when recrystallized from aqueous ethanol gave the N-methylamide (206) (700 mg.), m.p. 72° (Found: C, 63.77; H, 5.10; N, 4.32. C₁₈H₁₆F₃N₂O₂ requires C, 64.09; H, 5.34; N, 4.15%).

O-Benzyl-N-methyltyramine (205)

The amide (206) (640 mg.) was dissolved in ethanol (20 ml.) and 2N sodium hydroxide (5 ml.) added. The mixture was refluxed for 2.5 hr. After cooling, the reaction mixture was acidified and extracted with ether. The extract was dried (Na₂SO₄) and the ether evaporated to give an oil. The oil was treated with ethanolic hydrogen chloride and the solid hydrochloride thus formed was recrystallized from ethanol to give O-benzyl-N-methyltyramine hydrochloride (480 mg.), m.p. 214° (lit. 163-215°).
N-Methyltyramine

The above hydrochloride (480 mg.) was suspended in ethanol (60 ml.) and 10% Pd/C catalyst (60 mg.) added. Hydrogenation was carried out till no more hydrogen gas was absorbed. The reaction mixture was filtered and the filtrate evaporated to give a residue which, when recrystallized from ethanol, gave N-methyltyramine hydrochloride (350 mg.), m.p. 147-49°C (lit. 164-148.5°C).

N-(6-Bromopiperonoyl)-N-methyltyramine (202)

N-Methyltyramine hydrochloride (550 mg.) was dissolved in a mixture of dry pyridine (20 ml.) and ether (30 ml.) and 6-bromopiperonoyl chloride, prepared from 6-bromopiperonylic acid (750 mg.), in ether (50 ml.) was added dropwise with stirring. The mixture was stirred for 4 hr., after which time dilute hydrochloric acid was added till the mixture became acidic. The two layers were separated and the aqueous layer further extracted with more ether. The combined ethereal extracts were further washed first with dilute hydrochloric acid and then with water. The washed ethereal solution was dried (Na₂SO₄) and the ether evaporated. The residue was dissolved in ethanol (20 ml.) and 2N sodium hydroxide (10 ml.) was added and the mixture refluxed for 30 min. The excess of ethanol was evaporated and the solution acidified. The acidic solution was repeatedly extracted with ether. The ethereal extract was extracted first with saturated sodium bicarbonate solution and then with 2N sodium hydroxide solution. The latter extract was acidified.
and extracted with ether. The ethereal solution was dried (Na₂SO₄) and the ether evaporated. The residue on recrystallization from ether gave the compound (202) (330 mg.), m.p. 170-72°. (Found: C, 54.05; H, 4.36. C₁₇H₁₆BrNO₄ requires C, 53.96; H, 4.23%).

**Potassium Treatment of the Compound (202)**

The compound (202) (300 mg.) in liquid ammonia (50 ml.) was treated with potassium amide (5 moles) prepared from potassium metal (170 mg.). The treatment was carried out for 8 hr., after which time ammonium chloride (1 g.) was added followed by ether (100 ml.). The reaction mixture was left overnight. Water (100 ml.) was added and the two layers separated. The aqueous layer was further extracted with chloroform and the two organic extracts combined. Evaporation of the solvent gave a residue (70 mg.), the t.l.c. examination of which showed it to be a mixture of one major and two minor components. The major compound was separated by p.l.c. on alumina plates (0.5 mm). Recrystallization from ethanol gave piperonylamide (18 mg.), m.p. 167° (lit. 165-169°); ν max. 1675, 1590 cm⁻¹, accurate mass measurement: m/e 165.0433, calculated mass for C₆H₅O₃, m/e 165.0426.
References

18. O. Hesse,
    Ann., 1870, 152, 47.

115.
47. P.Horsewood and G.W.Kirby, unpublished work.
51. V.Klintz, Dissertation Univ. Wien 1944.


63. J.R.Lewis, Chem. and Ind., 1964, 1672.


78. W.Riedel, Ber., 1952, 85, 692.

118.


109. W.S.Johnson, P.J.Kropp, and K.O.Gelotte,


114. Reference 57, p. 139-40, and references therein.


140. Pscorr and Stohrer, Ber., 1902, 35, 4393.


