The reactions of thebaine with C-nitroso-compounds

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THE REACTIONS OF THEBAINE WITH

C-NITROSO COMPOUNDS

by

PETER HORSEWOOD, B. Tech.

A Doctoral Thesis

Submitted in partial fulfilment of the requirements
for the award of

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Supervisor: Prof. G.W. Kirby, M.A., Ph.D., Sc.D., F.R.I.C.
Department of Chemistry

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SUMMARY

The reactions of thebaine with nitrosoarenes to form Diels-Alder adducts have been investigated. Reversibility of the addition of a series of para-substituted nitrosoarenes to thebaine has been qualitatively studied by n.m.r. spectrometry. The direction of the addition was found to be highly stereospecific giving adducts that were readily hydrolysed to previously inaccessible 14-aminocodeinone derivatives. No adducts of nitrosoalkanes with thebaine could be prepared but the parent codeinone corresponding to a formal addition of monomeric hyponitrous acid to thebaine was readily formed by reaction of the latter with 1-chloro-1-nitrosocyclohexane in acid solution.

Nitrosyl cyanide, formed from reaction of nitrosyl chloride with silver cyanide, was found to react with thebaine to give a normal adduct. With the dienophile in excess an N-cyanomethylnorthebaine-nitrosyl cyanide adduct was obtained. Evidence for the existence and structure of nitrosyl cyanide was investigated further by undertaking a study of its reactions with other conjugated dienes to give N-cyano-1,2-oxazines. The visible spectrum of the green gaseous products from reaction of nitrosyl chloride with silver cyanide showed an n → π* transition with a maximum absorption at 738 nm. This is a typical absorption maximum for a blue monomeric nitrosoalkane.
Primarily I would like to express my sincere gratitude to Professor G.W. Kirby for his considerable help and encouragement throughout the course of this work.

I am indebted to the Science Research Council for a research studentship and to Loughborough University of Technology for the privilege of working in their laboratories. Thanks are also due to the Science Research Council through the P.C.M.U. (Harwell), and to those people who provided the background services necessary in any laboratory.

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Thebaine (1) possesses a cyclic, conjugated diene component and would therefore be expected to undergo addition of dienophiles. Sandermann first reported such Diels-Alder additions using maleic anhydride, p-benzoquinone and 1,4-napthoquinone as dienophiles. Schöpf and co-workers and later Bentley studied these reactions in more detail, the latter worker extending the Diels-Alder reactions of thebaine to produce a series of compounds from which a vast number of novel analgesics based on the morphine skeleton were formed.

One can envisage several modes of addition to the diene but models show that the addition can occur readily only on the exposed face of the diene system. In this manner derivatives of 6,14-endo-ethenotetrahydrothebaine are formed, e.g. (2), the endo implying disposition of the etheno bridge on the opposite side to the nitrogen ring bridge. Addition of the dienophile in two ways leading to 7a and 7e forms, i.e. below and above the plane of ring C respectively, is possible and there is little difference in steric crowding of the two forms. A consideration of the stereochemical factors generally governing the mode of addition in the Diels-Alder reaction would however be expected to give the 7a isomer preferentially. This is illustrated for part structures in Scheme 1, using methyl vinyl ketone as the dienophile. The reaction leading to the 7a isomer complies with the endo addition rule, i.e. with the components having maximum accumulation of double bonds.

Unsymmetrical dienophiles such as vinyl ketones, acrylic esters and acrylonitrile add under electronic control giving C-7 substituted products exclusively; consideration of structures (3) and (4) illustrate this principle. Bentley and colleagues found no evidence for C-8 substituted products, even on rigorous examination of the products from reaction of thebaine with such unsymmetrical dienophiles. These workers have also shown that with methyl vinyl ketone compound (2), with the 7a configuration, is obtained almost exclusively (93%), the 8 isomer being obtained in low yield (0.5%) from the mother liquors. By conversion of
both isomers to the same product, in a reaction involving loss of
asymmetry at C-7, proof that the two adducts were indeed C-7 epimers and
not C-7 and C-8 isomers was obtained.\textsuperscript{3b}

Nitroso compounds are intense blue or green substances that equilibrate to
variable extents with colourless dimers. Most exist as solid state dimers
that dissociate on melting or vaporization; dissociation may also occur on
solution as shown by the development of colour. Several dimeric nitroso
compounds exist in two forms, these being \textit{cis} and \textit{trans} isomers \textsuperscript{(5)}.
Nitrosoalkane dimers are thermodynamically more stable than the monomers
if electron-withdrawing substituents are absent.\textsuperscript{4} In contrast, nitrosoarenes
are generally more stable thermodynamically as monomers in solution, and
electron-donating substituents, in the \textit{p} position, enhance this stability.
Ortho substituents of any kind markedly enhance the relative stability of
the dimers; for example, \textit{p}-iodonitrosobenzene is a green monomer, even in
the crystalline state, while the \textit{o}-isomer is a colourless dimer.

Although examples of nitroso dimers acting as dienophiles in Diels-Alder
additions are known\textsuperscript{5} they are few and are subject to strict steric
requirements. The monomers however are subject to less rigid steric
requirements and numerous examples of their adding to dienes to give
dihydro-1,2-oxazines are known. Such Diels-Alder additions have been
extensively investigated by both Arbusov\textsuperscript{6} and Michterle\textsuperscript{7}. A comprehensive
review of the subject, covering the literature up to 1962, has been
published by Needleman and Chang Kud.\textsuperscript{8}

The nitrosoalkanes are invariably dimeric in the solid state. In the
absence of electron-withdrawing substituents one would expect them to form
less stable adducts with dienes than do nitrosoarenes. No examples of a
nitrosoalkane adding to a diene are in fact known. With electron-
withdrawing substituents in the \textit{a}-position adducts are formed, the stability
depending on the substituent. In this way stable adducts have been readily
obtained using \textit{gem}-cyanonitroso compounds but less stable adducts result
using \textit{gem}-chloronitroso compounds. However good yields of the parent
3,6-dihydro-1,2-oxazines may be obtained by \textit{in situ} alcoholysis with the
latter dienophile. Trifluoronitrosomethane has also been successfully used
as a dienophile, even with the less reactive perfluorocyclopentadiene.\textsuperscript{9}
Scheme I
Aromatic nitroso compounds readily form monomers and readily give 1,4-cycloadducts with dienes. The same substituents that promote monomer stability however reduce the reactivity of the dienophile. The ratio, for instance, of the rate constants of the reaction between 1,3-cyclohexadiene and p-nitronitrosobenzene or p-methoxynitrosobenzene is 1:3,500 at 10°C in 96% ethanol. 10

With the above factors in mind an investigation of the Diels-Alder reactions of thebaine with C-nitroso compounds was undertaken and the results obtained are described in this Thesis.
SECTION 1

The Reaction of Thebaines with Nitrosoarenes,
and with 1-Chloro-1-nitrosocyclohexane in
Acid Solution
INTRODUCTION

The work recorded in this Thesis arose out of experiments conducted in this laboratory on the nitrosation of thebaine (1). This alkaloid readily reacts with bromine in glacial acetic acid to give 14-bromocodeinone\(^\text{11}\) (6; \(X = \text{Br}\)) and with hydrogen peroxide in the same solvent to give 14-hydroxycodeinone\(^\text{12}\) (6; \(X = \text{OH}\)). Nitrosation therefore would possibly be expected to lead to 14-nitrosocodeinone (6; \(X = \text{NO}\)) by a similar sort of mechanism as that involved in other electrophilic substitutions. An early study\(^\text{13}\) of the reaction of thebaine with nitrosating agents showed that two similar products, of formulae \(\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_5\) and \(\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_5\), were obtained when ethanol and methanol were respectively used as solvent. Structural assignment for the two compounds were not given and the reactions were reinvestigated by Bentley, Kirby, Price and Serjinder Singh\(^\text{14}\). These workers found that nitrosation of thebaine hydrochloride with nitrosyl chloride or pentyl nitrite in methanol or ethanol gave 7-hydroxyimino-neopinone dimethyl or diethyl ketal (7; \(R = \text{Me or Et}\)). A second bimolecular product (8), best prepared using nitrosylsulphuric acid as nitrosating agent, was also isolated; the structure of which was firmly established by spectroscopic and chemical evidence. Data obtained in these reactions suggested a Diels-Alder addition of an intermediate 7-nitrosoneopinone dimethyl ketal to a second molecule of thebaine followed by a base catalysed rearrangement. The nature of this latter rearrangement will be discussed more fully later.

Serjinder Singh gained further evidence for the proposed Diels-Alder addition when he undertook a model reaction and showed that nitrosobenzene with thebaine gave a high yield of a 1:1 adduct (9; \(X = \text{H}\)).\(^\text{15}\) Solutions of this colourless crystalline adduct were observed to show a faint blue-green colour indicating some dissociation. Such a dissociation is not unprecedented since the cycloadduct from nitrosobenzene and 1,3-cyclopentadiene also dissociates in solution at room temperature.\(^\text{15}\)

The present work was undertaken to extend the scope of the 1,4-cycloadditions and to investigate the operative electronic effects on the dissociation of the adducts derived from \(\alpha\)-substituted nitrosoarenes.
and thebaine. During the course of the work a series of previously inaccessible 14-aminocodeinone derivatives were formed and conditions were developed for the formation of 14-aminocodeinone itself.
DISCUSSION

The colourless thebaine-nitrosobenzene adduct (9; \( X = H \)), prepared by evaporation of a chloroform solution of equimolar amounts of the addends followed by crystallisation from methanol, gave solutions that showed a faint blue-green colour. Confirmation of this suggested dissociation of the adduct in solution came from the n.m.r. spectrum in deuteriochloroform which showed weak signals corresponding to free thebaine and nitrosobenzene. Although the signals were too weak for accurate quantitative measurement they were estimated to represent approximately 10% of the free addends.

As expected, the amount of dissociation increased on warming a solution of the adduct. This was evident from the increase in signal strength of the free nitrosobenzene and thebaine in the n.m.r. spectrum and by the increase in intensity of colour of the solution. Thus at 80°C approximately 40% of the adduct had dissociated while at 100°C this rose to 65% (for an approximately 0.5 molar solution).

Since the cycloaddition results from the reaction of an electron deficient NO group with an electron rich diene system then any electronic effect in the nitrosoarene that tends to make the NO bond more electron deficient should increase the adduct stability, and vice versa. To test this hypothesis, a series of \( \pi \)-substituted nitrosoarenes were prepared\(^\text{17}\) and their adducts with thebaine studied. Since \( \sigma \)-substituents markedly enhance the relative stability of the dimers of nitrosoarenes and there was also the possibility of introducing undesirable steric effects they were not investigated. Two examples of \( \pi \)-substituted nitrosoarenes adding to thebaine were studied to compare the relative stability of these adducts with those derived from the corresponding \( \sigma \)-isomers.

The relative stability of the adducts were compared by preparing approximately 0.5 molar solutions in deuteriochloroform and recording their n.m.r. spectra at 35°C. \( \text{Para} \)-chloronitrosobenzene gave an adduct (9; \( X = \text{Cl} \)) in quantitative yield. The n.m.r. spectrum showed negligible amounts of free thebaine. In contrast \( \text{Para} \)-nitrosotoluene gave an adduct (9; \( X = \text{Me} \)) showing (n.m.r.) considerable (ca. 35% for 0.5 molar solution) dissociation. Similarly \( \text{Para} \)-nitroanisole gave an adduct (9; \( X = \text{OMe} \)) that showed approximately 45% dissociation; this decreased to approximately 17% at 0°C.
and 14% at -20°C. No evidence for any adduct formation between thebaine and \( p \)-dimethylaminonitrosobenzene was obtained. These trends were in agreement with the predicted operative electronic effects and were further confirmed by observations on the pale yellow thebaine-\( p \)-nitroanitrosobenzene adduct (9; \( X = \text{NO}_2 \)). This showed no dissociation at 35°C and less than 10% at 100°C.

Meta-substituents can manifest their influence on adduct stability only through inductive effects and to examine this effect adducts of thebaine with \( m \)-nitrosotoluene and \( m \)-nitrosoanisole were prepared. An approximately 0.5 molar solution of thebaine in deuteriochloroform with \( m \)-nitrosotoluene (equivalent amount) gave an n.m.r. spectrum which showed 15% dissociation; as expected this was less than that for the corresponding \( p \)-substituted adduct. With \( m \)-nitrosoanisole a colourless crystalline adduct was obtained whose n.m.r. spectrum showed no detectable dissociation. Comparison with the \( p \)-nitrosoanisole adduct, which showed approximately 45% dissociation, and with the nitrosobenzene adduct which showed approximately 10% dissociation, confirms that only a negative inductive effect operates.

Two modes of addition of nitroso dienophiles to thebaine may be envisaged just as with normal dienophiles. Thus nitrosobenzene may be expected to give adducts of either structure (9; \( Ar = \text{Ph} \)) or (10; \( Ar = \text{Ph} \)). While the latter structure may be favoured on steric grounds the former is favoured on electronic grounds. Proof that the adduct was in fact that with the nitrogen attached to C-14, i.e. (9), was obtained by chemical modifications as described below.

Treatment of the adduct (9; \( Ar = \text{Ph} \)) with IN-hydrochloric acid gave 14-(\( N \)-phenylhydroxyamino)codeinone (11; \( Ar = \text{Ph} \)) as a monohydrochloride salt. The free base showed \( \nu_{\text{max}} \) (CHCl\(_3\)) 3,360 and 1,687 cm\(^{-1}\); \( \tau \) (CDCl\(_3\)) 3.72 and 4.05(d, J 10Hz, 8-H and 7-H), 5.12(s, 5-H), 6.23(s, -OMe); \( \lambda \) (EtOH) 240(e 9,230), 280(2,510), 350 nm(sh, 636). Acetylation of (11; \( Ar = \text{Ph} \)) with acetic anhydride in pyridine gave an O-acetate (13; \( Ar = \text{Ph} \)); \( \nu_{\text{max}} \) (CHCl\(_3\)) 1773, 1688 cm\(^{-1}\). Catalytic hydrogenation (Pd/C) gave 14-phenylaminodihydrocodeinone (15; \( Ar = \text{Ph} \)); \( \nu_{\text{max}} \) (CHCl\(_3\)) 1726 cm\(^{-1}\). These data are consistent with an original adduct of
structure (9) but not one of structure (10) which would be expected to give a 14-phenylaminohydroxycodeinone (12) on hydrolysis. This in turn would be expected to give an $\text{N}$-acetate (14) on acetylation and 14-hydroxydihydrocodeinone (16) on catalytic hydrogenation. Similar hydrolysis products were obtained from the $p$-chloronitrosobenzene and $p$-nitrosotoluene adducts.

While the hydrochloride salt of 14-(N-phenylhydroxyamino)codeinone (11; $\text{Ar} = \text{Ph}$) was colourless the free base crystallised as pale yellow needles. This yellow colour, evident by the tailing of the long-wavelength absorption band at 350 nm (sh, 636), was thought to arise from some form of non-conjugated interaction between the 14-$\text{N}$ lone pair and/or the $\text{N}$-phenyl group with the enone system. The system may be compared with flavothebaone (17) where the absorption bands at similar long-wavelength have been attributed\(^\text{18}\) to charge-transfer between the aromatic nucleus and the enone. Bentley and co-workers have pointed out that such transfer is not possible in bases like flavonepenthone (18), where there is no oxygen substituent, although these compounds show similar long wavelength absorptions. He attributes such absorptions to the perturbation of the enone system by the spatially proximate $\pi$ orbitals of the unsaturated system, the precise nature of which appears to be of little importance.\(^\text{19}\)

Treatment of 14-(N-phenylhydroxyamino)codeinone (11; $\text{Ar} = \text{Ph}$) with base gave a compound which showed positive phenol tests with Gibbs reagent and with ferric chloride. The spectroscopic properties were consistent with formula (20); $\nu_{\text{max}}$ (CHCl$_3$) 3550, 1687 cm$^{-1}$; $\tau$ (CDCl$_3$) 3.89(s, vinyl protons, signal not separated at 60MHz), 4.81(s, 5-H); $\lambda_{\text{max}}$ (EtOH) 235(ε 10600), 317 (1,220), 361 nm(872); $\lambda_{\text{max}}$ (EtOH/EtONa) 254(12,200), 298(4,370), 361 nm (1,480). The position of the signal at $\tau$4.81 showed that C-5 still carried an oxygen function despite the phenolic nature of the substance. Treatment with acetic anhydride in pyridine gave a mono-$\rho$-acetyl derivative (21), $\nu_{\text{max}}$ (CHCl$_3$) 1772 cm$^{-1}$, confirming the phenolic nature of the compound. In the formation of (20) from (11) base removes the weakly acidic hydroxyamino proton and the resulting anion then attacks the oxide bridge giving the phenate ion (19) which is converted into the free phenol (20) on acidification with aqueous carbon dioxide. Analogous rearrangements
Thebaine + ArHO

(9) ——> H⁺/H₂O ——> (11) ——> Ac₂O/Py ——> (13)

(10) ——> H⁺/H₂O ——> (12) ——> Ac₂O/Py ——> (14)
producing phenols were observed by Bentley and co-workers\textsuperscript{20} when adducts of thebaine bearing electron-withdrawing substituents at C-7 were subjected to basic treatment. They found that the thebaine-acrylonitrile adduct (22; $X = \text{CN}$), when treated with potassium-t-butoxide in t-butanol, gave the rearranged phenolic product (23, $X = \text{CN}$). The latter arises as a result of removal of the C-7 proton, under reversible conditions, giving an intermediate enolate ion which opened the 4,5-oxide bridge to give the phenate ion which gave the phenol on treatment with aqueous ammonium chloride. Similar reactions were observed with the adducts (22; $X = \text{COPh}$, COMe and $\text{CO}_2\text{Et}$).\textsuperscript{20}

The rearrangement of the hydroxyamino compound (11) to the phenol (19) provided valuable support for the earlier proposal by Kirby and colleagues\textsuperscript{14} for the structure of the compound (8).

Attempted reduction of 14-($\beta$-phenylhydroxyamino)codeinone to the corresponding codeine (24) using either sodium borohydride or lithium aluminium hydride yielded phenolic material. This material was shown by i.r. spectrometry and thin layer chromatography to contain a major product identical to the crystalline phenolic codeine (25), obtained by sodium borohydride reduction of the phenol (20). It thus appeared that the conditions employed were sufficiently basic to bring about the rearrangement of the hydroxyamino compound (11) to the phenol (20), which was itself then reduced. To overcome the problem of the rearrangement it was proposed that the acetate (13) of 14-($\beta$-phenylhydroxyamino)codeinone (11) be reduced with sodium borohydride. Hydrolysis of the resulting acetate of 14-($\beta$-phenylhydroxyamino)codeine (26) should then give the desired product (24). The product obtained on reduction crystallised as white needles and the i.r. ($\text{CHCl}_3$) spectrum showed an absorption at 1765 cm\textsuperscript{-1} but none for an $\alpha\beta$-unsaturated carbonyl group. Thin layer chromatography of the material showed two spots in an approximate ratio of 70:30, but these could not be effectively separated by thick layer chromatography. The product was tentatively assigned as either a mixture of C-6 epimeric codeines or as a mixture of a codeine and the corresponding dihydrocodeine. N.m.r. evidence favoured the former of these two possibilities; integration showed that the ratio of lower field proton signals (5-H, 6-H, 7-H, and 8-H) to aromatic proton signals (N-Ph) was 4:5. This was not compatible
with a dihydrocodeine component. Further, the higher field (above τ 6.0) part of the spectrum was very similar to that of the unreduced acetate (13); no evidence of extra signals due to C-7 and C-8 methylene protons being observed. This conclusion is surprising since sodium borohydride reduction of codeinone occurs stereospecifically, with hydride attack occurring exclusively from the front giving only the normal 7α-isomer.21 The result is even more surprising in view of the fact that 14-alkenyl codeinones are also reduced with sodium borohydride to give the related codeines, with no evidence of more than one alcohol being found.22 One must assume that with more bulky groups than hydrogen on the group attached directly to C-14 that steric hindrance was increased and hence some 'backside attack' of hydride occurred.

Hydrolysis of the above mixture with 2N-hydrochloric acid gave a complex mixture of non-phenolic products while hydrolysis with dilute aqueous sodium hydroxide gave only phenolic material. This latter phenolic material was presumed to have arisen by a rearrangement analogous to that described earlier.

Reduction of the acetate of 14-[(N-phenylhydroxyamino)codeinone (13) with lithium aluminium hydride gave different products depending on the conditions employed but in no case was any of the desired codeine obtained.

To expand the scope of the 1,4-cycloaddition of nitroso compounds to thebaine a study of the nitrosoalkanes was carried out. The preparation and properties of these compounds are well documented in the literature, notable studies being undertaken by Emmons23 and Lütte24. The blue monomeric nitrosoalkanes are distinct from the green monomeric nitroso-arenes in that primary and secondary members invariably isomerise rapidly to the oxime.

\[
\begin{align*}
RCH_2NO & \quad \longrightarrow \quad RCH:NOH \\
R(R_1)CHNO & \quad \longrightarrow \quad R(R_1)C:NOH
\end{align*}
\]

The reaction of thebaine with nitrosocyclohexane generated in situ from cyclohexylamine and \( m \)-chloroperbenzoic acid gave unreacted thebaine. To
avoid loss of peracid by \( \text{N-oxide} \) formation, thebaine hydrochloride was used but a similar result was obtained. Nitrosocyclohexane, prepared as the colourless dimer from perbenzoic acid oxidation of cyclohexylamine, also failed to add to thebaine or its hydrochloride salt under a variety of conditions. It was hoped that in the presence of added acid any adduct formed in a reversible addition might be hydrolysed and so trapped as 14-({\( \text{H-cyclohexylhydroxyamino} \)} codeinone \( \text{(11;} \text{Ar = C}_{6}\text{H}_{11}) \). Under acidic conditions thebaine was again recovered along with cyclohexanone oxime whose formation from nitrosocyclohexane is acid catalysed. A restricting factor in choosing nitrosocyclohexane as the dienophile is that it only partially dissociates to monomer even in boiling toluene. A 0.1M solution in benzene is only 0.088% dissociated at 20°C while the corresponding figure for nitrosobenzene is 100%. No adduct was obtained using nitroso-t-butane as a potential dienophile even though this compound exists as a monomer in solution. An equimolar solution of nitroso-t-butane and thebaine in deuteriochloroform was studied by n.m.r. spectroscopy. Spectra were recorded 5, 15 and 60 minutes after mixing the components. None showed any evidence of adduct formation as judged by either disappearance of the diene proton signals or appearance of characteristic C-7, and C-8 adduct proton signals.

The evidence obtained suggested that nitrosoalkanes do not give stable adducts with thebaine. Since no examples of their adding to other dienes occur in the literature it may be that they are totally unreactive in such additions.

In contrast to unsubstituted nitrosoalkanes, those bearing an electron withdrawing group, such as cyano or chloro, in the \( \alpha \) position form Diels-Alder adducts to various degrees. 1-Chloro-1-nitrosocyclohexane, prepared from the reaction of chlorine with cyclohexanone oxime, gives only low yields of cycloadducts with dienes in non-protic solvents such as benzene, toluene and ether. Ethanolysis \( \text{in situ} \) removes the cycloadduct from the equilibrium and provides high yields of oxazines. This is illustrated for butadiene and 1-chloro-1-nitrosocyclohexane in Scheme 2. Such a reaction offered an attractive route to the preparation of the parent adduct of thebaine with nitroso dienophiles, i.e. that corresponding to the formal addition of hyponitrous acid.
Reaction of thebaine with 1-chloro-1-nitrosocyclohexane in ethanol/benzene at 0°C in the dark gave no addition products; even after one week thebaine was recovered unchanged. With thebaine hydrochloride a white crystalline salt was obtained from the benzene/ethanol solution after 48 hrs at 0°C in the dark. The yield of this product was increased to 94% by using an added excess of hydrochloric acid with thebaine in preference to the hydrochloride salt. The free base of the compound showed αβ-unsaturated carbonyl, hydroxyl and N-H bands in its i.r. spectrum and an AB quartet, typical of the 14-substituted codeinones, in its n.m.r. spectrum. Mass Spectrometry indicated a molecular formula of $C_{18}H_{20}N_2O_4$. These data and the compound's chemical reactions were consistent with 14-hydroxyaminocodeinone (28), presumably derived from acid hydrolysis and ethanolysis of the intermediate adduct (27), Scheme 3. It appears that the direction of the equilibrium of the reaction of 1-chloro-1-nitrosocyclohexane with thebaine lies well on the side of the reactants as witnessed by the recovery of thebaine after mixing the two compounds in ethanol. With acid present the equilibrium is displaced to the right by essentially irreversible acid hydrolysis of the adduct.

Acetylation with acetic anhydride in pyridine of 14-hydroxyaminocodeinone (28) gave 14-(acetoxyamino)codeinone (29). Acylation of hydroxylamines ordinarily takes place on the nitrogen, if an unsubstituted position remains, giving hydroxamic acid derivatives. O-Acylation may occur under circumstances where steric hindrance prevents attachment on nitrogen, as with $N$-tritylhydroxylamine.\(^{27}\) It would appear therefore that the nitrogen atom on C-14 in the hydroxylamine (28) is sterically hindered. Treatment of the hydroxylamine (28) with sodium methoxide in methanol followed by acidification with aqueous carbon dioxide gave the phenol (30) which formed a diacetate (31). In the phenol the nitrogen on C-14 is apparently no longer so sterically hindered and acetylation proceeds as expected.

Catalytic hydrogenation of the hydrochloride of 14-hydroxyaminocodeinone (28) using 10% Pd/C did not give the expected 14-aminodihydrocodeinone but gave 14-hydroxyaminodihydrocodeinone (32). This proved difficult to crystallize and it readily rearranged on chromatography on alumina to the reduced phenol (33). This same product was obtained by treating the reduced hydrochloride (32) with sodium methoxide followed by acid work up.
using carbon dioxide. Acetylation, using acetic anhydride in pyridine, of either the reduced hydrochloride or free base (32) gave a crystalline acetate (34) identical to the product from catalytic reduction (Pd/C) of the acetate (29). The above transformations are shown in Scheme 4. Strict control over the hydrogenation was necessary since competing reductions occurred, one of which was undoubtedly amine formation. However parallel with amine formation was oxide bridge cleavage since a minor product was isolated by column chromatography on two separate occasions which showed no low field C-5 proton in its n.m.r. spectrum.

Selective reduction of the hydroxyamino function of 14-hydroxyaminocodeinone (28) should lead to 14-aminocodeinone (35), arylation, alkylation and acylation of which should provide a series of 14-aminocodeinone derivatives. Standard procedures for reducing hydroxylamines, such as catalytic hydrogenation, and treatment with sodium borohydride, lithium aluminium hydride, tin and hydrochloric acid, and concentrated hydroiodic acid appeared undesirable since they would either reduce the enone system and/or cause possible rearrangements. Basic reducing agents were obviously also undesirable since they bring about rearrangement to phenols. Zinc in acetic acid or in ammonium chloride solution has been used to reduce nitro compounds to amines in certain cases but erratic behaviour is common. Iron filings in the presence of acids or salts has also been widely and successfully used to give amines from nitro compounds. Use of zinc and iron as reducing agents under various neutral and acidic conditions failed to give any desired 14-aminocodeinone (35); in all cases phenolic material was produced. The production of phenolic material resulted from the ketonic function at C-6 aiding opening of the 4,5-oxide bridge, as shown in (36).

Conversion of the codeinone (28) into its dimethyl ketal (37) should prevent phenol formation in iron and zinc reductions. Formation of a dimethyl ketal under various conditions was however, unsuccessful as was attempted formation of a thioketal from ethane-1,2-dithiol.

In the formation of 14-hydroxyaminocodeinone (28) from thebaine and 1-chloro-1-nitrosocyclohexane in ethanol containing concentrated hydrochloric acid, water is essential for hydrolysis of the intermediate adduct (27). Reaction under anhydrous acidic conditions, with methanol in place of
Scheme 4
ethanol, should then lead to 14-hydroxyaminocodeinone dimethyl ketal. When thebaine hydrochloride and 1-chloro-1-nitrosocyclohexane reacted in absolute methanol the only product isolated was 14-hydroxyaminocodeinone (28) but in much lower yield than non-anhydrous conditions. This result appeared rather puzzling until it was realized that thebaine hydrochloride possesses one molecule of water of crystallization, sufficient no doubt to cause hydrolysis. Preparation of anhydrous thebaine hydrochloride was achieved by adding one equivalent of thebaine to absolute methanol to which one equivalent of acetyl chloride had previously been added. Addition of 1-chloro-1-nitrosocyclohexane in dry benzene then gave the desired ketal (37) after the reaction mixture had been kept at 0°C for 70 hr then quenched by pouring into saturated aqueous sodium bicarbonate. The ketal was hydrolysed to the codeinone (28) identical in all respects with material prepared under non-anhydrous conditions. Reduction of the ketal with zinc dust in methanolic ammonium chloride solution gave 14-aminocodeinone dimethyl ketal (37; NH₂OH = NH₂) which was hydrolysed by dilute acid to the codeinone (35). Conditions were optimised such that the conversion of thebaine into 14-aminocodeinone could be achieved without isolation of the intermediates in an overall yield of 35%. The 14-aminocodeinone dimethyl ketal prepared by this procedure had the same melting point, with no depression on mixing, as material prepared in these laboratories by R.M. Allen. He reduced 14-nitrocodeinone dimethyl ketal (37; NH₂OH = NO₂) with zinc dust in methanolic ammonium chloride solution. He was, however, unable to isolate any intermediate reduction products such as 14-hydroxyaminocodeinone from various reductions of the nitro compound.

In the early experiments directed at ketal formation under anhydrous conditions, thebaine was normally added to absolute methanol under a nitrogen atmosphere and acetyl chloride then added through a septum cap. Such experiments invariably gave a minor product, isolated as long orange needles, identified as 3,6-dimethoxyphenanthrene-1,4-quinone (38) from its melting point and n.m.r., u.v., i.r. and mass spectra. The origin of this quinone is not fully understood but may arise by oxidation of intermediate thebaol (39; R = H). Acetolysis of thebaine is known to give acetylthebaol (39; R = CH₃CO) but this is very difficult to hydrolyse, hot alcoholic sodium ethoxide being required. However, Fleischhaker and co-workers reported that acetyl chloride reacted with thebaine to give codeinone-acetyl-normethine (40) which was converted into thebaol
The conditions used to prepare the ketal could thus have given rise to thebaol and oxidation would then have given the quinone (38). Thebaol, prepared by lithium aluminium hydride reduction of acetylthebaol, was found to be oxidized to 3,6-dimethoxyphenanthrene-1,4-quinone (38) by 1-chloro-1-nitrosocyclohexane. Attempted oxidation of 1-napthol under similar conditions failed.

Previous experiments in these laboratories on the nitrosation of thebaine have been discussed earlier, and these showed that nitrosation occurred, apparently exclusively, at C-7 rather than C-14. Selective oxidation of 14-hydroxyaminocodeinone (28) was expected to give 14-nitrosocodeinone (41) and in this way further possible information on the nitrosation of thebaine would be obtained. 14-Nitrosocodeinone is a tertiary nitrosoalkane and would be unable to isomerise to an oxime; it might however be cleaved to codeinone and a nitroso compound as indicated, $\text{(41)} \rightarrow \text{(42)}$.

Perbenzoic acid oxidation of 14-hydroxyaminocodeinone was without effect but periodic acid gave a pale yellow crystalline product. A similar product was isolated from both bromine water and chromic acid oxidations, albeit in much lower yield. The n.m.r. spectrum showed signals at $\tau$(CDCl$_3$) 3.38 (q, 2H), 3.43 (s, 1H), 4.70 (s, 1H), 6.23 (s, OMe), and 7.66 (s, NMe); the signal at 4.70 was found to be slowly exchangeable with deuterium oxide. Absorptions in the i.r. were observed at $\nu_{\text{max}}$(nujol) 2560 (vbr), 1715, 1660 (w), 1635 (w) and 1605 cm$^{-1}$; and the mass spectrum showed a molecular ion at m/e 326 indicating removal of two hydrogens during oxidation. An unstable diacetate was formed on treatment with acetic anhydride in pyridine and this showed $\nu$$_{\text{max}}$(CHCl$_3$) 1772 cm$^{-1}$ (broad doublet). The n.m.r. spectrum showed two new methyl singlets at 7.72 and 7.80 but no signal around $\tau$ 4.70 indicating loss of the C-5 proton. The unacetylated product was found to be soluble in base from which it could be recovered unchanged on treatment with carbon dioxide. However, it gave negative phenol tests. On the basis of the above data the compound was assigned the 7-hydroxyiminoneopinone structure (44). Formation of the oxime may be envisaged as occurring via the initial formation of 14-nitrosocodeinone (41) which breaks down to a nitrosating species and the codeinone enolate (42). Under the conditions of the oxidation these may...
then react to give an intermediate 7-nitroacneopinone (43) which would be expected to isomerise to 7-hydroxyiminoneopinone (44), Scheme 5.

The slowly exchangeable proton signal at $\tau 4.70$ was attributed to the 5-H. Enolization of the carbonyl group then accounted for this exchange and the formation of the diacetate (46). The proton signal at $\tau 3.43$ was assigned to 8-H, the low field position suggesting a syn-configuration of the oxime function. Confirmation of the oxime structure was obtained by ketalization, using anhydrous methanolic hydrogen chloride, to give 7-hydroxyiminoneopinone dimethyl ketal (7). The ketal obtained in this way was spectroscopically identical to that obtained from nitrosation of thebaine, and had an identical melting point which was undepressed on mixing. Further confirmation of the structure was obtained by nitrosation of neopinone (47) using the procedure of Lester and colleagues, when 7-hydroxyiminoneopinone (44), identical in all respects to material from the oxidation reaction, was again obtained.

Nitrosation of thebaine would appear therefore to be a reversible process, with initial attack occurring at C-14. Equilibration of the product with a C-7 nitroso species would then account for the observed reactions.
EXPERIMENTAL

General Methods

M.p.s. were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer and u.v. spectra were recorded for ethanol solutions using Unicam SP800 and SP8000 spectrometers. \(^1\)H n.m.r. spectra were recorded for solutions in deuteriochloroform or \(^2\)H\(\text{D}_{6}\) dimethylsulphoxide using a Perkin-Elmer R10 instrument with tetramethylsilane as internal standard. Mass spectra were recorded with A.E.I. MS9 and MS12 instruments.

Organic solutions were dried over anhydrous sodium sulphate before evaporation of the solvent. Solvents were dried and purified by standard procedures and absolute methanol refers to methanol distilled from magnesium turnings.

Preparative layer chromatography used silica (Merck PF\(_{254}\)) or alumina (Merck GF\(_{254}\)) as support, spread at 0.5 mm layers on 1 m x 20 cm plates. Column chromatography was carried out using silica gel (Fisons) or neutral alumina (Camag), grade III.

Unless otherwise stated free bases were prepared from hydrochloride salts by neutralization with saturated sodium bicarbonate solution followed by extraction with chloroform. The separated organic phase was then dried and evaporated.

**Thebaine-Nitrosobenzene Adduct (9; \(R = H\))**: A solution of thebaine (1) (7.44 g, 24 mmol) in chloroform (20 ml) was added to nitrosobenzene (2.56 g, 23.6 mmol) in chloroform (20 ml) when the green colour of the latter was rapidly discharged. Filtration and removal of the solvent gave a crystalline yellow mass which was recrystallised from methanol as colourless needles of the adduct (9; \(R = H\)) (8.8 g, 90%), m.p. 115-118\(^\circ\) (decomp.); \(\tau\)(CDCl\(_3\)) 2.87(s, NPh), 3.40 and 3.48 (doublets, \(J 8.5\) Hz, 1-H and 2-H), 3.80(q, \(J 9\) Hz and 1 Hz, 7-H), 4.74(d, \(J 9\) Hz, 8-H), 5.31(d, \(J 1\) Hz, 5-H), 6.24 and 6.30 (singlets, 3 and 6 -OMe), 7.55(s, NMe); \(\nu_{\text{max}}\) (nujol) 1632 w, 1598 m, 1504 s, 1485 s, 880 s and 775 w cm\(^{-1}\); \(M^+\) m/e 311, corresponds to thebaine.
Thebaine-4-Chloronitrosobenzene Adduct (9; X = Cl): - This was prepared as described for (9; X = H) and gave a crude adduct which was recrystallised, with difficulty, from dichloromethane as off-white feathery needles (76%) of the adduct (9; X = Cl), decomposing in the range 125-130° (Found: C, 65.69; H, 5.46; N, 5.75. C_{25}H_{23}ClN_2O_4 requires C, 66.27; H, 5.53; N, 6.18%). T(CDC1_3) 2.80(s, NAr), 3.30 and 3.40 (doublets, J 8.5 Hz, 1-H and 2-H), 3.72(q, J 9 Hz and 1 Hz, 7-H), 4.68(d, J 9 Hz, 8-H), 5.25(d, J 1 Hz, 5-H), 6.17 and 6.26 (singlets, 3 and 6 -OMe), 5.33(s, NMe); ν max (nujol) 1628 w, 1603 w, 1502 s, 1225 s, and 880 s cm⁻¹; M+ m/e 311, corresponds to thebaine.

Thebaine-4-Nitronitrosobenzene Adduct (9; X = NO_2): - This was prepared as described for (9; X = H) and gave, from methanol, yellow needles of the adduct (9; X = NO_2) (97%), m.p. 166-167° (decomp.) (Found: C, 64.48; H, 5.70; N, 8.84. C_{25}H_{23}N_3O_6 requires C, 64.78; H, 5.44; N, 9.07%). T(CDC1_3) 1.57 and 2.43 (doublets, J 9.5 Hz, N-NO_2C_6H_4), 3.12 (m, 1-H and 2-H), 3.56(q, J 10 Hz and 1.5 Hz, 7-H), 4.50(d, J 10 Hz, 8-H), 5.17(d, J 1.5 Hz, 5-H), 6.14 and 6.20 (singlets, 3 and 6 -OMe), 7.52(s, NMe); ν max(CHC1_3) 1602 m, 1588 m, 1508 s, and 1340 cm⁻¹ M+ m/e 311, corresponds to thebaine.

Thebaine-4-Nitrosotoluene Adduct (9; X = Me): - This was prepared as described for (9; X = H) and crystallised, with difficulty, from methanol as soft nodules of the adduct (9; X = Me) (65%) having no sharp melting point but decomposing slowly on heating (Found: C, 71.83; H, 6.40; N, 5.99. C_{26}H_{28}N_2O_4 requires C, 72.23; H, 6.48; N, 6.47%). T(CDC1_3) 2.92(s, N-Ar), 3.35(m, 1-H and 2-H), 3.73(q, J 9 Hz and 1.4 Hz, 7-H), 4.67(d, J 9 Hz, 8-H), 5.26(d, J 1.4 Hz, 5-H), 6.18 and 6.26 (singlets, 3 and 6 -OMe), 7.53(s, NMe) and 7.73(s, ArMe); ν max (CHC1_3) 1602 m, 1580 m, 1507 s, and 878 s cm⁻¹; M+ m/e 311, corresponds to thebaine.

Thebaine-3-Nitrosoanisole Adduct (9; X = m OMe): - This was prepared as described for (9; X = H) and crystallised from methanol as colourless needles of the adduct (9; X = m OMe) (92%), m.p. 142-143° (decomp.) (Found: C, 69.93; H, 6.46; N, 6.16. C_{26}H_{28}N_2O_5 requires C, 69.62; H, 6.29; N, 6.25%). T(CDC1_3) 2.70 - 3.60(m, 1-H, 2-H and N-Ar), 3.82(q, J 8.5 Hz and 1.5 Hz, 7-H), 4.70(d, J 8.5 Hz, 8-H), 5.35(d, J 1.5 Hz, 5-H), 6.24 and 6.29 (singlets, 3, 6 and Ar -OMe) and 7.55(s, NMe); ν max (nujol) 1628 w, 1608 w, 1503 s, 1225 s and 880 s cm⁻¹; M+ m/e 311, corresponds to thebaine.
3100 m, 1630 m, 1604 s, 1585 m, 1504 s, 1282 s, 892 s and 783 cm⁻¹.

Other adducts (9, X = OMe and X = mM) were not isolated from the deuteriochloroform solutions in which their n.m.r. spectra were recorded.

14-(N-Phenylhydroxyamino)codeinone (11; Ar = Ph):- Thebaine-nitrosobenzene adduct (9, X = H) (8 g) was warmed and triturated with 2N-hydrochloric acid (20 ml) to give a pasty mass which solidified on further trituration to a white solid. The solid was filtered, dried and crystallised from 96% ethanol as colourless needles of the 14-hydroxyaminocodeinone derivative (11; Ar = Ph) hydrochloride (90%), beginning to decompose at ca. 125°

(Found: C, 63.2; H, 5.95; N, 6.15; Cl, 7.8. C24H24N2O4HClH2O requires C, 62.80; H, 5.94; N, 6.10; Cl, 7.73% \(\tau [CD_3]_2SO\) 2.62(s, NPh), 3.13 and 3.20 (doublets, J 8.5 Hz, 1-H and 2-H), 3.61 and 3.76 (doublets, J 10 Hz, 7-H and 8-H), 5.02(s, s-H), 62.25(s, OMe) and 6.92 (broad s, +NMe); \(\nu_{max}\) (nujol) 3400 b, 1863 s, 1620 m, 1510 s and 1045 m cm⁻¹.

The free base crystallised from ethanol as pale yellow needles; mp. 201° (decomp.). \(\tau(CDCl_3)\) 2.78(m; NPh), 3.43(m, 1-H and 2-H), 3.72(d, J 10 Hz, 8-H), 4.05(d, J 10 Hz, 7-H), 5.12(s, s-H), 6.23(s, OMe), and 7.63(s, NMe), spectrum also showed one mole of ethanol and in \(\tau[C(D_3)]_2SO\) 0.82(s, OH, exchangeable with deuterium); \(\nu_{max}\) (CHCl₃) 3360 b, 2860 m, 2830 m, 1688 vs, 1598 m, 1490 vs, 1270 s and 808 m cm⁻¹; \(\lambda_{max}\) (EtOH) 240(€ 9,230), 280 (2,510) and 350 nm (sh, 636); \(M+m/e\) 404; C₂₄H₂₄N₂O₄ requires M 404.

14-(N-p-Chlorophenylhydroxyamino)codeinone (11; Ar = pClC₆H₄):- Prepared in the same manner as (11; Ar = Ph) and crystallised from ethanol to give white feathery needles of the 14-hydroxyaminocodeinone derivative (11; Ar = pClC₆H₄) hydrochloride (88%), decomposing slowly above 150°

(Found: C, 58.8; H, 5.4; N, 5.4; Cl, 14.5. C₂₄H₂₃ClN₂O₄H₂OCl requires C, 58.4; H, 5.31; N, 5.67; Cl, 14.4%); \(\nu_{max}\) (nujol) 3400 b, 1678 vs and 1515 cm⁻¹.

The free base crystallised as pale yellow needles from ethanol m.p.

108-108.5° (Found: C, 64.0; H, 6.05; N, 5.9. C₂₄H₂₃ClN₂O₄EtOH requires C, 64.39; H, 6.03; N, 5.8%) \(\tau(CDCl_3)\) 2.79(s, NAr), 3.40(m, 1-H and 2-H), 3.70(d, J 10 Hz, 8-H), 4.08(d, J 10 Hz, 7-H), 5.10(s, 5-H), 6.21(s, OMe), 7.64(s, NMe) and spectrum showed one mole of ethanol; \(\nu_{max}\) (CHCl₃) 3340 b,
14-(N-p-Tolylhydroxyamino)codeinone (11; Ar = p-Me-C₆H₄): Pre pared as for (11; Ar = Ph) as off-white feathery needles, from ethanol, the 14-hydroxyaminocodeinone derivative (11; Ar = pMeC₆H₄) hydrochloride (82%), began to slowly decompose on heating above 150° (Found: C, 63.85; H, 6.14; N, 6.5; Cl, 7.4. C₂₅H₂₆N₂O₄.H₂O.HCl requires C, 63.50; H, 6.17; N, 5.92, Cl, 7.5%). δ (CDCl₃) 2.02 (s, NAr), 3.15 (s, 1-H and 2-H), 3.60 (d, J 10 Hz, 7-H), 3.74 (d, J 10 Hz, 8-H), 5.05 (s, 5-H), 6.26 (s, OMe), 6.95 (s, 14NMe) and 7.72 (s, ArMe); ν max (nujol) 3260 b, 1682 vs, 1615 m, 1502 s and 720 m cm⁻¹.

14-(N-Phenylacetoxyamino)codeinone (13; Ar = Ph): 14-(N-Phenylhydroxyamino)codeinone (11, Ar = Ph) (1.0 g) was added to a solution of acetic anhydride (0.25 ml) in dry pyridine (25 ml) and stirred overnight. Water (10 ml) was added followed by saturated aqueous sodium bicarbonate (excess). The solution was then extracted with chloroform, the organic layer separated and washed twice with water (25 ml) and then dried and evaporated to give a crude solid. Crystallisation from benzene gave off-white cubes of the acetate (13; Ar = Ph) (1.0 g, 90%), m.p. 167-168° (decomp.) (Found: C, 69.72; H, 5.62; N, 6.13; N⁺ m/e 446. C₂₆H₂₆N₂O₅ requires C, 69.94; H, 5.83; N, 6.28%; N 446) δ(CDCl₃) 2.70 (m, NPh), 3.40 (m, 1-H and 2-H), 3.66 (d, J 10 Hz, 8-H), 3.78 (d, J 10 Hz, 7-H), 5.39 (s, 5-H), 6.20 (s, OMe), 7.65 (s, NMe) and 8.03 (s, COMe); ν max (CHCl₃) 1774 s, 1690 s, 1190 s and 680 m cm⁻¹.

14-Phenylaminodihydrocodeinone (15; Ar = Ph): 14-(N-Phenylhydroxyamino)codeinone hydrochloride (11; Ar = Ph) (290 mg) in methanol (6 ml) was hydrogenated using 10% palladised charcoal (40 mg) for 4 hr at room temperature and pressure. The catalyst was removed by filtration through 'Celite' and the filtrate evaporated giving a residue that crystallised from water. The free base was prepared and crystallised from ethanol as colourless cubes of the dihydrocodeinone (15; Ar = Ph) mp. 188-189° m/e 390.1945 (M⁺, C₂₄H₂₄N₂O₃ requires M, 390.1943) (Found: C, 72.9; H, 6.7; N, 6.7. C₂₄H₂₄N₂O₃.SEtOH requires C, 72.7; H, 7.0; N, 6.8%). δ(CDCl₃) 2.85 (m, NPh), 3.34 (s, 1-H and 2-H), 5.32 (s, 5-H), 6.13 (s, OMe) and 7.68 (s, NMe); ν max(CHCl₃) 3360 b, 2850 m, 2820 m, 1730 vs, 1603 m, 1494 vs, 1282 s and 700 m cm⁻¹.

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Base Catalysed Rearrangement of 14-(N-Phenylhydroxyamino)codeinone:-

14-(N-Phenylhydroxyamino)codeinone (11; Ar = Ph) hydrochloride (500 mg) was dissolved in a minimum of methanol and sodium methoxide, from sodium (50 mg) in methanol (10 ml), was added. The solution turned yellow and a crystalline solid separated; more methanol was added (10 ml) and the solid dissolved. After leaving for 10 min at room temperature the solvent was removed and the residue dissolved in water. Solid carbon dioxide was added and a precipitate formed which was filtered off and crystallised from ethanol as fine yellow needles of the phenol (20) (380 mg, 90%), m.p. 207-208° (Found: C, 70.0; H, 6.8; N, 6.1; M+ m/e 404. C_{24}H_{24}N_{2}O_{4}EtOH requires C, 69.4; H, 6.72; N, 6.2%; M 404) τ(CDC1₃) 2.82(m, NAr), 3.33(s, 1-H and 2-H), 3.89(s, 7-H and 8-H, not separated at 60 MHz), 4.12(s, -OH), 4.81(s, 5-H), 6.20(s, OMe) and 7.45(s, NMe), spectrum shows one mole of ethanol; νmax(CHCl₃) 3550 b, 2850 m, 2820 m, 1687 vs, 1594 m, 1280 s and 875 cm⁻¹. λmax (EtOH) 235(ε 10,600), 317 (1,220), 361 nm (872); λmax (EtOH/NaOEt) 254(ε 12,200), 298 (4,370), 361 nm (1,480).

Sodium Borohydride Reduction of the Phenol (20):- The phenol (20) was dissolved in methanol (10 ml) and sodium borohydride (250 mg) was added in portions (ca. 25 mg) over a 30 min period. The reaction was followed by t.l.c. and when no starting phenol remained the solvent was removed and the residue dissolved in water. Solid carbon dioxide was added and the resulting precipitate was filtered off and discarded; on leaving the filtrate overnight colourless crystalline cubes of the phenolic alcohol (25) were deposited (190 mg, 63%), m.p. 205°, M+ m/e 406. C_{24}H_{26}N_{2}O_{4} requires M 406; τ(CDC1₃) 2.90(m, NPh), 3.32(s, 1-H and 2-H), 4.32(m, 1H), 4.70(s, 1H), 4.92(m, 1H), 5.62(m, 3H, 1H after deuterium exchange), 6.20(s, OMe) and 7.50(s, NMe); νmax(CHCl₃) 3520 s, 2850 m, 2820 m, 1625 m, 1600 s, 1280 s, and 1000 s cm⁻¹.

Sodium Borohydride Reduction of 14-(N-Acetoxyphenylamino)codeinone:-

14-(N-Acetoxyphenylamino)codeinone (13) (1 g) was dissolved in 50/50 chloroform/methanol (12 ml) and sodium borohydride (200 mg) was added in four portions over 30 min. After the last addition there remained only very little starting material as judged by t.l.c. Chloroform (10 ml) was added and the solution washed with water (10 ml). The organic phase was separated, dried, and evaporated to give an amber gum which crystallised.
from ethanol as pale yellow cubes of the codeine acetate (26) (560 mg, 55%). T.l.c. on alumina using chloroform as developer showed two spots \( R_f \) ca. 0.5 and 0.45, ca. 30:70 respectively. \( M^+ m/e 448; C_{26}H_{28}N_2O_5 \) requires M 448; \( \tau (\text{CDCl}_3) 2.70(\text{m, NPh}), 3.40(\text{m, 1-H and 2-H}), 3.94(\text{q, J 10 Hz and 1 Hz, 7-H}), 4.78(\text{q, J 10 Hz and 2.5 Hz, 8-H}), 5.14(\text{b.s, 5-H}), 5.30(\text{m, 6-H}), 6.18(\text{s, OMe}), 7.67(\text{s, NH}) \) and 7.92(\text{s, COCH}_3); \( \nu_{\text{max}}(\text{CHCl}_3) 2850 \text{ w}, 1765 \text{ vs, 1596 m, } 1280 \text{ s and } 1110 \text{ s cm}^{-1} \).

14-Hydroxyaminocodeinone (28):- Thebaine (6.22 g) was dissolved in ethanol (140 ml) containing concentrated hydrochloric acid (4 ml). 1-Chloro-1-nitrosocyclohexane (3.0 g) in benzene (20 ml) was added and the solution left 48 hr at 0\(^\circ\) in the dark. The resulting white crystalline hydrochloride of 14-hydroxyaminocodeinone (28) was filtered off (7.6 g, 94%), m.p. 243-245\(^\circ\) (from ethanol) (Found: C, 59.69; H, 5.90; N, 7.43. \( C_{18}H_{20}N_2O_4 \cdot HCl \) requires C, 59.30; H, 5.80; N, 7.68%); \( \nu_{\text{max}}(\text{nujol}) 3280 \text{ b}, 3225 \text{ m, 1683 vs, 1620 m, 1510 s, 1290 s and 800 m cm}^{-1} \).

The free base formed pale yellow needles from ethanol, m.p. 109-110\(^\circ\), \( M^+ m/e 328, C_{18}H_{20}N_2O_4 \) requires M 328; \( \tau (\text{CDCl}_3) 2.53(\text{s, exchangeable with deuterium}), 3.34(\text{s, 1-H and 2-H}), 3.43(\text{d, J 10 Hz, 7-H}), 3.93(\text{d, J 10 Hz, 8-H}), 5.27(\text{s, 5-H}), 6.28(\text{s, OMe}) \) and 7.68(\text{s, NH}); \( \nu_{\text{max}}(\text{CHCl}_3) 3320 \text{ b}, 3225 \text{ m, 1683 vs, 1620 m, 1510 s, 1290 s and 800 m cm}^{-1} \); \( \lambda_{\text{max}}(\text{EtOH}) 227(\epsilon 7,340) \) and 283 (1510); \( \lambda_{\text{max}}(\text{EtOH/NaOH}) 227(\epsilon 6,210), 263 (4,570) \) and 295 nm (3,280).

14-Acetoxyaminocodeinone (29):- 14-Hydroxyaminocodeinone (28) (328 mg) was dissolved in dry pyridine (5 ml) and acetic anhydride (0.5 ml) was added. After leaving overnight the solution was basified with saturated aqueous sodium bicarbonate and the mixture extracted with chloroform (2 x 10 ml). The combined chloroform extracts were washed with water (4 x 10 ml), dried and evaporated giving an oil from which crystals separated. These were filtered off and washed with a little ether leaving very pale yellow cubes of 14-acetoxyaminocodeinone (29) (340 mg, 92%), m.p. 147-148\(^\circ\) (decomp.) (from benzene) (Found: C, 64.84; H, 5.57; N, 7.57; \( M^+ m/e 370, C_{20}H_{22}N_2O_5 \) requires C, 64.85; H, 5.99; N, 7.56%; \( M 370) \tau (\text{CDCl}_3) 1.65(\text{s, NH}), 3.36(\text{s, 1-H and 2-H}), 3.53(\text{d, J 10 Hz, 8-H}), 3.84(\text{d, J 10 Hz, 7-H}), 5.25(\text{s, 5-H}), 6.19(\text{s, OMe}), 7.62(\text{s, NH}) \) and 8.03(\text{s, COCH}_3); \( \nu_{\text{max}}(\text{CHCl}_3) 3230 \text{ m, 2850 w}, 227(\epsilon 7,340) \) and 283 (1510); \( \lambda_{\text{max}}(\text{EtOH/NaOH}) 227(\epsilon 6,210), 263 (4,570) \) and 295 nm (3,280).
Treatment of 14-Hydroxyaminocodeinone with Sodium Methoxide:

14-Hydroxyaminocodeinone (28) hydrochloride (400 mg) was suspended in 5 ml of methanol and sodium methoxide solution, from sodium (80 mg) in methanol (5 ml), was added. The suspension dissolved giving a bright yellow solution and after 10 min at room temperature the solvent was removed giving a residue that was dissolved in water (15 ml). Solid carbon dioxide was added and a white precipitate formed which was extracted into chloroform (2 x 10 ml). The combined organic layers were dried and evaporated giving a gum which crystallised from ethanol as very pale yellow cubes of the phenol (30) (197 mg, 64%); m.p. 187° (decomp.) (Found: C, 63.82; H, 7.48; N, 7.32; M+ m/e 328. C_{18}H_{20}N_{2}O_{4} requires C, 64.15; H, 7.00; N, 7.48%; M 328) T(CDC1_{3}) 2.85 and 3.80 (broad s, 1H each and exchangeable with deuterium), 3.22(d, J 9.5 Hz, 8-H), 3.38(s, 1-H and 2-H), 4.05(q, J 9.5 Hz and 2 Hz, 7-H), 5.02(d, J 2 Hz, 5-H), 6.24(s, OMe), 7.65(s, NMe) and spectrum shows one mole of ethanol; v_{max}(CHCl_{3}) 3540 b, 3230 m, 2820 w, 1766 vs, 1693 vs, 1682 vs, 1500 m, 1280 s and 887 w cm\(^{-1}\).

Acetylation of the phenol (30):

14-Hydroxyaminocodeinone (28) hydrochloride (400 mg) was treated with sodium methoxide as described for the preparation of the phenol (30). The crude phenol was then dissolved in dry pyridine (5 ml) and acetic anhydride (0.6 ml) added. After leaving overnight the solution was basified with aqueous sodium bicarbonate and the resulting precipitate extracted into chloroform (2 x 10 ml). The combined organic extracts were washed with water (2 x 15 ml) and then dried and evaporated giving a solid residue. Crystallisation from ethanol gave colourless cubes of the diacetate (31) (190 mg, 50%); m.p. 221-223° (decomp.) (Found: C, 64.35; H, 5.84; N, 6.79; M+ m/e 412. C_{22}H_{24}N_{2}O_{6} requires C, 64.06; H, 5.87; N, 6.79%; M 412) T(CDC1_{3}) 2.87(d, J 10 Hz, 8-H), 3.04 and 3.24 (doublets, J 8.5 Hz, 1-H and 2-H), 4.02(q, J 10 Hz and 1.5 Hz, 7-H), 5.23 (d, J 1.5 Hz, 5-H), 6.28(s, OMe), 7.58 and 7.67 (singlets, ArO, CMe and NMe), and 7.94(s, NCOME); v_{max}(CHCl_{3}) 2850 w, 2820 w, 1775 vs, 1698 vs, 1682 vs, 1620 w, 1490 s, 1375 vs, 1270 s, 960 m and 880 m cm\(^{-1}\).

14-Hydroxyaminodihydrocodeinone (32):

14-Hydroxyaminocodeinone (28)
hydrochloride (400 mg) was dissolved in water (12 ml) and hydrogenated using 10% palladised charcoal (150 mg) for 70 min at room temperature and pressure. The catalyst was removed by filtration through 'Celite' and the solvent removed under reduced pressure to give a white solid. Ethanol was added when the solid initially dissolved and then crystallised out as white cubes of 14-hydroxyaminodihydrocodeinone (32) hydrochloride (250 mg, 62%), began to decompose on heating above 240° with no melting below 320° (Found: C, 56.50; H, 6.72; N, 7.42. C18H22N2O4H2OCl requires C, 56.17; H, 6.55; N, 7.28%); M+ m/e 330; C18H22N2O4 requires M 330; T CDCl3 2.75 and 1.92 (broad singlets, 1H each and exchangeable with deuterium), 3.20 (s, 1-H and 2-H), 5.00 (s, 5-H), 6.22 (s, OMe) and 7.10 (s, NHMe); vmax (nujol) 3220 m, 3150 m, 1720 vs, 1640 m, 1615 m, 1504 s, 1282 m and 850 m cm\(^{-1}\).

The free base crystallised from ethyl acetate (with much difficulty) as white needles; m.p. 100-101°C (decomp.), 330; C18H22N2O4 requires M 330; T CDCl3 3.34 (s, 1-H and 2-H), 4.10 (b, 2H replaceable with deuterium), 5.32 (s, 5-H), 6.13 (s, OMe) and 7.63 (s, NHMe); vmax (CHCl3) 3250 b, 2840 w, 2810 w, 1725 vs, 1640 w, 1610 w, 1500 m, 1275 s and 880 m cm\(^{-1}\).

Treatment of 14-Hydroxyaminodihydrocodeinone with Sodium Methoxide:- 14-Hydroxyaminodihydrocodeinone (200 mg) was suspended in methanol (5 ml) and sodium methoxide, from sodium (50 mg) in methanol (5 ml), was added. The solution turned yellow and after leaving for 10 min the solvent was removed and the residue dissolved in water (15 ml). Solid carbon dioxide was added and the resulting precipitate was extracted with chloroform (2 x 10 ml). The combined organic layers were dried and evaporated leaving a pale yellow oil which crystallised from ethanol as white needles of the reduced phenol (33), (150 mg, 75%) m.p. 210-212° (Found: C, 65.44; H, 6.96; N, 8.37; M+ m/e 330. C18H22N2O4 requires C, 65.44; H, 6.71; N, 8.48%; M 330) T CDCl3 2.75 (b, 1H, exchangeable with deuterium), 3.34 (s, 1-H and 2-H), 5.28 (s, 5-H), 6.22 (s, OMe), and 7.70 (s, NHMe); vmax (nujol) 3310 bs, 1730 s, 1618 m, 1586 m, 1490 s, 1275 s and 800 m cm\(^{-1}\).

A spectroscopically identical compound to the above was obtained from
column chromatography, using alumina grade III, of the free base of 14-hydroxyaminodihydrocodeinone (32). This gave white needles from ethanol m.p. 211-213°, mixed m.p. with product from sodium methoxide treatment 211-213°.

14-Aminocodeinone dimethyl ketal (37; NHOH = NH₂): Acetyl chloride (0.710 ml, 0.01 m) was added via a syringe to absolute methanol (40 ml) in a 100 ml conical flask fitted with a septum cap. After 5 min thebaine (3.11 g, 0.01 m) was added quickly so as to expose the dry methanol solution to the air only briefly. Freshly distilled 1-chloro-1-nitrosocyclohexane (1.90 g, 0.013 m) was then added, via a syringe, through the septum cap and the solution then left at 0°C in the dark for 50 hr. The dark coloured solution was poured into a rapidly stirred saturated solution of sodium bicarbonate (100 ml). Extraction with chloroform (2 x 30 ml) gave a dark organic solution which was dried and evaporated to give a golden yellow gum (4.93 g). The gum was chromatographed on neutral grade III alumina (4 x 30 cm column, ca. 300 g) using ether as eluent and collecting 50 ml fractions.

Fractions 1-10 contained cyclohexanone dimethyl ketal and fractions 11-17 gave a crude crystalline solid identified as thebaine. The eluting solvent was changed to chloroform and, after three fractions free of products, fractions 21-26 were collected and these showed essentially one major component on t.l.c. Removal of the solvent from the combined fractions 21-26 gave a pale yellow foam (2.5 g) which crystallised with difficulty from ethanol giving 14-hydroxyaminocodeinone dimethyl ketal (2.1 g, 56%) (37).

The 14-hydroxyaminocodeinone dimethyl ketal (1.0 g) was dissolved in methanol containing ammonium chloride (1.5 g). Zinc dust (1.5 g) was added and the mixture heated under reflux with vigorous stirring for 1 hr. The mixture was filtered, and the residues washed with a little methanol. After removing the methanol the residue was partitioned between water and chloroform and the chloroform layer then separated, dried and evaporated to give an orange oil. Percolation through a short (10 x 2 cm) grade III alumina column gave a very pale orange oil which crystallised on trituration (0.535 g, 56%) as cubes of 14-aminocodeinone dimethyl ketal (37, NHOH = NH₂).
m.p. 133-134° (mixed m.p. with sample from reduction of 14-nitrocodeinone dimethyl ketal,\(^{28}\) 133-134°) m/e 358; \(\text{C}_{20}\text{H}_{26}\text{N}_{2}\text{O}_{4}\) requires M 358; \(\tau\) (CDCl\(_3\)) 3.37 and 3.48 (doublets, J 8.5 Hz, 1-H and 2-H), 4.20 (d, J 10 Hz, 8-H), 4.37 (q, J 10 Hz and 1 Hz, 7-H), 5.31 (d, J 1 Hz, 5-H), 6.15 (s, ArOHe), 6.56 (s, 6f OMe), 6.80 (s, 6\(\alpha\) OMe), 7.25 (s, NH\(_2\) exchangeable with deuterium) and 7.64 (s, NMe); \(\nu\)\(_{\text{max}}\) (CHCl\(_3\)) 3385 m, 3310 m, 2850 m, 2820 m, 1640 m, 1610 m, 1502 s, 1470 s, 1050 vs and 940 s cm\(^{-1}\).

**14-Aminocodeinone (35):**

(a) **Via Hydrolysis of 14-Aminocodeinone Dimethyl Ketal** -
14-Aminocodeinone dimethyl ketal (100 mg) was dissolved in ethanol (3 ml) and benzene (3 ml) and concentrated hydrochloric acid (2 drops) was added. The colourless solution was left overnight and deposited colourless needles of 14-aminocodeinone hydrochloride (99 mg).

The hydrochloride salt was dissolved in water (10 ml) and basified with saturated aqueous sodium bicarbonate. The clear solution was then extracted with chloroform (2 x 5 ml). The combined chloroform extracts were dried and evaporated to give a colourless dendritic mass (90.0 mg, 100%), recrystallising from methanol as tiny star shaped crystals of 14-aminocodeinone hydrochloride (99 mg).

(b) **Via Thebaine Without Isolation of Intermediates** -

Acetyl chloride (780 mg, 0.71 ml, 0.01 m) was added via a syringe to cooled absolute methanol (40 ml) in a 200 ml conical flask (oven dried and flushed with nitrogen) fitted with a septum cap. Thebaine (3.11 g, 0.01 m) was added as quickly as possible after temporarily removing the cap. To the anhydrous solution of thebaine hydrochloride was added freshly distilled, dry 1-chloro-1-nitrosocyclohexane (2.0 g, 0.0136 m), also via a syringe through the septum cap. The blue solution was left at 0°C in the dark (i.e. refrigerator) for 48 hr when it turned greenish-brown.

The solution was poured with vigorous stirring into saturated aqueous
sodium bicarbonate (250 ml). Extraction of the aqueous solution with chloroform (2 x 50 ml), followed by drying of the combined organic phases and evaporation, gave a dark viscous oil.

The oil was dissolved in methanol (200 ml) and zinc dust (5 g) and ammonium chloride (5 g) added. The solution was stirred vigorously with heating under reflux for 1 hr, and the solvent then removed under reduced pressure. The residue was partitioned between water (150 ml) and chloroform (50 ml) and after separation the aqueous phase was extracted further with chloroform (50 ml). The combined extracts were evaporated to give a yellow gum which was dissolved in dilute hydrochloric acid (100 ml of 0.5 N). After 2 hr at room temperature the aqueous solution was washed once with chloroform (30 ml) and then basified with saturated sodium bicarbonate solution. The basified solution was extracted with chloroform (2 x 25 ml) and the combined extracts were dried and evaporated to give an amber coloured gum. The gum was percolated through a short column of grade III, neutral alumina, using chloroform as eluent and the solution then evaporated to give a gum. Addition of a little methanol gave a mass of star shaped crystals (1.10 g; 35%) of 14-aminocodeinone (35) which crystallised from methanol as needles, m.p. 194-195°; spectroscopic data as above.

3,6-Dimethoxyphenanthrene-1,4-quinone (38):- Thebaol (250 mg, 1 mmol) was dissolved in absolute methanol (15 ml) and 1-chloro-1-nitrosocyclohexane (300 mg, 2 mmol) was added in benzene (1 ml). The resulting solution was left at 0° for 15 hr during which time an orange crystalline precipitate had formed. After filtration of the solid (124 mg) the mother liquors were concentrated and a further crop of orange needles was isolated (70 mg). Total yield of 3,6-dimethoxyphenanthrene-1,4-quinone (38) was (194 mg, 73%), m.p. 231-233° (from acetic acid) (lit. 29, 233°), M+ m/e 268; C16H12O4 requires H 268; \( \text{T(CDCl}_3) = 0.98 (d, J 3 \text{ Hz}, 5-H), 1.97 (s, 9H and 10-H), 2.36 (d, J 8.5 \text{ Hz}, 8-H), 2.76 (q, J 8.5 \text{ Hz} \text{ and } 3 \text{ Hz}, 7-H), 3.90 (s, 2-H), 6.03 \text{ and } 6.08 (\text{singlets, } 3 \text{ and } 6 - \text{ OMe}); \nu_{\text{max}}^{\text{KBr}} 1674 \text{ s}, 1646 \text{ vs}, 1623 \text{ vs}, 1464 \text{ s}, 1240 \text{ s}, 1218 \text{ s}, 1090 \text{ s} \text{ and } 840 \text{ s cm}^{-1}; \lambda_{\text{max}}^{\text{EtOH}} 232 (\epsilon 49,400), 290 (17,080), 314 (sh, 6,400), 393 (2,800), \text{ and } 496 \text{ nm (2,650).} 

7-Hydroxyiminoneopinone (44):- Method (a). 14-Hydroxyaminocodeinone (28)
hydrochloride (800 mg) was dissolved in water (20 ml) and periodic acid (500 mg) in water (8 ml) was added dropwise. After leaving for 5 min after the final addition of periodic acid the precipitated iodine was filtered off. The aqueous filtrate was washed with carbon tetrachloride (3 x 15 ml) to remove dissolved iodine, and the aqueous layer was then basified with saturated aqueous sodium bicarbonate. The precipitated solid was extracted into chloroform (2 x 10 ml) and the combined chloroform extracts were dried and evaporated to give a pale yellow crystalline solid. After washing with a little chloroform yellow needles of 7-hydroxyimino-neopinone (44) remained (430 mg, 63%), m.p. 193-194° (from chloroform) \( \text{[CD}_3\text{]}_2\text{SO} \) 3.33 (m, 1-H and 2-H), 3.43 (s, 8-H), 4.70 (s, slowly exchangeable with deuterium, 5-H), 6.22 (s, OMe) and 7.65 (s, NH); \( \nu_{\text{max}} \) (nujol) 2600 b, 1716 s, 1658 m, 1635 m, 1505 s, 1280 s, 932 s and 760 s cm\(^{-1}\); \( \lambda_{\text{max}} \) (EtOH) 213 (e 20,800), 231 (17,380) and 775 (sh, 7,050); \( \lambda_{\text{max}} \) (EtOH/NaOH) 231 (e 26,150), 285 (11, 780) and 347 nm (9,330); \( \text{M}^+ \) m/e 326; \( C_{18}H_{18}N_2O_4 \) requires M 326.

Method (b). Neopinone (200 mg) was dissolved in chloroform (1 ml) and ethanol (1 ml) containing dry hydrogen chloride (60 mg) (from a stock solution of the gas (1.81 g) in ethanol (30 ml)) was added. After cooling to 0° amyl nitrite (100 mg) in chloroform (1 ml) was added and the solution left at 0° overnight. The solution was basified with 2N-sodium hydroxide solution (1 ml) and after diluting with water the layers were separated; the aqueous layer extracted with chloroform and the combined extracts were dried and evaporated giving a pale yellow solid (100 mg). The aqueous layer was acidified with solid carbon dioxide giving a precipitate which was extracted into chloroform (2 x 5 ml). The chloroform extracts were combined, dried and evaporated to give a viscous oily residue which crystallised as pale yellow needles on trituration with ethanol (48 mg, 23%) m.p. 192-193° (mixed m.p. with product from periodic oxidation 192-194°).

An identical product (i.r. and n.m.r.) was also obtained by hydrolysis of the ketal (7), obtained by Serjinder Singh in these laboratories from nitrosation of thebaine with nitrosyl chloride in methanol, m.p. of hydrolysed product 192-193° (mixed m.p. with product from periodic oxidation 192-193°).
SECTION 2

Some Studies on Nitrosyl Cyanide
INTRODUCTION

In the previous section the preparation and stability of thebaine-nitrosoarene adducts were described. From that work and from the study of the reaction of thebaine with 1-chloro-1-nitrosocyclohexane and nitrosoalkanes it was shown that stable adducts were formed only when strong electron-withdrawing effects were in operation.

While Diels-Alder reactions with nitrosoarenes and nitrosoalkanes carrying electron-withdrawing α-substituents are well documented the only other nitroso-containing group of compounds known to undergo this addition are the arylsulphonyl nitrosites. These compounds are intermediates in the reaction of alkyl nitrites with sulphinic acids. No examples of either N-nitroso compounds or alkyl nitrites adding to conjugated dienes to give 1,4-cycloadducts are known. Similarly, nitrosyl halides do not form 1,4-cycloadducts with conjugated dienes.

With the above factors in mind it was hoped that the scope of the addition of nitroso-dienophiles to thebaine could be extended. Thus it was envisaged that nitrosyl cyanide, the cyanogen analogue of the nitrosyl halides, might act as a reactive dienophile. Such a species would, unlike the nitrosyl halides, be a C-nitroso compound and would also fulfil the electronic and stereochemical requirements for 1,4-cycloaddition to conjugated dienes. To test the dienophilic nature of this nitroso compound reactions were devised in which any nitrosyl cyanide formed would be trapped by thebaine, since this diene readily gives 1,4-cycloadducts with suitable C-nitroso compounds as shown earlier.
DISCUSSION

Nitrosyl cyanide has been postulated as an unstable intermediate in the gas phase photochemical reactions involving nitric oxide and cyanogen or cyanogen halides. This procedure seemed of little preparative use for our purposes and was not pursued.

Initial, unfruitful attempts at generating nitrosyl cyanide were carried out by treating penty1 nitrite with potassium cyanide in various solvents and at various temperatures. Sodium cyanide was then substituted for potassium cyanide because of its greater, but still very low, solubility in organic solvents. With thebaine present in the reaction solutions the alkaloid was recovered unchanged in every case. Similarly the u.v. spectrum of the reaction solution, in the absence of thebaine, showed no decrease in the nitrite chromophore absorption with time.

\[
\text{RONO} + \text{H}^+\text{CN}^- \rightarrow \text{H}^+\text{OR}^- + \text{ONCN}
\]

The heterogeneous silver cyanide-nitrosyl chloride system was then considered as a possible route to nitrosyl cyanide.

\[
\text{NOCl} + \text{AgCN} \rightarrow \text{AgCl} + \text{ONCN}
\]

Since silver cyanide reacts with alkyl halides to give alkyl isocyanides one must consider the alternative possibility in which nitrosyl isocyanide is formed.

\[
\text{AgCN} + \text{NOCl} \rightarrow \text{AgCl} + \text{ONNC}
\]

Perrot has published a brief report on the action of nitrosyl chloride with a series of silver salts. He found that with silver perchlorate nitrosyl perchlorate was formed while with silver cyanate he observed the formation of silver chloride, carbon dioxide and nitrogen. With silver cyanide he reported that a temperature of 150°C was necessary for reaction to occur and gave no information regarding the products. However, we found that reaction of an excess of nitrosyl chloride with a stirred suspension of dry, freshly precipitated silver cyanide (grey) in
chloroform at room temperature gave silver chloride. This was identified by its changing from white to purple on exposure to light and by its i.r. spectrum which, unlike silver cyanide, showed no absorption in the 2100-2300 cm\(^{-1}\) region. Analysis, by i.r. spectrometry, of the volatile components collected in cold traps at 0\(^\circ\), -20\(^\circ\) and -196\(^\circ\) placed in series, showed only nitrosyl chloride to be evolved. The failure to detect any nitrosyl cyanide may have been due to its rapid decomposition. Such a drawback could possibly be overcome by the use of lower reaction temperatures and the presence of a trapping agent, such as thebaine.

Nitrosyl chloride was then added to a stirred suspension of a molar equivalent of silver cyanide in chloroform at 0\(^\circ\)C. After 5 min a 0.5 molar equivalent solution of thebaine in chloroform was added and the mixture stirred for a further 15 min. Thin layer chromatography (alumina) of the crude product remaining after filtration and evaporation of the solvent showed thebaine to be the major constituent with a minor, less polar material and a minor very polar material. The less polar minor product was isolated by column chromatography and showed nitrile absorption at 2210 cm\(^{-1}\). The n.m.r. spectrum showed a low field AB quartet characteristic of the 7-H and 8-H protons of thebaine-nitrosoarene adducts\(^32\). The mass spectrum had a molecular ion at m/e 365 which was consistent with a thebaine-nitrosyl cyanide adduct; loss of 56(ONCN) then gave an ion at m/e 311 (thebaine), the breakdown pattern thereafter closely resembling that of thebaine itself. The structure (48; \(R = \text{Me}\)) was tentatively proposed for the adduct, the direction of addition being inferred by analogy with the known direction of addition of nitrosoarenes to thebaine\(^32\). Final proof of the proposed structure was obtained by chemical modification as shown later.

In contrast to the thebaine-nitrosoarene adducts the nitrosyl cyanide adduct showed no sign of dissociation in solution as judged by its colour and n.m.r. spectrum. Even at 100\(^\circ\) the n.m.r. spectrum of the adduct showed no detectable free thebaine. The stability of the adduct was shown even more significantly by the mass spectrum which showed a molecular ion at m/e 367.1535 corresponding to \(C_{20}H_{21}N_3O_4\). In contrast all the thebaine-nitrosoarene adducts, including that from p-nitro-nitrosobenzene, which was shown earlier to be the most stable of those
adducts studied, showed no molecular ion corresponding to the adduct itself. With such adducts the molecular ion occurred at m/e 311, corresponding to thebaine \( \text{C}_{19}\text{H}_{21}\text{NO}_3 \) and thus indicating a ready reversal of the addition.

To improve the preparation of nitrosyl cyanide optimisation reactions were carried out in which the effects of temperature, solvent, time, and molar ratios were investigated. It was found from these experiments that the best yields of the adduct were obtained using a reaction temperature of \(-20^\circ\text{C}\) to \(-30^\circ\text{C}\). Temperatures above this gave very little adduct and produced an unidentified, very polar, insoluble yellow solid which was believed to be derived from reaction of nitrosyl chloride with thebaine. A similar yellow solid, but no adduct, was obtained by reaction of nitrosyl chloride with a solution of thebaine in chloroform at room temperature. Lower temperatures, e.g. \(-60^\circ\text{C}\) to \(-80^\circ\text{C}\), also resulted in a decreased yield of adduct and a further complication was the insolvability of the thebaine. The lower yields are a result of decreased reaction between the nitrosyl chloride and silver cyanide. It was shown (see later) that the two reactants, in the absence of solvent, could be 'frozen out' at low temperatures, e.g. \(-196^\circ\text{C}\) to \(-80^\circ\text{C}\), and stored until needed, when warming to \(-20^\circ\text{C}\) to \(-30^\circ\text{C}\) gave a green vapour which contained nitrosyl cyanide.

Reactions were carried out using laboratory distilled chloroform which was shown by comparative i.r. spectrometry to contain 1% ethanol. This solvent mixture gave better yields of adduct than ethanol-free chloroform. Dichloromethane gave similar yields of adduct as when ethanol-free chloroform was used as solvent. Other solvents were not used owing to the insolubility of thebaine or their reaction with the nitrosyl chloride. A procedure was devised whereby the extent of the reaction between nitrosyl chloride and silver cyanide (1:2 mole ratio) was determined by analysis of the chloride content in the residual silver cyanide-silver chloride mixture. Thus, the solid from the reaction between nitrosyl chloride and silver cyanide in the various solvents was filtered off, washed with a little of the solvent and dried in the dark. A portion of the residue was dissolved in a minimum of hot ammonia solution (0.880) and an excess of sodium sulphide added when the total silver was
precipitated out as silver sulphide. The silver sulphide was filtered off, washed well with distilled water and the filtrate and washings then boiled until ammonia free. The solution was acidified with acetic acid and boiled further to expel hydrogen sulphide and hydrogen cyanide. When boiled to about half its original volume it gave a negative test with lead acetate paper and the solution was then made up to a standard volume. Titration of the solution, in two portions, with standard silver nitrate solution gave the chloride content and hence the percentage reaction. Control runs using prepared mixtures of known amounts of silver chloride and silver cyanide showed the method to be accurate to within 5%. From the results with the three solvents used it was found that the chloroform/1% ethanol gave 40% reaction while the ethanol-free chloroform and dichloromethane gave only 12% and 20% reaction respectively.

In a similar set of experiments nitrosyl chloride was added to a stirred suspension of silver cyanide in chloroform containing 1% ethanol at -20°C and thebaine in the same solvent was then added after 1 minute. The amount of adduct formed was determined by column chromatography of the residue after work-up. Similarly, thebaine solutions were added after 2, 3, 4, 5 and 10 minutes and the results showed that best yields of adducts were obtained with addition of the diene after 3 to 5 minutes.

In optimising the conditions with respect to the molar proportions of the reactants one must consider the fact that the production of nitrosyl cyanide is a heterogeneous process. Such processes normally require a large excess of the solid reactant since reaction can occur at the surface only. This is particularly so in the case under consideration since the silver cyanide becomes coated with insoluble silver chloride and is thus effectively removed from the sphere of the reaction. This probably explains the incompleteness of the reaction. One would like to choose therefore as large an excess of solid reactant as possible but owing to economic and residue disposal problems some compromise was necessary. Silver cyanide was always used in a twofold molar excess over nitrosyl chloride and typical experiments used 0.50 molar equivalents of thebaine. It was found that addition of glass boiling chips to the mixture gave a better reaction since on vigorous stirring these tended to expose new
silver cyanide surfaces.

Under optimum conditions adduct yields of ca. 15-50% (typically 20%) with recovery of thebaine (50-10%) were achieved. The large discrepancies in observed yields of adduct were a result of differences in silver cyanide condition and the degree of effective stirring.

Substitution of copper cyanide for silver cyanide in the reaction gave the adduct but in much poorer yield. A very low yield of adduct was also obtained using Schotten-Bauman type conditions in which an aqueous potassium cyanide solution above chloroform containing nitrosyl chloride and thebaine, was stirred at -20°C.

It was mentioned earlier (and see later) that in the absence of solvent nitrosyl chloride reacted with an excess of silver cyanide at -20°C to give a green gas. Analysis of the residue in the manner described above showed the extent of reaction in this case to be about 40%. The yields of adduct obtained by adding a solution of thebaine in dichloromethane or chloroform to the green vapour mixture were very similar to those obtained using chloroform 1% ethanol as solvent and the method was adopted as the normal mode of producing nitrosyl cyanide.

That the adduct obtained with thebaine was an N-cyano compound was shown by its i.r. absorption at 2205 cm\(^{-1}\) (nujol) and its hydrolysis by prolonged contact with alumina to the urea (49: \(R = \text{CH}_3\)), \(v_{\text{max}}\) (nujol) 3380, 3305, and 1695 cm\(^{-1}\). Simple hydrolysis with dilute aqueous sodium hydroxide in a variety of water miscible solvents, and alone, proved less effective than the hydrolysis on alumina. Reactions of the urea with nitrous acid failed to give the known 14-hydroxy-aminocodeinone (28); only starting material was recovered.

The cyclic nature of the adduct was shown by catalytic hydrogenation over platinum oxide when one mole equivalent of hydrogen was taken up (reaction followed by t.l.c.). Isolation of the product gave a compound with spectroscopic and analytical properties expected for the cyanamide (50); \(v_{\text{max}}\) (CHCl\(_3\)) 3220, 2218, and 1695 cm\(^{-1}\). The cyanamide presumably arises via an intermediate hemiacetal. A spectroscopically
identical product, which showed no depression of melting point on mixing, was obtained in these laboratories\textsuperscript{28} by reaction of cyanogen bromide with 14-aminocodeinone (35).

With a larger excess of nitrosyl cyanide, e.g. using 0.25 mole equivalent of thebaine with two mole equivalent of silver cyanide and one mole equivalent of nitrosyl chloride, a compound very similar to the adduct (48; \( R = \text{Me} \)) was formed. This compound showed an additional weak absorption in its i.r. spectrum (nujol) at 2245 cm\(^{-1}\) and its n.m.r. spectrum, though very similar to that of the adduct (48; \( R = \text{Me} \)), showed no \( N-\text{Me} \) signal but instead a methylene quartet, \( \tau(\text{CDCl}_3) \) 6.20 and 6.35 (J 11 Hz). This same compound was formed from the adduct (48; \( R = \text{Me} \)) by reaction with silver cyanide-nitrosyl chloride and was concluded to be the \( N-\text{cyanomethyl} \) derivative (48; \( R = \text{CH}_2\text{CN} \)). By way of comparison, diethylaminoacetonitrile was prepared and this showed a very weak i.r. absorption at 2235 cm\(^{-1}\) while the n.m.r. spectrum showed a methylene singlet at \( \tau(\text{CDCl}_3) \) 6.51. Hydrolysis of the \( N-\text{cyanomethyl} \) adduct (48; \( R = \text{CH}_2\text{CN} \)) on alumina, in the same manner as with the \( N-\text{methyl} \) adduct gave the analogous urea (49; \( R = \text{CH}_2\text{CN} \)). Treatment with sodium methoxide in methanol gave the \( O-\text{methylisourea} \) (51).

The non-equivalence of the methylene protons of the cyanomethyl group in the adduct (48; \( R = \text{CH}_2\text{CN} \)) results from asymmetry in the rest of the molecule. Cortisone acetate (52) also exhibits this effect, the C-21 methylene group giving rise to an \( AB \) quartet (J 15 Hz)\textsuperscript{35}. If the asymmetry is slight or if the asymmetric group is far removed the degree to which the methylene protons are non-equivalent may be too small to result in an observable effect. The observed magnitude of the geminal coupling constant between methylene protons decreases with increasing electronegativity of the attached substituent. The values for methane, methanol, and fluoromethane are 12.4, 10.8, and 9.6 Hz respectively\textsuperscript{37}. However if the geminal protons can assume all possible rotational conformations with respect to any adjacent \( \pi \) system then the observed coupling increases by about 1.9 Hz for each adjacent \( \pi \) bond. The value for acetonitrile is 16.2 Hz\textsuperscript{37}. In the adduct (48; \( R = \text{CH}_2\text{CN} \)), the decrease in the geminal coupling constant brought about by the attached electronegative nitrogen would not be expected to be great enough to compensate for the increase brought about by the attached nitrile group. One would expect therefore
a coupling constant greater than that in methane, i.e. 12.4 Hz. Since the observed coupling constant is 11 Hz it must be that not all rotational conformations of the methylene group are possible with the result that the N-contribution is much less than expected for a freely rotating methylene group.

Attempts at deuteriating diethylaminoacetonitrile (0.5 mole equivalent of D₂O) to obtain a value of the geminal coupling constant in a freely rotating system were unsuccessful.

The mass spectrum of the N-cyanomethyl compound (48; R = CH₂CN) showed a molecular ion at m/e 392.1490 corresponding to a nitrosyl cyanide adduct with N-cyanomethylnorthebaine. The parent ion in the spectrum was at m/e 336 and this corresponded to N-cyanomethylnorthebaine; the breakdown pattern thereafter closely resembled that of thebaine itself but was displaced to higher mass by 25 units.

The cyanation of the N-methyl group appeared to be unusual but it may in fact be a general reaction for the system used. Further investigation of the effect was undertaken in these laboratories by D.A. Hardie and G.W. Kirby. They found that N-methylmorpholine was converted by silver cyanide-nitrosyl chloride into N-cyanomethylmorpholine, identical with a sample prepared from morpholine by reaction with formaldehyde bisulphite complex and acetone cyanohydrin. The mechanistic origin of the cyanomethyl group is not known but one may envisage it as arising by attack of cyanide on an intermediate immonium ion (53). The latter may arise by attack of the nitrogen on nitrosyl cyanide followed by an elimination of the anion (54); Scheme 6. Another possibility is that the immonium ion (53) may arise via nitrosation with nitrosyl chloride. Although normally considered to be inert to nitrosation tertiary amines react readily if the acidity of the medium is not too high and cleavage of the resulting nitrosammonium ion (55) to form a dialkyimmonium ion (56) and nitroxyl is thought to occur. Normally the immonium ion is hydrolysed to a nitrosamine (57) and an aldehyde; Scheme 7. In strong acid the concentration of free base is too low for the reaction to proceed.

Acid hydrolysis of the adduct (48; R = Me) would be expected to give 14-
(N-cyanoxyhydroxyamino)codeinone (58; X = CN). Treatment of the N-methyl adduct with dilute acid followed by neutralisation with sodium bicarbonate gave an uncrystallisable compound, pure by t.l.c., which had $v_{\text{max}}$ (CHCl$_3$) 3400 and 1687 cm$^{-1}$. The n.m.r. spectrum showed only one OMe signal at $\tau$(CDCl$_3$) 6.20 with other signals at 2.90(d, J 9.5 Hz, 2H), 3.96(q, J 9.5 Hz and 2 Hz, 1H), 4.88(d, J 2 Hz, 1H) and a broad singlet at 4.53(2H) replaceable with deuterium. A positive phenol test with Gibbs reagent was obtained. From these data it was concluded that the product was the phenol (59). Similar phenols were reported in section 1, when rearrangements of 14-hydroxyaminocodeinone derivatives were effected with sodium methoxide. In the above example it appears, rather surprisingly, that sodium bicarbonate is a sufficiently strong base to bring about the transformation. The difference between the two examples obviously lies in the acidities of the hydroxylamine functions. Hydroxylamine itself, like its N-alkyl analogues is only weakly acidic with an estimated pKa of about 12. An N-carboxamide, or N-cyanide substituent would however give a hydroxamic acid derivative and this would be expected to be much more acidic (pKa ca. 8.5-9.5 for hydroxamic acids$^4$). An initial hydrolysis of the system would be expected therefore to give an intermediate N-substituted 14-hydroxyaminocodeinone derivative (58; X = CONH$_2$ or CN) which, with sodium bicarbonate, rearranges to the observed phenol (59). That the substituent on the nitrogen of the isoxazolidine ring in (59) was aminocarbonyl and not cyano was shown by preparation of a spectroscopically identical phenol from the urea (49) by treatment with dilute acid and sodium bicarbonate. It is not known whether the nitrile group was hydrolysed before or after the rearrangement but in either case the hydrolysis proceeds extremely rapidly; Scheme 8.

The n.m.r. spectrum of the N-methyl adduct (48) dissolved in D$_2$O containing one mole equivalent of DCl was consistent with the intermediate N-substituted 14-hydroxyaminocodeinone derivative (57; X = CN or CONH$_2$). Signals were observed at $\tau$ 3.27(d, J 10 Hz, 8-H), 3.82(d, J 10 Hz, 7-H), 6.31(s, OMe) and 6.95(s, $^1$NMe); no signal for 5-H was observed and this was probably masked by the large DHO peak at 4.95.

The u.v. spectrum of the phenol (59) closely resembled that of the
Scheme 8
similar phenol \((30; \text{i.e. } 59; \text{CONH}_2 = \text{H})\) and also that of dihydrothebaine-\(\phi\). These compounds showed \(\lambda_{\text{max}}^{\text{EtOH}}\) 284 (\(\epsilon 3,330\)), 285 (2,250), and 285 nm (2,130) respectively. All showed typical bathochromic shifts of phenols with sodium hydroxide thus \(\lambda_{\text{max}}^{\text{EtOH/NaOH}}\) 256 (\(\epsilon 8,140\)), 294 (5,670) for phenol (58); 258 (5,050), 295 (3,705) for phenol (30); and 263 (4,070), 300 nm (3,590) for dihydrothebaine-\(\phi\).

To establish the generality of the 1,4-cycloaddition of nitrosyl cyanide its reactions with other dienes were undertaken. Trans-trans-1,4-diphenylbutadiene is known to give a low yield (13\%) of a cycloadduct with nitrosobenzene, but it does not react with 1-chloro-1-nitrosocyclohexane presumably because of steric hindrance. Since nitrosyl cyanide gave a more stable adduct with thebaine than did nitrosobenzene and does not have any foreseeable steric effects one would expect a cycloadduct with trans, trans-1,4-diphenylbutadiene. Reaction of the diene with nitrosyl chloride-silver cyanide in chloroform at \(-20^\circ\text{C}\) gave a crude product from which a low yield of a white solid crystallised on adding methanol. This gave a yellow crystalline product on treatment with base or on elution down an alumina column. The same yellow solid was also obtained (88\%) on column chromatography of the crude reaction mixture. Spectroscopic and analytical data for the two compounds showed that the white crystalline product was 3-chloro-4-nitro-1,4-diphenylbut-1-ene (60) and the yellow product was 1-nitro-1,4-diphenyl-1,3-butadiene (61). This is derived from the chloro compound by a base catalysed elimination of hydrogen chloride. An authentic specimen of 1-nitro-1,4-diphenyl-1,3-butadiene (61) was prepared by addition of dinitrogen tetroxide to 1,4-diphenyl-1,3-butadiene followed by a base catalysed 1,4-elimination of nitrous acid. The sample so prepared had identical spectroscopic properties to the above yellow compound and their melting point was undepressed on mixing.

The n.m.r. spectrum (CDCl\(_3\)) of the chloro compound showed a complex aromatic proton signal centred at \(\tau 2.60\) and signals at \(\tau 3.19 (d, J 15.4 \text{ Hz, } 1-\text{H}), 3.72 (q, J 15.4 \text{ Hz and } 8.2 \text{ Hz, } 2-\text{H}), 4.36 (d, J 9.4 \text{ Hz, } 4-\text{H}), \) and \(4.69 (q, J 9.4 \text{ Hz and } 8.2 \text{ Hz, } 3-\text{H})\). The spectrum is consistent with a 1,2-, but not a 1,4-disubstituted product. It is not possible to tell from the spectrum whether cis or trans addition to the double
bond took place since the two most likely conformations (62) and (63) for the two modes of addition both have trans-coplanar 3,4 protons.

There was no evidence of the crude reaction mixture's containing a nitrosyl cyanide-1,4-diphenyl-1,3-butadiene cycloadduct.

Since no required adduct was obtained it was assumed that under the reaction conditions, 3-chloro-4-nitro-1,4-diphenylbut-1-ene (60) was formed much faster than addition of nitrosyl cyanide. The formation of this nitro compound may arise from the excess of nitrosyl chloride which is known to be always present in the mixture due to incomplete reaction with silver cyanide. Nitro rather than nitroso formation in the reaction of nitrosyl chloride with alkenes has been briefly reviewed\(^4\). In those cases in which the addition of nitrosyl chloride to alkenes is difficult, e.g. with alkenes containing electron-acceptor groups, the rate of nitro compound formation exceeds the rate of addition of nitrosyl chloride. Nitro-formation is apparently initiated by the presence of nitrogen dioxide probably by a free radical trans addition of nitryl chloride\(^4\). The presence of nitrogen dioxide in the reaction mixture is very likely since nitrosyl cyanide is known to break down to give this gas (see later). The observed product may then result from nitryl chloride addition to the diene. Nitration does in fact seem to be a feature of the silver cyanide-nitrosyl chloride system since it occurred in other cases.

1,3-Diphenylisobenzofuran with nitrosyl chloride-silver cyanide in chloroform at -20° gave a high yield (80%) of ortho-dibenzoylbenzene, identical in all respects with the authentic material. No evidence was available as to the origin of this product, whether it be formed by straight oxidation of the isobenzofuran or by breakdown of an intermediate adduct such as (64; \(XY = \cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot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gum showed only a complex aromatic signal while the i.r. spectrum showed $\nu_{\text{max}}$ (film) 2245 m, 1784 m, 1560 vs, 1450 m, 1340 m and 750 s cm$^{-1}$, the strong band at 1560 cm$^{-1}$ suggesting the presence of a nitro group. All attempted purifications of the product failed; thus chromatography on alumina showed several spots including a fast running purple one. The latter could possibly arise as a result of a retro-Diels-Alder reaction giving tetrphenylcyclopentadienone, or more likely a base catalysed cleavage of an addition product to reform the diene. No pure products were obtained from the crude reaction mixture.

Norbornadiene, a homoconjugated system, has been used to form adducts with certain dienophilies. While it decolourises the green solution of monomeric nitrosobenzene$^{17}$, no cycloadduct was isolated and the compound very likely reacted as an alkene.

When norbornadiene was added in dichloromethane to the green vapour produced by the reaction of nitrosyl chloride with silver cyanide at -20°C, a pale blue solution was formed which on standing decolourised with precipitation of a white solid. The solid was removed by dissolving in hot chloroform giving a green-blue solution which on cooling gave the white solid. Crystallisation from toluene gave tiny white cubes which had a melting point identical (162°C) with that reported for 5-chloro-6-nitrosobornene dimer (65).$^{16}$

Mass spectrometry of the dimer showed molecular ions at m/e 159 and 157 (1:3) and fragment ions at m/e 129 and 127 (1:3) corresponding to loss of NO; the base peak occurred at m/e 91 corresponding to loss of NOCl. No peak for the dimer was observed. Similarly, the mass spectrum of nitrosocyclohexane dimer shows only a molecular ion of the monomer, even though this compound is known to dissociate to monomer with difficulty$^{19}$. One can conclude from the results that cycloaddition is unfavourable with the homoconjugated system and addition of nitrosyl chloride is faster than any possible addition of nitrosyl cyanide to the double bond.
Butadiene should present no steric or anomalous electronic effects as a diene and indeed when this gas was bubbled into silver cyanide-nitrosyl chloride in dichloromethane at -20° it gave, on work-up, a pale yellow oil whose spectroscopic properties were those expected for the adduct (66; R = CN). Molecular distillation gave a colourless oil, bp. 50° at 0.5 mm Hg, which had absorptions in the i.r. (film) at 2215 and 1645 cm⁻¹. The 60 MHz n.m.r. spectrum showed three 2-proton multiplets at t(CDCl₃) 4.03, 5.45, and 6.00. The low field multiplet at t 4.03 was resolved at 220 MHz into an AB quartet (J 11.7 Hz) with further multiple splitting for each component. High resolution mass spectrometry confirmed the molecular formula C₅H₆N₂O and showed fragment ions C₄H₄N₂, C₄H₆, and C₃H₃ and metastable peaks for C₅H₆N₂O → C₄H₄N₂ and C₄H₆ → C₃H₃; Scheme 9.

Treatment of the butadiene adduct with sodium methoxide in methanol gave the expected Q-methylisourea (66; R = C(OMe)NH) and hydrolysis with 30% sulphuric acid gave the urea (66; R = CONH₂). Arbuzov and Onishchenko have prepared the parent oxazine (66; R = H) by in situ alcoholysis of the 1-chloro-1-nitrosocyclohexane adduct. Treatment of this oxazine with cyanogen bromide should yield the cyanamide (66; R = CN) and thus provide unequivocal proof of the nitrosyl cyanide-butadiene adduct structure.

Treatment of the oxazine (66; R = H) in ether at 0°C with 0.5 mole equivalent of cyanogen bromide gave the cyanamide (66; R = CN) (16%) and the hydrobromide salt of the starting oxazine (30%) which crystallised out from the ether solution. A third product crystallised out of solution after removal of the hydrobromide salt and this was shown to be the guanidine (67), formed by coupling of the oxazine (66; R = H) with the cyanamide (66; R = CN). The i.r. spectrum of the guanidine (67) had ν max (nujol) 3150, 1650 and 1565 cm⁻¹; no n.m.r. spectrum could be obtained owing to the low solubility of the compound. Mass spectrometry showed a molecular ion at m/e 195 and from other ions at m/e 178, 166, 111, 85 (base peak) the fragmentation map shown in Scheme 10 was established. The same guanidine (67) was obtained as its hydrochloride by treatment of the cyanamide (66; R = CN) with the oxazine (66; R = H) hydrochloride in ethanol.
Scheme 9.

\[
C_4H_4N_2 \leftrightarrow \text{CH}_2O \quad \text{m/e 80.0374}
\]

\[
\text{NCO} \quad \text{m/e 110.0477 (110.0480)}
\]

\[
\text{NCO} \quad \text{m/e 54.0466 (54.0469)}
\]

\[
\text{CH}_3 \quad \text{m/e 39.0233 (39.0235)}
\]

calculated values in brackets

Scheme 10.

\[
C_9H_10N_2O_2 \quad \text{m/e 166}
\]

\[
\text{HCO (or HCN)} \quad \text{m/e 178}
\]

\[
\text{NCO} \quad \text{m/e 195}
\]

\[
C_9H_{13}N_2O_2 \quad \text{m/e 111}
\]

\[
\text{CH}_7N_0 \quad \text{m/e 85}
\]

Scheme 10.
Addition of the oxazine (66; \( R = H \)) hydrochloride in water to a solution of sodium bicarbonate containing one mole equivalent of cyanogen bromide gave the cyanamide (66; \( R = \text{CN} \)) in high yield (93%), with no guanidine or salt formation. The product was identical with material prepared from reaction of butadiene with nitrosyl cyanide.

A cycloadduct (68; \( R = \text{CN} \)) was obtained as an oil b.p. 66° at 0.4 mm Hg, using 2,3-dimethyl-1,3-butadiene as a nitrosyl cyanide trap. An identical product was prepared by treatment of the known 4,5-dimethyl-oxazine (68; \( R = H \)) hydrochloride with cyanogen bromide in aqueous sodium bicarbonate. The adduct showed the expected spectroscopic properties and gave a crystalline urea (68; \( R = \text{CONH}_2 \)) on hydrolysis with 25% sulphuric acid in methanol/water (50:50).

Leonard and Playtis have prepared 1-(4-hydroxy-3-methyl-cis-but-2-enyl) guanidine (69), a naturally occurring hydroxygalegine, by treating the amino alcohol (70) with \( \beta \)-methylisothiouronium chloride. They obtained the amino alcohol by zinc reduction of the product from in situ ethanolysis of the isoprene-1-chloro-1-nitrosocyclohexane adduct. We envisaged a simpler preparation of the naturally occurring compound from the isoprene-nitrosyl cyanide adduct (71) by zinc reduction and treatment with ammonium chloride. However no pure adduct was obtained from nitrosyl cyanide and isoprene. The crude product, isolated in low yield from the reaction, streaked on silica and alumina t.l.c. plates and decomposed on attempted distillation. The n.m.r. spectrum of the crude product indicated the presence of the two isomeric adducts (71) and (72).

Nitrosobenzene gives only a low yield of adduct with isoprene and azoxybenzene is a byproduct. A possible explanation for this low yield, and a possible cause of the complex products in our own reaction, is that an 'ene' reaction is occurring; Scheme 11. Saville and co-workers have investigated such 'ene' reactions in connection with their work on the use of nitroso compounds as rubber antioxidants.

The use of unsymmetrical dienes in the cycloaddition reaction with nitroso compounds could give rise to two possible isomers (73A) or (73B). The product ratio of these isomers will be determined by the steric and
electronic effects of the system.

While trans-1,3-pentadiene is reported to give a mixture of isomers with nitrosobenzene, (73A; \( R = H, R_1 = Me, R_2 = Ph \)) and (73B; \( R = H, R_1 = Me, R_2 = Ph \)), trans-1-phenyl-1,3-butadiene with the same dienophile gives 2,6-diphenyl-3,6-dihydro-1,2-oxazine (73A; \( R = R_2 = Ph, R_1 = H \)) as the sole product. Hamer and Ahmad in their review on nitroso compounds as dienophiles think this difference may be due to rigid steric requirements of the dienophile and that electronic factors seem to play less important roles in governing the direction of addition. In further support of this apparent lack of electronic directivity they quote the work of Kresze and Firl. These workers showed that trans-1-(p-substituted phenyl)-1,3-butadienes and p-chloronitrosobenzene gave only 2,6-diaryloxazines, i.e. isomers of type (73A; \( R = R_2 = Aryl, R_1 = H \)).

Substituents employed in this study were nitro, chloro, hydrogen, methyl, and methoxyl; thus ranging from electron withdrawing to electron releasing.

Kresze and Firl have also made a comprehensive study of the orientation of nitroso compound addition to a series of trans, trans-1,4-disubstituted-1,3-butadienes. From this they conclude that steric effects only direct the orientation of addition in the absence of electronic effects. To explain their findings they argue that the nitroso group acts as an electrophilic reagent with the electrophilic centre localised on nitrogen. The electrophilic nitrogen is then attacked by the more nucleophilic double bond of the diene system and this nucleophilicity is governed by the substituents present. This addition can be compared with the addition of bromine to similar dienes. Thus like bromine the nitrogen reacts with the double bond which is furthest from any electron accepting substituents in the diene. Hence, when \( R \) in (73) is \(-\text{CO}_2\text{alkyl}, \text{aryl}, -\text{CN}, \text{etc.} \), one would expect isomer A to be preferentially formed, and this is in fact found. With electron withdrawing substituents on the diene the effects decrease rapidly with distance and a substituent in the 1- position exerts a greater nucleophilic deactivation on the 1,2 double bond than on the 3,4 double bond. One would again therefore expect isomer A to be preferentially formed. With a heteroatom at the 1- position of the diene it is possible to get electron donation into
the $\pi$ system effectively pushing the electrons to the 3,4 double bond and so making it more nucleophilic. The negative inductive effect of the heteroatom deactivates the 1,2 double bond with the overall result that formation of isomer A is favoured. Kresze also states that the above general rules are equally applicable to 2-substituted buta-1,3-dienes and to other dienophiles although the electrophilic localisation in other cases may not be so clear and the orientation effects may then be only secondary.

With the arguments just formulated one can readily explain the observed orientation of the thebaine adducts with nitroso-compounds.

Methyl sorbate and nitrosyl cyanide would be expected to give an adduct of structure (74; $R = \text{CN}$). This $\text{H}$-cyano-oxazine was indeed obtained as the sole adduct from the reaction and the structure was supported by its chemical and spectroscopic properties. The parent oxazine (74; $R = \text{H}$) has previously been prepared from methyl sorbate and 1-chloro-1-nitroso-cyclohexane and shown to be the 3-methyl isomer by its conversion into 6-methyl-3-piperidinol (75)\(^n\). The n.m.r. spectrum of the piperidinol showed it to have the stereochemistry shown (75) and consequently the addition of the nitroso group to the diene must have been cis and in the predicted orientation; Scheme 12. An identical product to that from reaction of nitrosyl cyanide with methyl sorbate was obtained by cyanation, with CNBr, of the parent oxazine (74; $R = \text{H}$) prepared as described above. Thus the direction and stereochemistry of the addition of nitrosyl cyanide to methyl sorbate has been proved.

Sorbic acid does not give cycloadducts with nitroso compounds\(^n\) and it was hoped therefore that the methyl sorbate adduct (74; $R = \text{CN}$), which was isolated as an oil, would yield the corresponding carboxylic acid as a solid on hydrolysis. However, treatment of the ester with dilute sodium hydroxide gave a crystalline solid whose spectroscopic properties were inconsistent with the desired acid. The n.m.r. spectrum of the product $(\text{CD}_3)_2\text{SO}$ had signals at $\tau$ 7.67(d, $J$ 1.5 Hz, 3H), 3.65(q, $J$ 7 Hz and 1.5 Hz, 1H), 3.30(d, $J$ 7 Hz, 1H), and 0.02(b.s., 1H exchangeable with deuterium) and indicated loss of the ester methoxy group and one other proton. The i.r. spectrum had $\nu_{\text{max}}$ (KBr) 3280, 2255, 1668 and

61
Scheme 12
The compound was thought to be a phenol, and not a carboxylic acid, since it dissolved in aqueous sodium hydroxide and was precipitated unchanged on addition of solid carbon dioxide. Further evidence for the phenolic nature of the compound was obtained from the u.v. spectrum which had $\lambda_{\text{max}}$ (EtOH) 212 (ε 11,800) and 323 nm (7,700); and $\lambda_{\text{max}}$ (EtOH/NaOH) 223 (ε 10,850), 265 (4,470), and 349 nm (8,320). Methylation gave a methyl ether which showed little change in its u.v. spectrum on addition of sodium hydroxide. These data are consistent with $\text{N}$-cyano-3-hydroxy-6-methylpyrid-2-one (78).

A plausible mechanism for the formation of the pyridone is shown in Scheme 13. The first stage involves base abstraction of the acidic C-6 proton followed by ring cleavage giving an intermediate cyanamide anion (76). An analogous reaction occurs when $\text{N}$-alkoxy-ammonium salts are treated with base, the products being an aldehyde and an amine$^99$.

$$\text{R-CH}_2\text{-O-N}^+\text{(R}_1\text{)}_3\text{Cl}^- \xrightarrow{\text{base}} \text{RCHO} + \text{N(R}_1\text{)}_3\text{HCl}$$

Intramolecular nucleophilic attack of the nitrogen anion at the ester carbonyl group followed by loss of methoxyl ion gives the diketo compound (77) which tautomerises to the pyridone (78).

A search of the literature showed that Kresze and Firl$^60$ had prepared a similar pyridone (80) by treatment of the methyl sorbate-p-chloronitrosobenzene adduct (79; $R = \text{Me}$, $\text{Ar} = \text{CIC}_6\text{H}_4$) with potassium hydroxide in methanol at room temperature. Under more forcing conditions or on treatment with triethylamine or alumina they found that the adducts of nitrosoarenes with dienecarboxylic esters gave $\text{N}$-arylpyrroles (81). The mechanism proposed by them for these conversions is almost identical to our own and is shown in Scheme 14. Treatment of the methyl sorbate-nitrosyl cyanide adduct (74) with a catalytic amount of triethylamine gave a high yield (93%) of the pyridone with no evidence for a pyrrole being formed. It may be therefore that the $\text{N}$-cyano group is sufficiently different from an $\text{N}$-aromatic group to favour pyridone over pyrrole formation.
Scheme 13
Scheme 14
To examine these base catalysed rearrangements in more detail further adducts of nitrosyl cyanide with dienes containing a terminal ester or cyano group were prepared. Sorbonitrile gave an adduct (82) isolated about 85% pure; attempted purifications were unsuccessful. On distillation a small amount of colourless oil was collected and this solidified to long needles on cooling; the majority of the product however underwent extensive decomposition. An identical crystalline solid was obtained from the crude adduct (82) on treatment with a catalytic amount of triethylamine in ether. The spectroscopic data for this compound, viz., $\tau^1\text{(CDCl}_3\text{)}$ 2.57(q, J 6 Hz and 2 Hz, 1H), 3.80(q, J 6 Hz and 1.5 Hz, 1H), 5.27(q, J 7 Hz with each component split further, 1H), and 8.45(d, J 7 Hz, 3H); $\nu^1\text{max (KBr)}$ 2,250 and 1737 cm$^{-1}$; and a molecular ion at m/e 122, were consistent with the pyrrolinone structure (84). A mechanism for the origin of the pyrrolinone is shown in Scheme 15 and this can be seen to be very similar to that given in Scheme 14 for the formation of the pyrrole (81). A comparison of the two reaction schemes shows that the intermediate ion (83) in the former is very similar to the 2-hydroxypyrrroline in the latter. One may have envisaged therefore N-cyano pyrrrole formation to have occurred in the reaction of base with the sorbonitrile adduct. No detectable pyrrrole was formed in the reaction and this may be compared with the case of the nitrosyl cyanide-methyl sorbate adduct when an N-cyanopyridone, and again no pyrrrole, resulted from a similar reaction sequence.

The i.r. stretching frequency at 1737 cm$^{-1}$ in the pyrrolinone (84) appeared rather high for an $\alpha\beta$-unsaturated five-membered ring lactam since N-methyl-$\Delta^3$-pyrrrolin-2-one absorbs at 1667 cm$^{-1}$\textcite{4}. This value however may be low since Hafner and Kaiser\textcite{62} quote a value of 1735 cm$^{-1}$ for the ring carbonyl in N-ethoxycarbonyl-$\Delta^3$-pyrrrolin-2-one. Willians and Fleming\textcite{63} quote a general value of 1700 cm$^{-1}$ for a five-membered ring lactam and this is shifted by ca. +15 cm$^{-1}$ for $\alpha\beta$-unsaturation. This unusual shift to higher frequency induced by an additional double bond is said to be due to the -I effect of the double bond on the conjugated NCO system. The presence of a cyano group on the nitrogen must also have some effect in raising the frequency to the observed value since electron withdrawing substituents on the nitrogen greatly increase the stretching frequency of amides.
Reaction of the pyrrolinone (84) with potassium t-butoxide in both t-butanol and dimethylsulphoxide failed to bring about dehydrocyanation with concomitant formation of 3-methyl-2-azacyclo-pentadienone. Such a species would have been of interest since it could have possibly undergone Diels-Alder dimerisation to give four possible products, each with exo and endo configurations.

The reaction of nitrosyl cyanide with 5-phenyl-2,4-pentadienoic acid methyl ester gave a crude product which appeared from its n.m.r. spectrum to be a mixture of the 3-phenyl oxazine (85) and the 6-phenyl oxazine (86), with the former predominating. The product from the reaction of the same diene with p-chloronitrosobenzene has also been shown to be a mixture of the 3-phenyl and 6-phenyl isomers in the ratio of 82:18 respectively\(^5\). All attempts at purification of the crude product failed. Attempted distillation caused decomposition while extensive streaking occurred on chromatography using both alumina and silica systems.

Reactions of the crude adduct with both aqueous sodium hydroxide and triethylamine resulted in complex mixtures. On one occasion however treatment with methanolic sodium hydroxide gave a low yield of a crystalline product whose n.m.r. and i.r. spectra suggested it to be N-cyano-3-hydroxy-6-phenylpyrid-2-one by analogy with the product from the methyl sorbate adduct. Further attempted preparations of this product gave only complex mixtures from which no desired pyridone could be isolated.

A crude adduct (87) estimated (n.m.r.) to be about 90% pure, was obtained from the reaction of nitrosyl cyanide with diethyl muconate. Diethyl muconate was used in preference to the dimethyl ester since this was found to be insoluble in suitable solvents. The olefinic protons in the n.m.r. spectrum (CDCl\(_3\)) appeared as a broadened singlet at \(\tau 3.80\) and the spectrum also showed overlapping signals of two ethyl groups. The i.r. spectrum showed the expected nitrile absorption at 2230 cm\(^{-1}\) and a broad absorption for the two ester groups at 1760 cm\(^{-1}\). As with the sorbonitrile and methyl-5-phenyl-2,4-pentadienoate adducts, all attempted purifications of the adduct failed.

The adduct has two acidic hydrogen atoms and consequently two distinct
Scheme 15
base catalysed rearrangement pathways are possible. \textit{A priori} it is not possible to tell which of the two protons would be preferentially removed by base. Scheme 16 shows the possible pathways and products that one might expect by analogy with similar adduct rearrangements in base. The n.m.r. spectrum of the crystalline product obtained by treatment of the adduct (87) with triethylamine shows overlapping signals of two ethyl groups and consequently the pyrone (89) and pyridone (91) shown in the scheme may be ruled out as possibilities for this product. Further signals in the n.m.r. spectrum (CDCl$_3$) were at $\tau$ 3.58(q, J 6 Hz and 2 Hz, 1H), 4.13(m, 1H), 4.59(m, 1H), and 3.76(b.s, exchangeable with deuterium, 1H). The i.r. spectrum showed absorptions at 3,200, 2240 cm$^{-1}$ and absorptions for two carbonyl groups at 1756 and 1740 cm$^{-1}$, each band being split into a doublet. From this and analytical data it was not possible to decide between the alternative pyrroline (90) or dihydrofuran (88) structure for the compound.

Attempted dehydration (or removal of cyanamide) with formation of a pyrrole (or furan), using acid under a variety of conditions and using thionyl chloride in pyridine, failed. Treatment of the compound with acetyl chloride in pyridine caused no aromatisation$^{60}$ nor acetylation and consequently no information to distinguish between the two possibilities was obtained.

Comparative n.m.r. and mass spectral evidence were however in favour of the product's being the dihydrofuran (88). Thus the C-6 proton of the methyl sorbate-nitrosyl cyanide adduct had a chemical shift (CDCl$_3$) of $\tau$ 5.03. Then of the two protons at $\tau$(CDCl$_3$) 4.80 and 5.35 in the diethyl muconate adduct one may assign the signal at 4.80 to the C-6 proton since the exchange of a methyl group for a carboethoxy group in the methyl sorbate ester adduct would not be expected to raise the chemical shift from 5.03 to 5.35. The exchange may however be expected to lower the shift from 5.03 to 4.80. Now for the product from the base catalysed rearrangement we wish to compare chemical shifts of the C-5 proton of the dihydrofuran (88) with that of the C-5 proton of the pyrroline (90). The former can be likened to the C-6 proton of either the methyl sorbate adduct or, better, the C-6 proton of the diethyl muconate adduct and the latter to the C-3 proton of the diethyl muconate adduct. Since the
Scheme 16
product shows a chemical shift for the non-olefinic proton at T 4.59, and this is closer to 4.80 and 5.03 than 5.35, we tentatively conclude that the product is (88).

In the mass spectrum of the compound the molecular ion occurs at m/e 254 with fragment peaks at m/e 213, 212, 181 (base peak), 167, 140, 109 and 95. The fragment at m/e 213 may correspond to loss of HNCN and that at 212 to loss of H₂NCN; these and the other breakdowns shown in Scheme 17 better fit the dihydrofuran (89) than the pyrroline (90). No peaks occurred at m/e 236 and 237 which would be expected from the pyrroline by loss of H₂O and HO respectively.

It appeared from the n.m.r. spectrum that the product was a mixture of diastereoisomers. The methine proton centred at T 4.59 appeared as two separate and identically shaped signals at 4.51 and 4.72 T and these were in an approximate ratio of 1.5:1 respectively. The overlapping signals for the two ethyl groups confirmed this ratio. The i.r. spectrum also showed the diastereoisomeric nature of the product with each of the ester carbonyl groups appearing as a clearly defined double peak.

Repeated crystallisation of the product from benzene failed to give material with a sharp melting point, the melting range being from 68-78°C.

It would appear from the results of the base catalysed rearrangements of the three adducts studied that pyrrole formation was unfavourable. In contrast Kresze found numerous examples of similar N-aryl adducts undergoing pyrrole formation. No examples of simple N-cyanopyrroles could in fact be found in the literature and it may be that such compounds are relatively unstable.

Cycloreversion of the nitrosyl cyanide-diene adducts should lead to the generation of free nitrosyl cyanide which would not be expected to survive under the conditions of its generation. With a suitable trapping agent present, however, the liberated nitrosyl cyanide might be captured before decomposing. A second diene, present in excess in the reaction mixture, might serve as such a trapping agent and investigations along these lines were undertaken.
Scheme 17
No spontaneous decomposition was observed on heating the nitrosyl cyanide-butadiene adduct in a nitrogen atmosphere. The colourless adduct merely turned slowly darker until at 180°C only a black, charred residue remained. Nitrosoarene-diene adducts are known to dissociate in solution to various extents and the possibility of achieving the reversion and capture in solution was investigated. Thebaine was used as a trapping agent since the adduct obtained from nitrosyl cyanide and this diene is known not to dissociate (n.m.r.) on heating to ca. 100°C in deuteriochloroform. No change occurred when the butadiene-nitrosyl cyanide adduct and an excess of thebaine were heated under reflux in toluene. Both compounds were recovered unchanged even after 10 hrs. The butadiene adduct appeared therefore to be stable under the conditions employed and to achieve cycloreversion with generation of free nitrosyl cyanide a more suitable system was required. Such a system might well be provided by an adduct in which the liberated diene formed part of an aromatic system. Diels-Alder adducts with aromatic systems are well documented. One must also consider the possibility of alternative breakdowns of possible arene adducts. These are common in the pyrolysis of the 1,4-cycloaddition products of arynes with aromatic compounds. For instance the adduct (92) on heating to 325°C eliminates acetylene with formation of 1,2,3,4-tetrafluoronaphthalene but no cycloreversion with generation of benzene and a high energy tetrafluorobenzene species is observed.

The reactions of nitrosyl cyanide with suitable aromatic species were therefore studied. No adducts were obtained from nitrosyl cyanide, generated in the absence of solvent, and 1-methoxynaphthalene or anthracene. In both of these cases nitrination products were isolated. With the naphthalene, column chromatography of the crude reaction mixture gave unreacted starting material (36%), 1-methoxy-4-nitronaphthalene (39%) and two unidentified, minor, polar products. That the product of the reaction was 1-methoxy-4-nitronaphthalene and not the 1,2-isomer was shown by n.m.r. and i.r. spectrometry and also by its reaction with sodium hydroxide to give 4-nitro-1-naphthol. Anthracene gave mainly unreacted starting material (86%) and a product identified as 9-nitroanthracene (11%).
This nitro compound formation may result from initial nitrosation followed by oxidation or from attack by nitryl chloride present in the system. The presence of the latter compound was discussed earlier in connection with the nitration of 1,4-diphenylbutadiene. A tentative explanation for the large recovery of anthracene may be that an unstable anthracene-nitrosyl cyanide adduct was formed and this dissociated on warming from the reaction temperature of \(-25^\circ C\) to room temperature. In this way the anthracene may have been protected from extensive nitration.

The effect of electronic changes in the nitroso-compounds on the stability of diene-nitroso adducts has been studied earlier in connection with the thebaine-nitrosoarene adducts. The influence of electronic effects operating in the diene moiety is more difficult to assess. No comparison can be made between nitroso compounds and conventional dienophiles since certain differences exist between the two types. Maleic anhydride for instance does not add to 1,3-cyclooctadiene while nitrosobenzene does. Maleic anhydride does add to anthracene while nitrosobenzene does not even under forcing conditions\(^{66}\). We considered that adduct formation might be observed with suitably substituted anthracenes. These substituents will have the greatest effect when in the 9 and 10 positions and, since anthracenes have a great tendency to undergo substitution at these positions, undesirable nitration products might also be avoided by using 9,10-disubstituted anthracenes.

The reaction of nitrosyl cyanide with 9,10-dimethylanthracene gave a crude product which was separated into two major components by fractional crystallisation. A benzene insoluble, pale yellow, crystalline product was obtained and was shown to be anthraquinone by comparison with authentic material. The residue remaining after removal of all the anthraquinone crystallised from methanol as white needles. The n.m.r. spectrum of this product showed a complex aromatic multiplet between \(\tau(CDCl_3)\) 1.60 and 2.50 (8H) and a singlet at 7.09 (3H). The i.r. spectrum had absorptions (KBr) at 1682, 1603, 1595 and 755 cm\(^{-1}\). Mass spectrometry (70eV) showed a strong peak at m/e 218 with only very small peaks above this. At 20eV the spectrum showed the same strong peak at m/e 218 with two small peaks at m/e 249 and 234. Other peaks were at m/e 190, 163 and 151 with a doubly charged peak at m/e 124.5 and a metastable at m/e 166
corresponding to \(218 \rightarrow 190\). Analysis gave a molecular formula of 
\(C_{16}H_{11}NO_2\), and from these data the compound was tentatively identified as 10-cyano-10-methoxyanthrone (93). A possible mass spectral breakdown of this product could be loss of a methoxyl radical to give the aromatic ion (94) and loss of carbon monoxide from this to give the fluorene ion (95). This latter breakdown is common for phenols and aromatic ethers giving a cyclopentadienyl cation. Accurate mass spectrometry showed the peak at \(m/e\ 218.0606\) to correspond to \(C_{15}H_{8}NO\) and this was consistent with the proposed structure. Further evidence for the compound’s being an anthrone was obtained from the u.v. spectrum which had \(\lambda_{max}\) \((\text{EtOH})\ 278\ nm (\varepsilon\ 11,000)\). Anthrone itself has \(\lambda_{max}\) \((\text{EtOH})\ 275\ nm (\varepsilon\ 15,100)\). The lack of a nitrile absorption in the i.r. spectrum of the proposed anthrone (93) is thought to be due to the \(\alpha\)-methoxyl group since many examples of cyanohydrins are known that show no nitrile absorption. The anthrone (93) is the first C-cyano product to be isolated from reactions involving the nitrosyl chloride-silver cyanide system.

The origin of the anthraquinone and 10,10-disubstituted anthrone is not known although the anthraquinone may arise via an initial nitrosyl cyanide adduct (96). Hydrolysis of this adduct under the conditions of formation might be expected to give an intermediate anthrone (97) which may then breakdown to the quinone.

9,10-Dimethylanthracene reacted with nitrosyl cyanide to give a crude semi-crystalline product from which a pale yellow crystalline adduct (98) was isolated, either by p.l.c. (47%) or column chromatography (43%). A small amount of starting material and two unidentified, very polar, materials were also isolated. The adduct showed the expected spectral properties with the two methyl groups appearing in the n.m.r. spectrum as singlets at \(\tau\ (\text{CDCl}_3)\ 7.75\) and 7.83. The aromatic protons appeared not as two separate multiplets as in anthracene derivatives but as a broadened singlet at \(\tau\ 2.70\). The spectrum showed no evidence of any dissociation into 9,10-dimethylanthracene and nitrosyl cyanide. I.r. spectrometry showed a nitrile absorption at (KBr) 2215 cm\(^{-1}\). Although analysis indicated a molecular formula of \(C_{17}H_{14}N_2O\) the mass spectrum showed no corresponding strong molecular ion. A large base peak occurred
at m/z 306 which corresponds to 9,10-dimethylanthracene and it appeared from this that the adduct readily decomposed in the mass spectrometer into its constituents. This same behaviour was also observed in the thebaine-nitrosoarene adducts and, like them, no metastable peak corresponding to the breakdown was observed.

Attempted preparation of an O-methylisourea derivative (99) from the reaction of sodium methoxide with the adduct in methanol gave only 9,10-dimethylanthracene. This result appeared puzzling at first and could only be explained by assuming a ready cycloreversion of the isourea once formed into the anthracene and the nitroso species (100). An alternative mechanism for the formation of the anthracene was advanced as a result of exchange reactions undergone by the adduct.

The product (98) is the first example of a nitrosyl cyanide-arene adduct and its stability and dissociation are of special interest. It was recovered unchanged after being heated to its melting point (171°C) but after 15 min in toluene at 85°C in the presence of a twofold excess of thebaine none of the adduct remained. T.l.c. examination of the solution showed four components corresponding to 9,10-dimethylanthracene, thebaine, the thebaine-nitrosyl cyanide adduct (48; R = Me), and an unidentified minor component whose n.m.r. spectrum showed it to be derived from thebaine. Separation of the components on alumina by column chromatography and p.l.c. gave 9,10-dimethylanthracene (95.5%) identical with authentic material. The thebaine-nitrosyl cyanide adduct was not isolated as such but as the urea (49; R = Me) (39%) which is readily formed from the adduct by hydrolysis on alumina. The urea so isolated was identical to that prepared from authentic adduct (48; R = Me). On being heated alone in toluene for 15 min at 85°C the 9,10-dimethylanthracene adduct (98) was recovered unchanged. It appears from these results that the adduct is dissociating in solution to its constituent addends. In the presence of thebaine the more stable thebaine-nitrosyl cyanide is formed with total transfer of the dienophile. Since the n.m.r. spectrum of (98) shows no signals corresponding to free 9,10-dimethylanthracene the amount of dissociation of the adduct in solution must be relatively small under such conditions. To investigate the dissociation of the adduct further, thebaine (slight excess) and the adduct (98) were left at 35°C in
(98) \[ \overset{?}{\longrightarrow} \text{-OME} \]

(99)

\( O=\text{NC(OME)}\text{NH} \)

(100)
deuteriochloroform. After 48 hrs the n.m.r. spectrum of the solution showed 9,10-dimethylanthracene and the thebaine-nitrosyl cyanide adduct to be present with none of the original adduct. P.l.c. separation of the products gave a sample of the thebaine-nitrosyl cyanide adduct identical with material prepared previously from thebaine. In view of this dissociation, it may be that the recovery of 9,10-dimethylanthracene from treatment of the adduct (98) with sodium methoxide resulted from attack of methoxide ion on free nitrosyl cyanide in solution.

The production of N-cyano-1,2-oxazines from conjugated dienes was considered good evidence, though not complete proof, for formation of nitrosyl cyanide from reaction of nitrosyl chloride with silver cyanide. Further evidence of its existence was obtained from the exchange reactions of the 9,10-dimethylanthracene adduct with thebaine. We felt however that isolation of nitrosyl cyanide would be desirable for complete characterisation. Investigations directed at the isolation and study of nitrosyl cyanide were carried out on a vacuum line. This essentially consisted of a manifold fitted with two mercury manometers and a terminal port for attachment of a reaction flask.

Using the above apparatus a sample of degassed nitrosyl chloride was condensed onto an excess of silver cyanide mixed with glass boiling chips held in a round bottomed flask surrounded by a cold bath at -70°C. The mixture was stirred (magnetic stirrer) vigorously and warmed to ca. -70°C when a green vapour developed in the flask. This vapour was condensed into a previously evacuated tube at -196°C (liquid nitrogen) where it formed a blue-green liquid and finally solidified to a solid of the same colour. The solid was warmed and evaporated and then condensed onto a second batch of silver cyanide at -70°C in order to remove any unreacted nitrosyl chloride. The resulting blue vapour was recondensed at -196°C but then had only one tenth of its original volume. At ca. -70°C the solid melted to a blue-green liquid and this was distilled into a frozen solution of thebaine in chloroform at -196°C. On warming to -70°C the chloroform melted and the blue colour rapidly disappeared leaving a
red-brown solution which faded to a pale yellow colour on further warming. Evaporation of the solvent gave a residue from which unreacted thebaine and the adduct (48; R = Me) were isolated. Analysis of the initial silver cyanide-silver chloride residue for chloride content, as described earlier, showed 30% reaction. It appears therefore that the green vapour probably contains a large proportion of unreacted nitrosyl chloride. It is this excess of nitrosyl chloride that probably accounts for the anomalous products observed in reactions of conjugated dienes with the green vapour. It may for example account for the nitration products and the frequent occurrence of unidentified very polar materials.

Molecular weight determinations of the green vapour were carried out on the vacuum line by weighing a known volume of the vapour at known temperature and pressure. The results obtained in two separate experiments gave values of 62 and 66 suggesting higher molecular weight impurities, probably nitrosyl chloride. A restricting factor in obtaining accurate results was the difficulty in obtaining reliable pressure measurements since the gas attacks mercury and consequently mercury manometers could not be used directly. To obtain a pressure measurement the mercury was protected from direct contact with the vapour by using silicone oil. Nevertheless this was not entirely satisfactory since the gas tended to dissolve in the oil. Analysis of the green vapour by mass spectrometry failed to show a peak at m/e 56 corresponding to nitrosyl cyanide. This failure, in several attempts, may be due to breakdown of the nitrosyl cyanide in the spectrometer. It may be equally likely that the operating conditions of the instrument were inappropriate since no peaks at m/e 65 or 67 (NOCl\textsuperscript{35} and NOCl\textsuperscript{37}) were detected. The i.r. spectrum of the green gas showed nitrosyl chloride and nitrogen dioxide to be present; additional absorptions appeared at 1515, 1495, 830 and 810 cm\textsuperscript{-1}. The strong N = O stretching frequencies for nitrosyl halides occur around 1800 cm\textsuperscript{-1} and for nitrogen dioxide around 1760 cm\textsuperscript{-1}. This same stretching frequency has been demonstrated by Lütke\textsuperscript{70} to occur in the region 1539-1621 cm\textsuperscript{-1} for aliphatic and halogenated nitroso monomers and 1488-1513 cm\textsuperscript{-1} for nitrosoarene monomers. The C-N frequency generally results in two bands about 1100 cm\textsuperscript{-1} and between 750 and 860 cm\textsuperscript{-1}. The nitrosyl cyanide would
appear therefore to have a possible resemblance to the nitrosoarenes.

An unusual feature of the blue-green solid obtained from the vacuum line experiments was its colour in various solvents. In carbon tetrachloride and benzene it gave a green solution from which a blue-green solid could be recovered on distillation and cooling to -196°C. With chloroform and dichloromethane it also gave a green solution but only at very low temperatures; on warming to ca. -60°C a yellow solution was obtained from which no blue-green solid could be recovered on distillation. These facts distinguish the blue-green solid from dinitrogen trioxide which is a blue liquid and solid but gives a yellow-brown vapour. On dissolving in chloroform dinitrogen trioxide gave a blue solution from which the blue solid trioxide could be recovered.

The most obvious property of a monomeric C-nitroso-compound is its blue or green colour. The electronic absorption spectra of a variety of nitroso-monomers have been investigated and three characteristic absorption bands located, namely 630-790 nm (ca. 1-60), 270-290 nm (ca. 80), and below 220 nm (ca. 5000). The first of these is given by all nitroso monomers, whereas the other two bands are characteristic of aliphatic nitroso-compounds only, being submerged in the strong phenyl absorption in the aromatic series. On the basis of the relatively low intensity of the visible absorption, Lewis and Kasha suggested that it was due to a singlet-triplet transition. A theoretical treatment by Orgel shows that the visible absorption is due to a singlet-singlet n→π* transition with one electron from the lone pair of the nitrogen being promoted to an antibonding π*-orbital. Since nitrosyl chloride or any other possible contaminants absorb outside the 630-790 nm region a study of nitrosyl cyanide is possible by visible spectrometry. The green vapour was prepared as previously described and partially purified by a double distillation. A sample of the vapour was then admitted to a gas cell fitted with sodium chloride windows and studied by visible spectrometry. A band at 738 nm was recorded and attributed to an n→π* transition of nitrosyl cyanide; determination of the molar extinction coefficient for this absorption was not possible; see Fig.

The disappearance of the band at 738 nm and the increase in absorption
A. initial recording \((t=0)\)
B. recording after 23 hr \((t=\infty)\)
C. evacuated cell

\(T = 37^\circ C\)

**Fig.**

A. initial recording \((t=0)\)
B. recording after 23 hr \((t=\infty)\)
C. evacuated cell

wavelength nm.

A. initial recording \((t=0)\)
B. recording after 23 hr \((t=\infty)\)
C. evacuated cell

\(T = 37^\circ C\)

**Fig.**

A. initial recording \((t=0)\)
B. recording after 23 hr \((t=\infty)\)
C. evacuated cell

wavelength nm.

absorbance

400 450 500 550 600 650 700 750 800
of a band at 485 nm (shoulder) were followed as a function of time. By leaving the sample for 24 hours an infinity absorbance reading was obtained for each band and from the results a study of the kinetics of the decomposition of nitrosyl cyanide was made. An isosbestic point occurred at 574 nm.

If the original amount of nitrosyl cyanide present was \( a \) and the amount after time \( t \) was \( (a - x) \) then

\[
A = k_1 (a - x) + k_2 x + k_3
\]

where \( A \) is the absorbance at 738 nm at time \( t \), \( k_1 (a - x) \) is the contribution to the absorbance by nitrosyl cyanide, \( k_2 x \) is the contribution to the absorbance by any nitrosyl cyanide decomposition products, and \( k_3 \) is the contribution of any other impurities present originally. Similarly then

\[
A_\infty = k_1 (a) + k_2 a + k_3
\]

where \( A_\infty \) is the absorbance at 738 nm after infinite time and the other quantities are as before. It then follows that

\[
A - A_\infty = k_1 (a - x) + k_2 x - k_2 a
\]

\[
or A - A_\infty = (k_1 - k_2) (a - x)
\]

The difference in absorbance at any time \( t \) and at infinite time is thus a measure of the nitrosyl cyanide concentration at time \( t \). If the nitrosyl cyanide decomposition follows second order kinetics it would obey the general equation

\[
t = \frac{1}{k (a - x)} - \frac{1}{ka}
\]

where \( k \) is the second order rate constant, \( a \) is the initial concentration of nitrosyl cyanide and \( (a - x) \) is the concentration of nitrosyl cyanide after time \( t \). A plot of \( t \) versus \( 1/(a - x) \) should thus give a straight line and by a combination of equations (3) and (4) a plot of \( t \) versus \( 1/(A - A_\infty) \) should also give a straight line.
If the nitrosyl cyanide decomposition follows first order kinetics then the general equation

\[ t = \frac{2.303 \log a}{k'} - \frac{2.303 \log (a - x)}{k'} \]  

(5)

would be followed, where \( k' \) is the first order rate constant and \( a \) and \( a - x \) are as before. A combination of equations (3) and (5) gives

\[ t = \frac{2.303 \log a}{k'} + \frac{2.303 \log (k_1 - k_2)}{k'} - \frac{2.303 \log (A - A_\infty)}{k'} \]  

(6)

Thus a plot of \( t \) versus \( \log (A - A_\infty) \) should give a straight line of slope \(-2.303/k'\) from which the first order rate constant \( k' \) could be obtained. Since for first order kinetics,

\[ t_{0.5} = \frac{2.303 \log 2}{k'} = \frac{0.693}{k'} \]  

(7)

then a value of \( t_{0.5} \), the half life of nitrosyl cyanide, could also be obtained.

Using the results obtained from the decomposition study good straight lines were obtained for both first and second order plots and consequently it was not possible to distinguish between the two possible decomposition modes. The first order plot showed a divergence from a straight line after approximately 100 min and gave a value of the half life of nitrosyl cyanide (37°C) of 88 min.

In a similar manner plots were made for the absorption of 485 nm and again there was little to distinguish between the two possible modes. The absorption at 485 nm was shown to be one of the peaks corresponding to the vibrational fine structure of an absorption band with a maximum at 400 nm. This band and its associated vibrational fine structure was found to be identical to that of nitrogen dioxide. It appeared therefore that the nitrosyl cyanide was decomposing to give nitrogen dioxide among other products. This was confirmed from the i.r. spectrum of the green gas after leaving for 24 hours by which time it had become brown coloured. The i.r. spectrum of this brown gas showed it to be a mixture of nitrosyl...
chloride, nitrogen dioxide and other species which were not characterisable by i.r. spectrometry alone.

Although the vacuum line isolation of pure nitrosyl cyanide was not as successful as hoped the results did yield further information regarding the nature of the species. It showed, for example, that the gas had a longer lifetime than was originally suspected. All the evidence together strongly suggested that nitrosyl cyanide was the species produced from the reaction of nitrosyl chloride with silver cyanide. A complete physical characterisation of the compound would require its isolation in a pure form, presumably by more refined vacuum techniques.

An alternative and more convenient method of studying nitrosyl cyanide would employ the 9,10-dimethylanthracene adduct (98). For instance the possible role of nitrosyl cyanide in the conversion of tertiary amines containing an N-methyl group into an N-cyanomethyl compound could be studied using this adduct. Hopefully capture of the 9,10-dimethylanthracene with another dienophile with liberation of the nitrosyl cyanide may also be possible.
EXPERIMENTAL

General Methods

Unless otherwise stated general methods were as described in section 1.

Distilled chloroform, prepared in the usual manner, was shown by comparative i.r. spectrometry to contain ca. 1% ethanol and was used as such.

Silver cyanide was prepared by slowly adding aqueous silver nitrate (ca. 40%) to an equimolar, aqueous, solution of potassium cyanide (ca. 40%). The mixture was cooled and stirred throughout the addition and the resulting white precipitate filtered off. After initially drying on the sinter the solid was finally dried by stirring, under vacuum, over silica gel for 48 hours.

Thebaine-Nitrosyl Cyanide Adduct (48; R = Me) - Method A. Nitrosyl chloride (0.2 ml at -60°C, ca. 4 mmol) was added to a stirred suspension of dry silver cyanide (1 g, 7.5 mmol) in chloroform (10 ml) at -20°C. After vigorous stirring for 3 min, thebaine (600 mg, 2 mmol) in chloroform (10 ml) was added. Stirring was continued for a further 30 min during which time the reaction mixture was slowly allowed to warm to room temperature. Filtration through 'Celite' gave a filtrate from which a pale yellow gum was obtained on evaporation of the solvent. Column chromatography on neutral, grade III alumina (50 x 1 cm column) using 50:50 ethyl acetate/benzene as eluent gave a fast running component isolated as a pale yellow oil (400 mg). Thebaine (186 mg, 31%) was recovered on further elution. The oil crystallised from cold ethanol to give colourless needles of the adduct (48; R = Me) (240 mg, 34%), m.p. 149-150°C (decomp.), m/e 367.1535 (M+, C_{20}H_{21}N_{3}O_{4} requires M, 367.1534) (Found: C, 65.11; H, 5.90; N, 11.35. C_{20}H_{21}N_{3}O_{4} requires C, 65.38; H, 5.76; N, 11.44%), v(CDCl_3) 3.35(s, 1-H and 2-H), 3.66(q, J 9 Hz and 1 Hz, 7-H), 4.00(d, J 9 Hz, 8-H), 5.47(d, J 1 Hz, 5-H), 6.20(s, ArOMe), 6.43(s, C-6 OMe), and 7.54(s, -NMe); \nu_{\text{max}}(\text{nujol}) 2205 m, 1635 m, 1602 m, 1505 s, 1240 s and 805 s cm^{-1}.
Yields in several similar experiments were in the range 11-46%.

Method B. Nitrosyl chloride (1.0 ml at -60°, ca. 20 mmol) was introduced into a partially evacuated, 50 ml round-bottomed flask containing silver cyanide (5.0 g, 37 mmol) and glass boiling chips (10 g); the whole was immersed in a bath at -20°C. The mixture was stirred vigorously and a green vapour began to fill the flask. After 5 min thebaine (4.0 g, 12.9 mmol) in dichloromethane (30 ml) was added and the mixture stirred a further 45 min during which time the whole was allowed to warm slowly to room temperature. Filtration through 'Celite' and evaporation of the filtrate gave a yellow gummy residue (4.4 g). Column chromatography on neutral, grade III alumina (50 x 2 cm column) using ethyl acetate as eluent gave a fast running fraction isolated as a pale yellow foam (1.2 g). Further elution gave recovered thebaine (2.42 g, 61%). The foam crystallised (on seeding) from ethanol as colourless cubes of the adduct (48; R = Me) (600 mg, 13%), identical in all respects to the material from method A.

N-Cyanomethylnorethebaine-Nitrosyl Cyanide Adduct (48; R = CH₂-CN) -

Method A, via Thebaine. Nitrosyl chloride (0.5 ml at -60°, ca. 11 mmol) was added to a vigorously stirred mixture of dry silver cyanide (2.5 g, 19 mmol) and glass boiling chips (5 g) contained in a partially evacuated, two-necked, round-bottomed flask, immersed in a cold bath at -20°C. After vigorous stirring for 7 min, during which time a green vapour had developed in the reaction flask, a solution of thebaine (1 g, 3.3 mmol) in dichloromethane (15 ml) was added. The mixture was stirred for a further 1 hr and allowed to slowly warm to room temperature. The mixture was filtered through 'Celite' to give an orange-yellow solution from which a precipitate of yellow, unidentified polar material was obtained (105 mg). After a second filtration the filtrate was evaporated leaving a pale brown foam (1.1 g). Chromatography on a neutral, grade III alumina column (15 x 2 cm) using ethyl acetate as eluent gave a front-running pale yellow band. This gave a pale tan crystalline solid (450 mg, 36%) which recrystallised from methanol/chloroform as colourless cubes of the adduct (48; R = CH₂-CN) (408 mg, 33%), m.p. 184-185° (decomp.), m/e 392.1490 (M+, C₂₁H₂₀N₄O₄ requires M 392.1485) (Found: C, 64.61; H, 5.34; N, 14.27. C₂₁H₂₀N₄O₄ requires C, 64.27; H, 5.14; N, 14.28%), δ(CDCl₃) 3.34 (m, 1-H and 2-H), 3.66 (q,
Method B, via Thebaine-Nitrosyl Cyanide Adduct. Nitrosyl chloride (0.1 ml at -60°C, ca. 2.2 mmol) was added to a vigorously stirred mixture of dry silver cyanide (0.5 g, 3.7 mmol) and glass boiling chips (1 g) contained in a partially evacuated, two-necked, round-bottomed flask, immersed in a cold bath at -20°C. After vigorous stirring for 7 min during which time a green vapour had developed in the reaction flask, thebaine-nitrosyl cyanide adduct (48; R = Me) (150 mg; 0.41 mmol) in dichloromethane (7 ml) was added. The mixture was stirred a further 30 min and allowed to slowly warm to room temperature. Filtration through 'Celite' gave a filtrate which showed only one spot on t.l.c. (plus polar material). Removal of the solvent gave a pale yellow gum (160 mg) which crystallised from methanol as colourless cubes (70 mg, 44%). Recrystallisation from chloroform/methanol gave colourless cubes of the adduct (48; R = CH₂CN), m.p. 184-185°C (decomp.) (mixed melting point with material as prepared via method A, 184-185°C), spectroscopic properties as given above.

Hydrolysis of Thebaine-Nitrosyl Cyanide Adduct to the Urea (49; R = Me). Thebaine-nitrosyl cyanide adduct (48; R = Me) (130 mg) was placed on a neutral, grade III alumina column (20 x 1 cm) and the column partially eluted with ethyl acetate until intimate contact between the adduct and adsorbant was achieved. After leaving overnight elution with ethyl acetate/ethanol (95:5) gave recovered adduct (20 mg, 15%) and a colourless crystalline solid (82 mg, 59%). Recrystallisation from ethanol gave colourless cubes of the urea (49; R = Me), m.p. 177°C (decomp.) (Found: C, 62.03; H, 6.11; N, 11.00; M+ m/e 385. C₂O₂H₂₃N₅O₂ requires C, 62.32; H, 6.02; N, 10.92%; N 385), τ(CDC₁₃) 3.37(m, 1-H and 2-H), 3.97(s, 7-H and 8-H, signals not separated at 60 MHz), 4.36(b.s, NH₂), 5.28(d, J 6.5 Hz, 9-H), 5.43(s, 5-H), 6.20(s, ArOMe), 6.40(s, C-6 OMe), and 7.54(s, NMe); νₘₐₓ(nujol) 3380 m, 3300 m, 1697 s, 1605 m, 1500 m, 1230 s, 890 m, and 805 m cm⁻¹.
Hydrolysis of the N-Cyanomethylnorthebaine-Nitrosyl Cyanide Adduct to the Urea (49; R = CH₂CN). Prepared as described for the urea (49; R = Ne) as a crystalline mass (90%) which recrystallised from methanol as colourless cubes of the urea (49; R = CH₂CN), m.p. 187-188.5° (decomp.) (Found: C, 61.71; H, 5.11; N, 13.60; M+ m/e 410. C₁₉H₂₂N₄O₅ requires C, 61.45; H, 5.40; N, 13.65; M 410), \( \nu(CDCl₃) \) 3.35 and 3.42 (doublets, J 8 Hz, 1-H and 2-H), 4.00(s, 7-H and 8-H, signals not separated at 60 MHz), 4.38 (b.s, NH₂), 5.13(d, J 6.5 Hz, 9-H), 5.43(s, 5-H), 6.22(s, ArOME and NCH₂CN), and 6.42(s, C-6 OMe); \( \nu_{\text{max}}(\text{nujol}) \) 3490 m, 3400 m, 2250 s, 1710 s, max 1672 s, 1633 m, 1503 m, 880 s, and 800 s cm⁻¹.

Reaction of Sodium Methoxide with the N-Cyanomethylnorthebaine Adduct.

To a suspension of the N-cyanomethyl adduct (48; R = CH₂CN) (110 mg, 0.28 mmol) in methanol (15 ml) was added a solution of sodium methoxide (52 mg, 1.3 mmol) in methanol (5 ml). The mixture was stirred for 30 min at 50°C during which time complete solution occurred. The methanol was removed and the residue dissolved in water to give an emulsion. Solid carbon dioxide was added and the aqueous mixture extracted with chloroform (2 x 10 ml). The combined chloroform extracts were dried and evaporated leaving a pale yellow oil (95 mg). Crystallisation from methanol gave colourless needles of the O-methylisourea (51) (53 mg, 46%), m.p. 180° (decomp.) (Found: C, 62.28; H, 5.68; N, 13.42; M+ m/e 424. C₂₂H₂₄N₄O₅ requires C, 62.25; H, 5.70; N, 13.20%; M 424), \( \nu(CDCl₃) \) 3.32 and 3.39 (doublets, J 8 Hz, 1-H and 2-H), 3.51(b.s, NH), 3.92(q, J 8.5 and 1.5 Hz, 7-H), 4.25(d, J 8.5 Hz, 8-H), 5.41(d, J 1.5 Hz, 5-H), 5.43(d, J 6.5 Hz, 9-H), 6.17, 6.20 and 6.38 (singlets, ArOME, C-6 OMe, and N C(OME)NH), and 6.32(s, CH₂CN); \( \nu_{\text{max}}(\text{nujol}) \) 3355 w, 1660 s, 1630 m, 1503 s, 1267 m, and 885 s cm⁻¹.

14-Cyanoaminocodeinone (50). Thebaine-nitrosyl cyanide adduct (367 mg, 1 mmol) was dissolved in a minimum of methanol and platinum oxide catalyst added (50 mg). Hydrogenation was carried out at room temperature and pressure when one mole equivalent of hydrogen was taken up after 5 hr. The catalyst was filtered off and the solvent removed giving an oil which gave colourless crystals from ethanol. A second crop of the crystals was obtained from p.l.c. of the mother liquors on alumina. Total yield of colourless rods of the cyanamide (50) was (110 mg, 30%), m.p. 201°.
3-Chloro-4-nitro-1,4-diphenylbut-1-ene (60). Nitrosyl chloride (1.0 ml at -60°C) was added to a stirred suspension of dry silver cyanide (4.5 g) in chloroform (40 ml) at -20°C. After stirring for 3 min trans, trans-1,4-diphenyl-1,3-butadiene (1 g) in chloroform (30 ml) was added. Stirring was continued for a further 40 min during which time the mixture was allowed to slowly warm to room temperature. The mixture was filtered through 'Celite' and the filtrate evaporated to give a yellow-orange gum. On addition of methanol (8 ml) an off-white semi-crystalline solid was obtained (150 mg, 11%). Recrystallisation from ethanol gave tiny, colourless needles of the nitroalkene (60), m.p. 161-163°C (Found: C, 66.68; H, 5.01; N, 5.00; Cl, 12.22. C₁₆H₁₄ClN₂O₂ requires C, 66.80; H, 4.91; N, 4.87; Cl, 12.32%), τ(CDCledged 3) 2.60 (m, 2 x Ph), 3.19 (d, J 15.4 Hz, 1-H), 3.38 (q, J 15.4 Hz and 8.2 Hz, 2-H), 4.36 (d, J 9.4 Hz, 4-H), and 4.69 (q, J 9.4 Hz and 8.2 Hz, 3-H); ν_max (CHCl₃) 1647 m, 1550 s, 1360 s, 1175 m, and 715 m cm⁻¹.

1-Nitro-1,4-diphenylbuta-1,3-diene (61) - Method A. 3-Chloro-4-nitro-1,4-diphenylbut-1-ene (60) (50 mg) was chromatographed on a neutral, grade III alumina column (20 x 1 cm) using chloroform as eluent. A yellow band formed and this was collected as a single fraction. Removal of the solvent left a yellow oil which crystallised as yellow rods (40 mg, 93%). Recrystallisation from methanol gave the nitrodiene (61), m.p. 110°C (lit.¹¹, 111°C), τ(CDCledged 3) 2.04 (d, J 11 Hz, 2-H), 2.40-2.90 (m, 2 x Ph), 2.89 (d, J 16 Hz, 4-H), and 3.38 (q, J 16 and 11 Hz, 3-H); ν_max (nujol) 1630 m, 1503 s, 1315 s, 1175 m, and 715 m cm⁻¹.

Method B. Nitrosyl chloride (0.2 ml at -60°C) was added to a stirred suspension of dry silver cyanide (1 g) in chloroform (10 ml) at -20°C. After stirring for 3 min trans, trans-1,4-diphenyl-1,3-butadiene (200 mg) in chloroform (10 ml) was added. Stirring was continued for a further 40 min during which time the mixture was allowed to slowly warm to room...
temperature. The mixture was filtered through 'Celite' and the filtrate evaporated to give a yellow-orange gum. Column chromatography on neutral, grade III alumina (1 x 15 cm) with chloroform as eluent gave a bright yellow fraction which crystallised as tiny yellow rods on removal of the solvent (215 mg, 88%), m.p. 108-110° (lit. 111°). I.r. and n.m.r. spectra identical with those of material prepared via Method A

Reaction of Silver Cyanide-Nitrosyl Chloride with 1-Methoxynaphthalene. Nitrosyl chloride (1 ml at -60°) was added to a stirred mixture of silver cyanide (5 g) and glass boiling chips (5 g) contained in a partially evacuated, two-necked, round-bottomed flask immersed in a cold bath at -20°C. After vigorous stirring for 3 min 1-methoxynaphthalene (2.0 g) in dichloromethane (15 ml) was added and the mixture allowed to slowly warm to room temperature while being stirred for a further 45 min. Filtration through 'Celite' gave a dark, red-brown filtrate which left a dark coloured gum (2.46 g) on removal of the solvent. Column chromatography using neutral, grade III alumina (15 x 2 cm) with 40/60 petrol as eluent gave recovered 1-methoxynaphthalene (718 mg, 36%). On changing to benzene as eluent a yellow band was collected which gave a yellow crystalline solid (989 mg, 39%) identified as 1-methoxy-4-nitronaphthalene, by i.r., n.m.r. and mass spectrometry; m.p. 82.5° (from ether) (lit. 76, 81°).

The nitronaphthalene (200 mg) was boiled under reflux with 5N-sodium hydroxide (4 ml) for 1 hr and the solution washed with ether after cooling. The aqueous layer was then acidified and pale lemon crystals of 4-nitro-1-naphthol were deposited (150 mg, 81%), m.p. 168° (from water) (lit. 74, 164°).

Reaction of Silver Cyanide-Nitrosyl Chloride with Anthracene. Nitrosyl chloride (1.0 ml at -60°) was added to a stirred mixture of silver cyanide (5 g) and glass boiling chips (1 g) contained in a partially evacuated, two-necked, round-bottomed flask immersed in a cold bath at -20°C. After 3 min stirring during which time a green gas had developed in the flask, anthracene (1.0 g) in dichloromethane (50 ml) was added.
Stirring was continued for a further 1 hr and the cold bath was slowly allowed to warm to room temperature. The mixture was filtered through 'Celite' and the filtrate evaporated leaving a pale yellow crystalline solid (1.31 g). Crystallisation from chloroform gave anthracene (760 mg). The mother liquors were chromatographed on a neutral, grade III alumina column (15 x 2 cm) with 40/60 petrol as eluent. Anthracene (100 mg) was eluted first and then on eluting with 40/60 petrol/benzene (80:20) a bright yellow band was collected. This gave yellow needles of 9-nitroanthracene (140 mg, 11%), m.p. 146-147° (ethanol) (lit. 74, 146°).

N-Cyano-3,6-dihydro-2H-1,2-oxazine (66; R = CN) - Method A.

Nitrosyl chloride (1.0 ml at -60°) was added to a stirred suspension of silver cyanide (5 g) in dichloromethane at -25°C, previously flushed with nitrogen. After 5 min butadiene was slowly bubbled through the solution (ca. 1 bubble per second) for 45 min. The temperature was maintained at -25° to -20°C throughout. After allowing to warm to room temperature the mixture was filtered through 'Celite'. The dichloromethane and excess butadiene were removed under vacuum at 0°C and an amber coloured oil remained (1.08 g). T.l.c. using an alumina/chloroform system showed a non-polar product and a very polar material. Chromatography on neutral, grade III alumina (15 x 2 cm) with chloroform as eluent gave a product isolated as a pale yellow oil (550 mg, 23%). Distillation gave N-Cyano-3,6-dihydro-2H-1,2-oxazine (66; R = CN) as a colourless oil, b.p. 67° at 1.5 mm Hg m/e 110.0477 (N+, C5H6N2O requires M, 110.0480) (Found: C, 54.46; H, 5.66; N, 25.49. C5H6N2O requires C, 54.54; H, 5.49; N, 25.44%). \( ^1H \) N.M.R (film) 3070 w, 2910 m, 2860 m, 2215 s, \( 1645 \) m, 1435 s, 840 m and 850 s cm\(^{-1}\).

Method B. 3,6-Dihydro-2H-1,2-oxazine (66; R = H) hydrochloride\(^x\) (1.21 g) in water (15 ml) was added dropwise over 30 min to a stirred solution of cyanogen bromide (1.2 g) in saturated aqueous sodium bicarbonate (40 ml). After being stirred for a further 30 min the solution was extracted with ether (3 x 20 ml). The combined ether extracts were dried and evaporated to give the N-cyano oxazine (66; R = CN) as a very pale yellow oil (1.02 g, 93%), b.p. 56° at 1 mm Hg. The oil was spectroscopically identical to that obtained via method A.

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Methyl-3,6-dihydro-2H-1,2-oxazin-2-ylcarbonimidate (66; \( R = C(O\text{Me})\text{NH} \)).

N-Cyano-3,6-dihydro-2H-1,2-oxazine (66; \( R = \text{CN} \)) was dissolved in methanol and sodium methoxide (119 mg) in methanol (10 ml) added. After stirring at room temperature for 1 hr the solvent was removed and the residue dissolved in water. Solid carbon dioxide was added and the solution extracted with chloroform (3 x 10 ml). The combined chloroform extracts were dried and evaporated to give the imidate ester (120 mg, 85%) as a very pale yellow oil (pure by t.l.c.), \( \tau (\text{CDCl}_3) \) 4.13(s, 4-H and 5-H), 5.52(m, 2H), 6.10(m, 2H), 6.17(s, C(O\text{Me})NH) and 4.30(b.s., NH); \( \nu_{\text{max}} \) (film) 3350 m, 1662 s, 1445 s, 1355 s, 1090 s, and 928 m cm\(^{-1}\); M+ m/e 142; \( C_6\text{H}_{10}\text{N}_2\text{O}_3 \) requires M 142.

N-Carbamoyl-3,6-dihydro-2H-1,2-oxazine (66; \( R = \text{CONH}_2 \)). N-Cyano-3,6-dihydro-2H-1,2-oxazine (66; \( R = \text{CN} \)) (110 mg) and 30% sulphuric acid (2 ml) were warmed slowly till boiling (ca. 30 min). After boiling under reflux for a further 15 min the cyanamide had dissolved completely. The solution was cooled and extracted with chloroform (3 x 10 ml). The combined extracts were dried and evaporated to give a colourless oil which crystallised slowly as long needles (105 mg, 82%). Recrystallisation from benzene gave long, colourless needles of the amide (66; \( R = \text{CONH}_2 \)), mp. 64-65° (Found: C, 46.91; H, 6.23; N, 21.92; M+ m/e 128. \( C_5\text{H}_8\text{N}_2\text{O}_2 \) requires C, 46.87; H, 6.29; N, 21.87%; M 128), \( \tau (\text{CDCl}_3) \) 4.13(m, 4-H and 5-H), 4.30(b.s., \text{CONH}_2), 5.55 and 5.92 (multiplets, 6-H\(_2\) and 3-H\(_2\)); \( \nu_{\text{max}} \) (CHC\(_3\)) 3545 m, 3430 m, 1695 s, 1685 s, 1665 m, 1565 s, 1430 s, 1200 m, 1040 m and 715 s cm\(^{-1}\).

Preparation of the Guanidine (67) Hydrochloride. N-Cyano-3,6-dihydro-2H-1,2-oxazine (110 mg) in ethanol (5 ml) was added to 3,6-dihydro-2H-1,2-oxazine hydrochloride (121.5 mg). After leaving at room temperature for 4.5 hr the solvent was removed leaving a crystalline residue which was recrystallised from iso-propanol as white needles of the guanidine (67) hydrochloride (140 mg, 62%), m.p. 207-209° (decomp.), \( \tau \left( \text{CD}_3\text{SO}_2 \right) \) 0.60 (very broad, \( +\text{NH}_2 \)), 4.00(s, olefinic protons), 5.39(m, 4H), and 5.78(m, 4H); \( \nu_{\text{max}} \) (KBr) 1652 s, 1565 s, 1422 m, 1045 m, and 670 s cm\(^{-1}\); M+ m/e 195; \( C_9\text{H}_{13}\text{N}_3\text{O}_2 \) requires M 195.
**N-Cyano-4,5-dimethyl-3,6-dihydro-2H-1,2-oxazine (68; \( R = \text{CN} \)).** Nitrosyl chloride (1.0 ml at -60°C) was added to a stirred mixture of dry silver cyanide (5.0 g) and boiling chips (5.0 g) contained in a partially evacuated, two-necked, round-bottomed flask immersed in a cold bath at -25°C. A green vapour filled the reaction flask and after vigorous stirring for 3 min, 2,3-dimethylbutadiene (1.5 g) in dichloromethane (15 ml) was added. The mixture was stirred a further 45 min and allowed to slowly warm to room temperature during this time. Filtration through 'Celite' gave a pale yellow filtrate which gave a mobile, amber oil on removal of the solvent. Column chromatography of the oil on neutral, grade III alumina (15 x 3 cm) with benzene as eluent gave a fast running yellow fraction which gave a yellow oil (615 mg, 25%). Repeated distillation gave the \( \text{N-cyano} \) oxazine (68; \( R = \text{CN} \)) as a very pale yellow oil, b.p. 68°C at 0.4 mm Hg; \( \nu (\text{film}) \) 2930 s, 2215 s, 1445 s, and 780 m cm \(^{-1} \); M+ m/e 133; \( C_{7}H_{10}N_{2}O \) requires M 138.

**\( \text{N-Carbamoyl-4,5-dimethyl-3,6-dihydro-2H-1,2-oxazine (68; \( R = \text{CONH}_{2} \)).}**

50% sulphuric acid (1 ml) was added to \( \text{N-cyano-4,5-dimethyl-3,6-dihydro-2H-1,2-oxazine (100 mg)} \) in methanol (1 ml) and the solution heated at 70°C for 3 hr. The solution was cooled and extracted with chloroform (3 x 10 ml). The combined extracts were then dried and evaporated to give a yellow gum. Crystallisation from benzene gave long colourless needles of the amide (68; \( R = \text{CONH}_{2} \)) (60 mg, 53%) m.p. 103-104°C (Found: C, 53.74; H, 7.74; N, 17.80; M+ m/e 156. \( C_{7}H_{12}N_{2}O_{2} \) requires C, 53.83; H, 7.74; N, 17.94%; M 156); \( \nu (\text{CHCl}_{3}) \) 3550 m, 3430 m, 1678 vs, 1569 s, 1440 s, and 1015 cm \(^{-1} \).

**N-Cyano-6-carbomethoxy-3-methyl-3,6-dihydro-2H-1,2-oxazine (74; \( R = \text{CN} \)).** Nitrosyl chloride (1.0 ml at -60°C) was added to a stirred mixture of dry silver cyanide (5 g) and glass boiling chips (5 g) contained in a partially evacuated, two-necked, round-bottomed flask immersed in a cold bath at -25°C. A green vapour developed and after 4 min, a solution of methyl sorbate (1.0 g) in dichloromethane (15 ml) was added. After being stirred for a further 45 min and allowed to slowly warm to room temperature, the crude mixture was filtered through 'Celite'. Evaporation of the solvent gave a yellow-orange gum which was rapidly
passed through a neutral, grade III alumina column (10 x 3 cm) using chloroform as eluent. The fast running pale yellow band was collected and gave a pale yellow oil (1.0 g, 70%). Distillation gave the N-cyanooxazine (74; R = CN) as a very pale yellow oil, b.p. 121° at 1.5 mm Hg \( \tau(\text{CDCl}_3) \) 4.04 (m, 4-H and 5H), 5.03 (m, 6-H), 5.90 (q, 3-J 7 Hz and 12 Hz), each component shows further splitting, 3-H), 6.19 (s, CO, Me), and 8.64 (d, J 7 Hz, 3-H); \( \nu_{\max} \) (film) 2215 s, 1765 s, 1440 m, 1215 s, 1072 m and 785 m cm \(^{-1} \); \( \text{M}^+ m/e 182; \text{C}_8\text{H}_{10}\text{N}_2\text{O}_3 \) requires M 182.

An identical product was obtained on addition of the oxazine (74; R = H) hydrochloride \(^58\) to cyanogen bromide in saturated aqueous sodium bicarbonate.

**N-Cyano-3-hydroxy-6-methylpyrid-2-one (78) - Method A.** N-Cyano-6-carbomethoxy-3-methyl-1,2-dihydro-2H-1,2-oxazine (74; R = CN) (193 mg) in methanol (1 ml) was treated with 5% sodium hydroxide in methanol (0.5 ml) when a tan coloured precipitate formed. The precipitate was dissolved by adding more 5% sodium hydroxide in methanol (0.5 ml) and a little water (0.5 ml). 2N-Hydrochloric acid was added till the solution was neutral to litmus and a crystalline solid separated. The solid was filtered off and the aqueous filtrate extracted with chloroform (2 x 10 ml). The combined organic extracts were dried and evaporated to give a crystalline residue. The total solid (160 mg) was recrystallised from a minimum of hot methanol to give colourless plates of the pyridone (78) (110 mg, 70%) m.p. 191-193° (decomp.) (Found: C, 56.04; H, 4.19; N, 18.80; \( \text{M}^+ \) m/e 150. \( \text{C}_7\text{H}_6\text{N}_2\text{O}_2 \) requires C, 56.00; H, 4.03; N, 18.66%; \( \text{M 150} \), \( \tau(\text{CDCl}_3) \) 3.31 (d, J 7 Hz, 4-H), 3.85 (q, J 7 Hz and 1.5 Hz, 5-H), 7.69 (d, J 1.5 Hz, 6-Me), and 8.03 (b.s, OH); \( \nu_{\max} \) (KBr) 3280 b.s, 2255 m, 1668 s, 1630 s, 1575 m, 1305 m, 1210 m, 840 m, and 760 m cm \(^{-1} \); \( \lambda_{\max} \) (EtOH) 212 (ε 11,800) and 323 nm (7,700); \( \lambda_{\max} \) (EtOH/NaOH) 223 (ε 10,850), 265 (4,470), and 349 nm (8,320).

**Method B.** N-Cyano-6-carbomethoxy-3-methyl-1,2-dihydro-2H-1,2-oxazine (74; R = CN) (100 mg) was added to 1 drop of triethylamine when an exothermic reaction occurred. The mixture was triturated when a dirty yellow crystalline solid formed. Water was added and the mixture filtered to give an off-white crystalline solid (80 mg, 97%). Recrystallisation
from methanol gave colourless plates, m.p. 191-193° and spectroscopically identical to the product from method A.

Methylation of N-Cyano-3-hydroxy-6-methylpyrid-2-one. N-Cyano-3-hydroxy-6-methylpyrid-2-one (78) (60 mg) in methanol was treated with an excess of ethereal diazomethane. After being left at room temperature for 30 min the solvent was removed to give a crystalline residue. Recrystallisation from methanol gave colourless rods of the methoxy-pyridone (78; OH = OMe) (50 mg, 77%), m.p. 124-125° \( \delta(CDCl_3) \) 3.24(d, \( J 7.5 \text{ Hz}, 4-\text{H} \)), 3.82(q, \( J 7.5 \text{ Hz and } 1 \text{ Hz}, 5-\text{H} \)), 6.20(s, OMe), and 7.62(d, \( J 1 \text{ Hz}, 6-\text{Me} \)); \( \nu_{\text{max}}(\text{KBr}) \) 2250 m, 1700 s, 1636 s, 1280 m, 840 m, and 762 m cm\(^{-1}\); \( \lambda_{\text{max}}(\text{EtOH}) \) 211 (\( \varepsilon 10,570 \)) and 318 nm (7,800); M+ m/e 164; \( C_8H_8N_2O_2 \) requires M 164.

N-Cyano-6-cyano-3-methyl-3,6-dihydro-2H-1,2-oxazine (82). Prepared as described for N-cyano-6-carboxymethoxy-3-methyl-3,6-dihydro-2H-1,2-oxazine (74; R = CN) using nitrosyl chloride (1.0 ml at -60°C), silver cyanide (5 g) and sorbonitrile (1.5 g) in dichloromethane (15 ml). The crude product was washed with petrol (b.p. 60-80°C) (3 x 10 ml) to remove unreacted sorbonitrile and then the product extracted into benzene (15 ml) leaving a dark brown residue. Removal of the benzene gave the oxazine (82) as a yellow viscous oil (1.15 g, 48%). The oil decomposed on attempted distillation under vacuum and had \( \delta(CDCl_3) \) 4.01(m, 4-H and 5-H), 4.81(m, 6-H), 5.75(q, \( J 12 \text{ Hz and } 7 \text{ Hz}, \) each component shows further splitting, 3-H), and 8.60(d, \( J 7 \text{ Hz}, 3-\text{Me} \)); \( \nu_{\text{max}}(\text{film}) \) 2220 s, 1660 m, 1555 s, 1050 s, and 980 m cm\(^{-1}\); M+ m/e 149; \( C_7H_7N_3O \) requires M 149.

N-Cyano-5-methyl-\( \delta \)-pyrrolin-2-one (84). One drop of a dilute solution of triethylamine in ether was added to the crude N-cyano-oxazine (82) (350 mg) in ether (10 ml) and the solution left at room temperature for 24 hr. The ether solution was decanted off and the solvent removed to give a mixture of a pale yellow oil and feathery needles. The oil was removed by dissolving in a little ether and then separated by p.l.c. on silica, and developing with ethyl acetate/benzene (50:50), into sorbonitrile and a crystalline product identical with the feathery needles above. The total yield of the pyrrolinone (84) was (165 mg, 65%), recrystallised from cold ether as needles, m.p. 77° m/e 122.0481 (M+, \( C_6H_6N_2O \) requires N, 122.0480) (Found: C, 58.68; H, 5.15; N, 23.15.

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N-Cyano-3,6-bisethoxycarbonyl-3,6-dihydro-2H-1,2-oxazine (87). Prepared as described for N-cyano-6-carbomethoxy-3-methyl-3,6-dihydro-2H-1,2-oxazine (74; R = CN), using nitrosyl chloride (1.0 ml at -60°C), silver cyanide (5 g) and diethyl muconate (0.8 g) in dichloromethane (15 ml). The crude product was extracted into ether (10 ml) leaving a brown tarry residue. Removal of the ether gave the diester (87) as a yellow oil (0.85 g, 83%). Decomposition occurred on attempted distillation under vacuum, and the oil had \( \delta (\text{CDCl}_3) \) 3.80 (m, 4-H and 5-H), 4.80 (m, 6-H), 5.35 (m, 3-H), 5.70 (m, 2 \times q, 3 and 5-CO₂CH₂CH₃), and 8.69 (m, 2 \times t, 3 and 6-CO₂CH₂CH₃), \( \nu_{\text{max}} \) (film) 3000 m, 2230 m, 1760 v.s, 1245 s, 1025 s, and 856 m cm\(^{-1}\); \( M^+ \) m/e 254, \( C_{11}H_{14}N₂O₅ \) requires \( M \) 254.

Treatment of the Diester (87) with Triethylamine. Triethylamine (1 drop) was added to the diester (87) (300 mg) in ether (10 ml) and the solution left at room temperature for 24 hr. The pale yellow ether solution was evaporated to give a viscous yellow oil which began to crystallise on trituration. The resulting solid and oil were washed with a little hot petrol (b.p. 60-80°C) and the residue then crystallised from benzene (183 mg, 61%). Recrystallisation from benzene gave tiny prisms of a compound tentatively assigned as 2,5-bisethoxycarbonyl-2-cyanoamino-\( \Delta^3\)-dihydrofuran (88), m.p. 68-78°C m/e 254.0900 (\( M^+ \), \( C_{11}H_{14}N₂O₅ \) requires \( M \), 254.0903) (Found: C, 51.9; H, 5.6; N, 10.9. \( C_{11}H_{14}N₂O₅ \) requires C, 51.96; H, 5.55; N, 11.02%), \( \delta (\text{CDCl}_3) \) 3.58 (q, J 6 Hz and 2 Hz, 3-H), 3.76 (b.s, NHCN), 4.13 (m, 4-H), 4.59 (m, 5-H), 5.83 (2 x q, 2 and 5-CO₂CH₂CH₃), and 8.84 (2 x t, 2 and 5-CO₂CH₂CH₃); \( \nu_{\text{max}} \) (KBr) 3200 m, 2215 m, 1757 s, 1740 s, 1280 s, 1075 s, and 725 m cm\(^{-1}\).

Reaction of 9,10-Dimethoxyanthracene with Silver Cyanide-Nitrosyl Chloride. Nitrosyl chloride (1.0 ml at -60°C) was added to silver cyanide (5.0 g) and glass boiling chips (10 g) contained in a partially evacuated, round-bottomed flask immersed in a cold bath at -22°C. The mixture was vigorously stirred and a green vapour filled the flask. After 4 min

\[ C_6H_6N_2O \text{ requires C, 59.01; H, 4.95; N, 22.94%, } \tau (\text{CDCl}_3) 2.57 (q, J 6 Hz and 2 Hz, 4-H), 3.80 (q, 6 Hz and 1.5 Hz, 3-H), 5.27 (q, J 7 Hz and 11 Hz, each component shows further splitting, 5-H), and 8.45 (d, J 7 Hz, 5-Me); \nu_{\text{max}} \text{ (KBr) 2250 s, 1738 v.s, 1593 w, 1360 s, 1260 s, and 820 s cm}^{-1}. \]
stirring 9,10-dimethoxyanthracene (1.0 g) in dichloromethane (20 ml) was added and the mixture stirred for a further 45 min during which time it was slowly allowed to warm to room temperature. Filtration through 'Celite' gave a yellow solution which gave a solid (1.0 g) on removal of the solvent. Crystallisation from benzene gave a pale yellow solid with two further crops of the same solid being obtained on concentration of the mother liquors. The solid was shown to be anthraquinone (485 mg, 56%) by comparison with authentic material. The residue after removal of all the anthraquinone was boiled with charcoal in methanol and after filtration and cooling gave almost colourless needles of a compound thought to be 10-cyano-10-methoxyanthrone (93) (350 mg, 34%), m.p. 109° (Found: C, 76.5; H, 4.3; N, 5.7. C_{16}H_{11}NO_{2} requires C, 77.04; H, 4.41; N, 5.62%). ν\text{max} (KBr) 1602 s, 1603 m, 1595 m, 1455 m, 1318 s, 1268 s and 755 m cm\textsuperscript{-1}; λ\textmax (EtOH) 278 nm (ε 11,000).

9,10-Dimethylanthracene-Nitrosyl Cyanide Adduct. Nitrosyl chloride (1.0 ml at -60°C) was added to a mixture of silver cyanide (5.0 g) and glass boiling chips (10 g) in a partially evacuated, round-bottomed flask immersed in a cold bath at -25°C. After vigorous stirring for 3 min, during which time a green vapour had developed, 9,10-dimethylanthracene (1.0 g) in dichloromethane (25 ml) was added. The mixture was stirred a further 45 min and allowed to slowly warm to room temperature during this time. Filtration through 'Celite' gave a yellow filtrate which gave a semi-crystalline pale brown solid on removal of the solvent (1.30 g).

Chromatography of the crude material (830 mg) on a silica column (12 x 3 cm) using benzene as eluent gave 9,10-dimethylanthracene (74 mg, 11%) and a pale yellow crystalline solid (347 mg, 42%). Further elution with chloroform gave a very polar amber gum which looked very impure by n.m.r. spectrometry (170 mg).

The pale yellow solid was crystallised from methanol, after boiling with charcoal, and gave white needles of the adduct (98), m.p. 169-171° (Found: C, 77.7; H, 5.5; N, 10.7. C_{17}H_{14}N_{2} requires C, 77.80; H, 5.37; N, 10.68%). ν\text{max} (KBr) 2215 s, 1465 s, 1387 m, 782 s and 745 m cm\textsuperscript{-1}.
Reaction of Silver Cyanide–Nitrosyl Chloride with 1,3-Diphenylisobenzofuran. Nitrosyl chloride (0.2 ml at -60°) was added to a stirred suspension of silver cyanide (1 g) in chloroform (10 ml) at -20°. After 3 min stirring diphenylisobenzofuran (300 mg) in chloroform (10 ml) was added. Stirring was continued for a further 45 min and the mixture then filtered through 'Celite'. Evaporation of the filtrate gave white, crystalline cubes of 2-dibenzoylbenzene (350 mg, 80%), m.p. (148°) (lit. 7, 148°). The compound was spectroscopically identical with an authentic sample of 2-dibenzoylbenzene.
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