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SYNTHESIS OF NEW CODEINONE
AND INDOLINOCODEINONE DERIVATIVES

A Thesis
Submitted to
Loughborough University of Technology

by
R. M. ALLEN, B. Tech.

Supervisor: Professor G. W. Kirby

In partial fulfilment of the Requirements
for the Degree of
Doctor of Philosophy

September 1971
SUMMARY

Derivatives of both 14-hydroxycodeinone and the Diels-Alder adducts of thebaine provide some of the most potent analgesics in the morphine-thebaine group of alkaloids. As an extension to the range of available compounds the preparation of modified thebaines and 14-N-substituted codeinones was a desirable objective. The synthesis of 7-alkyl- or arylthebaines from salutaridine via the corresponding salutaridinols was attempted but the acid-catalysed cyclisation of the latter was not successful. The preparation of desmethoxythebaine from various precursors, namely 6-desoxy-6β-chlorocodeine, codeine tosylate and 6-desoxy-6β-fluorocodeine, also failed. The reaction of isocodeine, prepared by a new route from codeine, with N-(2-chloro-1,1,2-trifluoroethyl)-diethylamine was investigated and the major product tentatively identified as 8-desoxy-8β-fluoropseudocodeine from its spectra.

The electrophilic reactions of thebaine are reviewed and two new reactions recorded. Nitration of thebaine with tetranitromethane in methanol gave 14β-nitrocodeinone dimethyl ketal. Reduction of the nitro group was affected with zinc and ammonium chloride. The product, 14β-aminocodeinone dimethyl ketal was hydrolysed with dilute acid to give the parent amino-
eneone from which a variety of 14-\(\text{N}\)-substituted compounds were prepared. Iodination of thebaine, with iodine and silver salts, unlike chlorination, bromination and nitration, but like nitrosation, occurred at C-7 rather than C-14 to give, in the presence of methanol, \(\beta\)-iodoneopinone dimethyl ketal. The reactions of thebaine hydrochloride and dihydrothebaine hydrochloride with trifluoromethyl hypofluorite were briefly investigated.

\(\beta\)-Iodoneopinone dimethyl ketal was found to be a convenient starting material for the synthesis of 9-substituted indolinocodeinone derivatives. In this way the following groups were introduced at C-9 by reaction of the iodo ketal with the appropriate nucleophile: \(-\text{OAc}, -\text{OH}, -\text{OMe}, -\text{ONO}, -\text{CN}, -\text{NC}, -\text{N}_2, -\text{NMe}_2\) and \(-\text{SCN}\). Reaction of the iodo ketal with strong bases (sodium methoxide or sodamide) gave \(\Delta^9\)-indolinocodeinone dimethyl ketal. \(\text{14}\beta\)-Bromocodeinone dimethyl ketal was found to undergo similar rearrangement reactions with nucleophiles, for example, with methanol to give \(\text{9}\alpha\)-methoxyindolinocodeinone dimethyl ketal. The mechanisms for conversion of the 7-iodo and 14-bromo ketals into 9-substituted indolino- codeinones are discussed and an aziridinium cation, believed to be the intermediate in the reaction, has been isolated as its perchlorate salt and converted into 9-substituted indolinocodeinones.
The pharmacology of the morphine alkaloids is briefly discussed and the results of tests, showing that certain of the new compounds possess powerful analgesic properties, are given.
ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor G. W. Kirby for his considerable help and encouragement throughout the course of this work. I am indebted to Loughborough University of Technology for the privilege of working in their laboratories and to Reckitt and Colman Ltd. for financial support, generous gifts of chemicals and for testing some of the new compounds. Thanks are also due to P.C.M.U. for the accurate mass measurements and to Mr Massey for details of the preparation of isocodeine. Finally I would like to thank my typist, Miss L. J. Redshaw, and those people who provide background services necessary in any laboratory.
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INTRODUCTION

Opium, the dried juice obtained from unripe seed capsules of the opium poppy (Papaver somniferum L), has been used in medicine since at least 1550 B.C.\(^1\) Morphine (1), the chief active ingredient of such preparations, was isolated by Serturner in 1805\(^2\) and has been used as an analgesic since then. It is readily available, relatively inexpensive, a powerful sedative and its analgesic action is rapid in onset, reliable and long lasting. However, the use of morphine in therapy is restricted by its side-effects, some of which are of a highly undesirable nature. With daily administration, tolerance to the analgesic action of the narcotic usually develops within a few weeks and the dose needs to be gradually increased to produce the required effect. Tolerance is closely associated with addiction, the most serious drawback of morphine, and it was widely believed until recently that effective analgesia and drug dependence were inseparable. Other undesirable effects include respiratory depression and action on intestinal tone and motility. In man respiration is depressed by doses which are below the narcotic threshold and this depressant effect is the prime cause of death with higher doses.

These side-effects of morphine have made the development of other analgesics lacking such properties a highly desirable objective. For many years determined efforts
have been made to produce an analgesic markedly superior to morphine by minor and major modifications of the molecule of the alkaloid. In this way several useful drugs as, or more, potent than morphine and with reduced side-effects have been prepared. Among the more potent analgesics are derivatives of the Diels-Alder adducts of thebaine (2) and the 14-substituted codeinones. Compounds can be divided into three groups:

I Analgesics with dependence liability, e.g. morphine;

II Antagonist-analgesics which will generally reverse the actions of compounds in group I, but will with a group I drug provide effective analgesia, e.g. nalorphine (3);

III Antagonists which reverse the effect of most compounds in group I and also those in group II. This type has little if any pharmacological activity of its own ("silent antagonists"), e.g. naloxone (4) and diprenorphine (5).

Enormous numbers of analgesics have been prepared some of which combine the desirable properties of analgesia and non-addiction. Unfortunately most possess other side effects and few are superior to morphine, e.g. nalorphine is an analgesic-antagonist but produces hallucinations and a feeling of unreality.

So far only morphine-thebaine derivatives have been described and many analgesics are not derived from this
group. On the other hand most possess the salient features of the morphine structure. For example pentazocine (6) is both a useful analgesic and antagonist and is used clinically. This thesis is, however, only concerned with compounds in the morphine-thebaine group, in particular the preparation of modified thebaines, new 14-substituted codeinones and 9-substituted indolino-codeinones. These are for convenience discussed separately in the next section together with the results of pharmacological tests on some of these new compounds.
(1) 

(2) 

(3) 

(4) 

(5) 

(6)
RESULTS AND DISCUSSION

SECTION 1. ATTEMPTED PREPARATIONS OF MODIFIED THEBAINES

Introduction

The diene system of thebaine (2) is highly reactive and readily undergoes Diels-Alder reactions with a wide range of dienophiles, e.g. methyl vinyl ketone,\textsuperscript{4} methacrylonitrile,\textsuperscript{5} and nitrosoarenes.\textsuperscript{6} The adducts produced are complex derivatives of codeine and thebainone which contain a new two-membered bridge across ring C rendering the molecule rigid. In addition, the adducts contain new functional groups and so many chemical modifications can be performed on the attached unit as well as on the parent molecule. While the adducts usually have some analgesic activity their derivatives are appreciably more potent being several thousand times more active than morphine in some cases. For example the reaction of thebaine with methyl vinyl ketone gives a mixture of $\alpha$- and $\beta$-acetyl-6,14-endoethenotetrahydrothebaine.\textsuperscript{4} The \textalpha epimer (7), the major component, has been treated with a vast range of Grignard reagents to produce tertiary alcohols of general structure (8; \( R^1 = \text{Me}, R^2 = \text{Me}, R^3 = \) alkyl or aryl), which, depending on the C-7 substituent, are usually more potent than the parent ketone.\textsuperscript{7} Potency is then further increased by preparation of the free phenol (8; \( R^1 = \text{H}, R^2 = \text{Me}, R^3 = \) alkyl or aryl) and by
catalytic reduction of the etheno bridge. Thus the dihydro phenol (R^1 = H, R^2 = Me, R^3 = n-Pr, 6, 14-ethano) is an unprecedented 12,000 times more active than morphine. For this group of compounds antagonists are obtained by conversion of the N-Me group into N-allyl, N-cyclopropylmethyl, etc. Cf. morphine (1) and nalorphine (3). The N-cyclopropylmethyl compound (R^1 = H, R^2 = CH_2, R^3 = Me) is 150 times more potent than nalorphine.

The adducts and derivatives have a pharmacological profile similar to that of morphine, i.e. on injection they produce analgesia, depression of the respiratory and cough centres, etc. The duration of action is usually less than morphine and they are antagonised by nalorphine. Despite the large increase in potency of many of the compounds, there appears to be only a minor degree of dissociation between their therapeutically desirable and undesirable properties when compared with equianalgesic doses of morphine. However, the very high potency of the phenol (R^1 = H, R^2 = Me, R^3 = n-Pr) makes it eminently suitable for use in large animals and the base and corresponding dihydro compound are widely used for the immobilization of wild animals for game conservation and veterinary purposes. It is therefore of considerable interest to prepare modified thebaines and compare the analgesic activity of the
Diels-Alder adducts and their derivatives with the corresponding thebaine compounds.
Results and Discussion

Two routes were devised in attempts to synthesise modified thebaine compounds. Firstly the preparation of 7-alkyl- or aryl-substituted thebaines (13) from salutaridine (10) was considered. The synthesis of salutaridine from thebaine had previously been established\(^\text{10}\) and was achieved as follows. Reduction of thebaine with sodium in liquid ammonia gave dihydrothebaine-\(\phi\) (9).\(^\text{11}\) This phenol was acetylated and oxidised successively with selenium dioxide and manganese dioxide to give 2-acetyl salutaridine which on mild hydrolysis with base yielded salutaridine (10). The overall yield from thebaine was not very high (11.5\%) mainly due to the poor yield in the manganese dioxide oxidation step. Attempts to improve the low yield using manganese dioxide of differing activities were not successful. Reduction of salutaridine with sodium borohydride gives two, easily separable, epimeric alcohols, salutaridinol-I (11; \(R = H\)) and salutaridinol-II (12; \(R = H\)), in almost equal amounts. Thebaine can then be obtained by acid-catalysed cyclisation of either dienol.\(^\text{10}\) By analogy, treatment of salutaridine with alkyl or aryl lithium should initially produce the epimeric 7-substituted alcohols from which the 7-substituted thebaines should be obtained by acid-catalysed ring closure.

Treatment of salutaridine in tetrahydrofuran with
an excess of methyl lithium in ether under reflux gave
two products together with some unreacted starting
material. The reaction could not be forced to completion
despite the addition of further quantities of reagent,
probably due to solubility difficulties. Unfortunately
the unreacted starting material was similar in polarity
to the major product and could not be separated by
chromatography. The minor product was appreciably more
polar and was easily isolated from the mixture by column
chromatography over alumina. The inseparable components
were then treated with sodium borohydride thus converting
salutaridine into the salutaridinols, which, being more
polar, were easily separated by chromatography from the
unreacted major product. The spectra of the separated
products confirmed the formation of the expected dienols.
For each compound two hydroxy bands were observed in the
i.r. spectrum and two olefinic singlets, for H-5 and H-8,
in the n.m.r. spectrum. The ratio (5:1) of the products
indicated preferential attack by the incoming reagent at
the least hindered side of the molecule i.e. above the
plane of ring C. Thus the structure (12; R = Me) was
assigned to the alcohol formed in highest yield, namely
7-methylsalutaridinol-II. In addition the 7-methyl
group in the n.m.r. spectrum of 7-methylsalutaridinol-I
was at higher field than in the epimer because of shielding
by the aromatic nucleus thereby confirming the
assigned stereochemistry. Salutaridine with phenyl lithium was completely converted into a mixture of epimeric alcohols in a slightly higher ratio (7:1). Again the major product was the least polar on t.l.c. The spectra of the separated dienols were similar to those of the 7-methylsalutaridinols and furnished further evidence for the stereochemistry at C-7. Because of interaction with the introduced phenyl group, a complex signal for the aromatic protons (H-1 and H-2) was observed in 7-phenylsalutaridinol-I (11; R = Ph).

Similarly the low field position of H-5 in alcohol-II was probably due to deshielding by the phenyl group. Salutaridine thus reacted with alkyl or aryl lithium to produce a mixture of epimeric dienols; the alcohol formed in highest yield was assigned the structure (12) and the minor component structure (11). The major alcohols were the least polar on t.l.c. and the most stable on storage. This is in contrast to the salutaridinols where alcohol-I (11; R = H) is the more stable on storage and least polar. The stereochemistry at C-7 of the salutaridinols has been determined unambiguously by chemical methods. No reaction occurred when attempts were made to confirm the structures of salutaridinols-I and-II by reduction of salutaridine with lithium tri-t-butoxyaluminium hydride, a hindered reducing agent.

The 7-substituted thebaines (13) could not be pre-
pared from the corresponding 7-substituted dienols despite the use of a wide range of reagents e.g. dilute hydrochloric acid, thionyl chloride/pyridine, toluene-p-sulphonic acid/acetone, pyridine hydrochloride/pyridine, acetic anhydride/perchloric acid, potassium hydrogen sulphate/toluene, aluminium oxide/toluene and phosphorus pentoxide/xylene. In all cases either the starting material was recovered unchanged or decomposition occurred and no identifiable product was obtained.

As an extension to previously observed results\textsuperscript{13} the u.v. spectra of the salutaridinols were determined in trifluoroacetic acid and trifluoroacetic acid - sulphuric acid. Thebaine when dissolved in trifluoroacetic acid gives the red ion (14 ←→ 15; R = H), which rapidly decomposes by loss of a proton from nitrogen to give the imine (16; R = H). In the presence of mineral acid the nitrogen is securely protonated and a stable solution of the ion (14; R = H) is obtained, $\lambda_{\text{max}}$ 420 nm. (ε 15,400).\textsuperscript{13}

Salutaridinol-I when dissolved in trifluoroacetic acid - sulphuric acid gave an oxonium ion, $\lambda_{\text{max}}$ 420 nm. (ε 12,300), presumably identical to that obtained from thebaine. Similarly 7-methylsalutaridinol-II gave the substituted ion (14; R = Me), $\lambda_{\text{max}}$ 422 nm. (ε 10,100), but the spectrum of 7-phenylsalutaridinol-II showed two peaks, $\lambda_{\text{max}}$ 433 nm. (ε 9,600) and 402 nm. (ε 8,860), possibly the result of conjugation of the oxonium.
CH$_3$O
HO
CH$_3$
(CH$_3$O)

HO
CH$_3$
CH$_3$

CH$_3$
HO
(NCH$_3$

R

(14)

R

(15)

(16)

14
chromophore with the phenyl substituent. A red ion, which rapidly decomposed, was obtained when the salutaridinols were dissolved in trifluoroacetic acid alone.

A possible preparation of 6-desmethoxythebaine (18) was considered as a second route to a modified thebaine compound. This involved a base-induced cis 1,4-elimination from 6-deoxy-6p-chlorocodeine* (17; R¹ = H, R² = Cl). The preparation of the precursor from codeine (17; R¹ = OH, R² = H) is well documented,14 but yields are only moderate because 8-deoxy-8p-chloropseudocodeine (19; R¹ = H, R² = Cl, originally called p-chlorocodide is usually obtained as a by-product arising by an allylic rearrangement. The reaction of anhydrous codeine with thionyl chloride was chosen as the most suitable method.15 The required product was separated from its isomer by column chromatography rather than by fractional crystallisation. A further very minor impurity was found in the mother liquors from the recrystallisation of 6-deoxy-6p-chlorocodeine. This impurity was almost inseparable.

* The use of α and β follows steroid nomenclature; α substituents are below the ring (i.e. on the opposite side of the ring to the nitrogen bridge) and β substituents are above the ring. Compounds containing a 7,8 double bond are referred to as codeine derivatives; the name isocodeine is retained for the 6α-alcohol. Compounds with a 6,7 double bond are referred to as either 8α- or 8β-pseudocodeine derivatives; the name allopseudocodeine is retained for the 8β-alcohol. For example, instead of the trivial name α-chlorocodide (17; R¹ = H, R² = Cl), 6-deoxy-6p-chlorocodeine is used.
from the major component on t.l.c. and on the basis of its spectra was assigned the structure 6-desoxy-1, 6β-dichlorocodeine. Only one aromatic proton was observed in the n.m.r. spectrum and the presence of the two chlorine atoms was shown by the mass spectrum. The compound was assumed to be the 1-chloro-rather than the 2-chloro-derivative by analogy with the reaction between codeine and thionyl bromide when 1-bromo-8-deoxy-8β-bromopseudocodeine is produced in quantity under appropriate conditions. The bromine was shown to be attached to C-1 and not C-2 by synthesis from 1-bromocodeine where the structure had been proved by degradation. 16

6-Desoxy-1,6β-dichlorocodeine is a known compound obtained by heating codeine with phosphorus pentachloride or phosphorus oxychloride at 60-70°C, but little physical data are recorded. 17

The reagent used in the elimination reaction must be reasonably bulky, a suitable base being the potassium salt of t-pentanol. The reaction between 6-deoxy-6β-chlorocodeine and potassium t-pentoxide was found in practice not to work as predicted. The sole, oily product was shown to be 6-chloro-6-desoxycodainine-A (20) arising by a cis 1,2-elimination. The same product was obtained using less bulky bases. A Dreiding model of the starting material showed that the C-6 proton was slightly more exposed than the C-14 proton but
another possible explanation of the very ready 1,2-elimination may be the ability of the chlorine atom to expand its electron shell and thereby stabilise a carbanion. Both codeine methyl ether \(17; R^1 = \text{OMe}, R^2 = H\)\(^{18}\) and 6-deoxy-6\(\eta\)-ethylthiocodide \(17; R^1 = H, R^2 = \text{SEt}\)\(^{19}\) undergo analogous reactions on heating with sodium ethoxide to give the corresponding phenolic dienes. The former process may involve a concerted \textit{trans} 1,2-elimination but the latter presumably requires a two step reaction via a carbanion. Also isocodeine methyl ether \(17; R^1 = H, R^2 = \text{OMe}\) does not undergo elimination reactions under these conditions. For 6-chloro-6-desoxycodeine-A chemical tests showed the presence of both a phenolic hydroxy group (confirmed by i.r.) and chlorine (confirmed by mass spectrum), and accurate mass measurement confirmed the molecular weight and empirical formula. The product was analysed as its crystalline picrate. The n.m.r. spectrum showed the 7 and 8 olefinic protons as a complex signal while H-5 was hidden beneath the aromatic protons. In the mass spectrum the base peak at m/e 178 represented the ion (21) and is a typical fragment of desoxycodeine-A derivatives.\(^{20}\) Acetylation gave a non-crystalline 4-\(\eta\)-acetyl derivative and catalytic hydrogenation yielded a very complex mixture of inseparable products. 3-Desoxy-8\(\eta\)-chloropseudocodeine \((19; R^1 = H, R^2 = \text{Cl})\), obtained as a by-product from the
preparation of the 6-chloro-compound and also by isomerisation of it, should not undergo an SN$_2$ reaction with the bulky base because of its hindered structure nor should removal of the proton at C-8 take place easily. Also a 1,4-elimination involving removal of H-6 would produce a strained diene. Accordingly this compound should be unreactive towards base and this was found to be so.

Codeine tosylate (17; $R^1 = OTs$, $R^2 = H$) and 6-desoxy-6β-fluorocodeine (17; $R^1 = H$, $R^2 = F$) were then considered as alternative precursors of 6-desmethoxy-thebaine. Codeine tosylate, prepared quantitatively from codeine, when treated with potassium t-amyloxide under identical conditions yielded a product of unknown constitution. From spectral data it appeared to be a dimeric species. 6-Desoxy-6β-fluorocodeine was chosen as a suitable starting material because of the inability of the fluorine atom to expand its electron shell. Reaction with base was slower than with the 6-chloro-compound but the product could not be identified and was not the required compound. The preparations of modified thebaine compounds were thus unsuccessful.

6-Desoxy-6β-fluorocodeine was prepared by a slight modification of the patented procedure in which codeine is treated with $N$-(2-chloro-1,1,2-trifluoroethyl)-diethylamine. The fluorinating agent was made by the literature method whereby chlorotrifluoroethylene is
added under pressure to diethylamine. \(^{22}\) Fluorination with this reagent leads exclusively to inversion of configuration, thus codeine gave the \(6\beta\)-fluoro-derivative. The mechanism is outlined below:\(^{23}\)

\[
\text{Et}_2\text{NCF}_2\text{CFCIH} \rightarrow \text{Et}_2\text{NF} = \text{CFCFClH} + F^- \rightarrow \text{Et}_2\text{NCOFCClH} + HF \rightarrow \text{Et}_2\text{NF} = \text{CORCFCIH} + F^- \rightarrow \text{RF} + \text{Et}_2\text{NCOCFCIH}
\]

where ROH = codeine.

The configuration of the fluoro product was deduced from the n.m.r. data. In the codeine series (6\(\alpha\) substituents) the dihedral angle between the \(5\beta\) and \(6\beta\) protons is 25-30°. Thus from the Karplus equation a coupling constant of 6.0-6.7 Hz would be expected. In the iso-codeine series (6\(\beta\)) the dihedral angle is 90-95° and therefore there is virtually no coupling between the \(5\beta\) and \(6\alpha\) protons;\(^{24,25,26}\) e.g. for codeine the \(5\beta\) proton appears as a doublet at 5.12\(\tau\) (J 6.3 Hz) while in 6-desoxy-6\(\alpha\)-chlorocodeine the \(5\beta\) proton is a singlet at 4.96\(\tau\). In the spectrum of 6-desoxy-6\(\beta\)-fluorocodeine H-5 appeared as a doublet at 5.10\(\tau\) (J 18 Hz) being coupled only to the vicinal fluorine atom. In addition the 6\(\alpha\) proton was a multiplet with a large coupling constant fluorine (48 Hz) arising from the geminal atom. This confirmed the expected \(\beta\) configuration for the substituent.

6-Desoxy-6\(\beta\)-fluorocodeine has recently been obtained by Bognár et al.\(^{27}\) from the reaction of codeine tosylate with tetrabutylammonium fluoride in acetonitrile. The
spectroscopic data given agree with those above.

In pursuit of other fluorinated compounds the re-
action of isocodeine (17; $R^1 = H$, $R^2 = OH$) with $N$-
(2-chloro-1,1,2-trifluoroethyl)-diethylamine was in-
vestigated. Isocodeine has traditionally been prepared
by hydrolysis of 6-desoxy-6α-chlorocodeine or the 8α-
halocodides (Cl, Br, I).14 The reaction mixtures also
contain the isomeric alcohols allopseudocodeine (19;
$R^1 = OH$, $R^2 = H$) and pseudocodeine (19; $R^1 = H$, $R^2 = OH$)
from which isocodeine is normally separated by fractional
-crystallisation of salts. Recently28 the hydrolysis of
codeine tosylate has been reported to give isocodeine
in 16.6% yield. Following a method developed in these
laboratories, codeine tosylate was treated with hexa-
decyltrimethylammonium acetate, prepared from the corres-
ponding bromide and silver acetate, in benzene at room
temperature. Under these non-solvolytic conditions
clean $SN_2$ attack by acetate at C-6 was expected since
codeine tosylate is known29 to react with chloride ions
to give 6-desoxy-6α-chlorocodeine. Indeed isocodeine
acetate was formed and was hydrolysed to give iso-
ocodeine in good yield (50-60% from codeine).
Isolation of the product from the first stage was made tedious
by the detergent properties of the hexadecyltrimethyl-
ammonium cation. Fluorination of isocodeine could
yield several isomeric species, namely 6-desoxy-6α-
fluorocodeine \((17; \text{R}^1 = \text{F}, \text{R}^2 = \text{H})\) by \(\text{SN}_2\) attack, and 8-desoxy-8\(\alpha\)-fluoropseudocodeine \((19; \text{R}^1 = \text{F}, \text{R}^2 = \text{H})\) or, more probably, its epimer \((19; \text{R}^1 = \text{H}, \text{R}^2 = \text{F})\) by \(\text{SN}_2\) attack. There are no recorded examples of \(6\alpha\)- or \(8\alpha\)-halocodides. 8-Desoxy-8\(\beta\)-fluoropseudocodeine is also unknown and attempts to prepare it by isomerisation of the 6\(\beta\)-fluoro-compound have not been successful.\(^{27}\) Isocodeine was treated with the fluorinating agent at 0\(^\circ\)C for 18 hours and t.l.c. examination, after work up, showed three products, the least polar being the major product. Separation proved very difficult and only a small quantity of the major product could be obtained pure. The product was assigned the structure \((19; \text{R}^1 = \text{H}, \text{R}^2 = \text{F})\) by comparison of the n.m.r. spectrum (for all values see experimental section) with the 8\(\beta\)-chloro-compound. The 6\(\alpha\)-fluoro structure was ruled out because of the small coupling constant observed for H-5 and also the high field position of the H-14 signal (\(-7.3\)). In codeine type compounds H-14 occurs typically at lower field (\(-6.8\)). Signals for the proton at C-5 were partly obscured by those for H-8, which showed a large fluorine coupling (50 Hz), smaller coupling to H-14 (10 Hz) and fine splitting presumably due to H-5, H-6 and H-7. The olefinic pattern was similar to that of the 8-chloro-derivative but showed further splitting to fluorine.
The remainder of the spectrum was almost identical to that of 8-desoxy-8β-chloropseudocodeine. Confirmation of the structure via the dihydro compounds, where allylic rearrangements are not possible, was unsuccessful. Catalytic hydrogenation of 6-desoxy-6β-fluorocodeine in the presence of acid yielded the expected dihydro compound (22; $R^1 = H$, $R^2 = F$). However contrary to the literature, the dihydrofluoro compound could not be prepared by fluorination of dihydrocodeine (22; $R^1 = OH$, $R^2 = H$), obtained quantitatively by catalytic hydrogenation of codeine. Similarly no reaction was observed with dihydroisocodeine (22; $R^1 = H$, $R^2 = OH$) and in both cases starting material was recovered unchanged. If fluorination of the dihydro compounds, including the 8-substituted derivatives, had been possible then a positive identification could have been made. The alternative approach, namely fluorination of allopseudocodeine ($SN_2$ reaction would give an 8β-fluoro product), would probably have been of little assistance since on chlorination allylic rearrangement takes place to give 6-desoxy-6β-chlorocodeine. Configuration is also retained on chlorination of pseudocodeine. The identity of the major product from the fluorination of isocodeine thus rested tentatively on comparison of the n.m.r. spectrum with other similar derivatives.
Section 2. SOME ELECTROPHILIC REACTIONS OF THEBAINE

Introduction

Thebaine (2) is both a diene and a dienol ether; electrophilic attack can therefore take place either at C-7 or C-14. In all the earlier examples 14-substituted products were exclusively formed. Thus bromination of thebaine gives 14-bromocodeinone (23; \( R_1 = R_2 = 0, X = \text{Br} \))\(^{30} \) and hydroxylation, normally with peracids, 14-hydroxycodeinone (23; \( R_1 = R_2 = 0, X = \text{OH} \)).\(^{31} \) Both products arise from a 1,4 addition to the diene system followed by decompositon of the resulting hemiketal. Both reactions have been reinvestigated. Lutz and Small\(^{32} \) claimed a 75% yield, Fel'dman\(^{33} \) an 85% yield and Seki\(^{34} \) an 88% yield for the hydroxylation reaction using modified conditions. 14-Bromocodeinone was obtained in good yield by Conroy\(^{35} \) using N-bromosuccinimide in aqueous acetone and the corresponding chloro compound (23; \( R_1 = R_2 = 0, X = \text{Cl} \)) has also been prepared in 80% yield using iodobenzene dichloride.\(^{36} \)

The stereochemistry at C-14 in 14-hydroxycodeinone (and 14-hydroxydihydrocodeinone) has been assigned from the i.r. spectrum.\(^{37} \) The hydroxyl group shows a single hydroxyl band at 3385 cm.\(^{-1} \) implying intramolecular hydrogen bonding to nitrogen. The closeness of the hydroxyl group and nitrogen atom has also
been demonstrated.\textsuperscript{38} Firstly the nitrogen is difficult to quaternize because of the hydrogen bond, secondly with Cl\textsubscript{2}CH\textsubscript{2}COCl 14-hydroxycodeinone yields a lactone and thirdly the compound forms a well defined copper complex. The C-14 substituent was therefore assigned a $\beta$ configuration.

Two preparations of 14-bromocodeinone dimethyl ketal (23; $R^1 = R^2 = \text{Ome}, \ X = \text{Br}$) have been described. Rüll\textsuperscript{39} treated thebaine with bromine followed by sodium methoxide while Fleischhacker\textsuperscript{40} used N-bromoacetamide in methanol, although the product of the latter reaction was originally described as 7-bromoneopinone dimethyl ketal in an Austrian patent.\textsuperscript{41} Both 14-bromocodeinone dimethyl ketal and the parent enone have proved useful starting materials for a wide variety of chemical transformations. Sodium borohydride reduction of the enone at room temperature produces, as expected, 14-bromocodeine (23; $R^1 = \text{OH}, \ R^2 = \text{H}, \ X = \text{Br}$), but further treatment at a slightly higher temperature gives neopine (24; $R^1 = \text{OH}, \ R^2 = \text{H}, \ X = \text{H}$).\textsuperscript{35} Neopinone (24; $R^1 = R^2 = 0, \ X = \text{H}$) has been obtained by catalytic hydrogenation of 14-bromocodeinone.\textsuperscript{35} Solvolysis of the enone with sodium acetate in methanol was claimed to give 7-acetoxyneopinone (24; $R^1 = R^2 = 0, \ X = \text{OAc}$) in very low yield,\textsuperscript{42} but solvolysis of 14-bromocodeine gives mainly re-
arranged products (see section 3). Other 7-substituted neopinones have recently been prepared from 14-bromo-codeinone dimethyl ketal. 7β-Hydroxyneopinone dimethyl ketal (24; R1 = R2 = OMe, X = OH) and the α epimer (25; R1 = R2 = OMe, X = OH), the minor component, have been produced by shaking the ketal with alcoholic sodium hydroxide on a specially prepared palladium-carbon catalyst and 7β-methoxyneopinone dimethyl ketal (24; R1 = R2 = OMe, X = OMe) by methanolation. Finally thebaine has been regenerated by debromination of the bromoketal.

Nitrosation of thebaine with nitrosyl chloride in methanol yielded 7-oximinoneopinone dimethyl ketal (24; R1 = R2 = OMe, XH = N-OH); the first example of electrophilic attack at C-7. Possibly nitrosation can occur at C-14 but the 14-nitroso product is unstable relative to the 7-oximino-derivative. Bach et al. have reported that bromination of thebaine metho salts gives 7-bromo-derivatives. Presumably an additional substituent on nitrogen hinders approach of the reagent to C-14. Hydroboration of thebaine can also be considered an electrophilic attack although only 1,2-addition to the diene can occur. A mixture of 7β-hydroxyneopinone methyl ether (24; R1 = OMe, R2 = H, X = OH) and 7α-hydroxyisoneopinone methyl ether (25; R1 = H, R2 = OMe, X = OH) are obtained from the
reduction of thebaine borane with one equivalent of diborane followed by oxidation with hydrogen peroxide. With an excess of the reagent the reaction is more complex and in addition to $\gamma\beta$-hydroxyneopine methyl ether and $\gamma\alpha$-hydroxydesoxyneopine (25; $R_1 = R_2 = H$, $X = OH$) dihydro compounds containing $14\alpha$-substituents are produced by attack at the remaining double bond. These are the only reported examples of electrophilic attack at C-7.

The $14\alpha$-substituted codeinones are not only important as precursors for a wide range of chemical transformations but also because of their pharmacological properties. For example in the $14\beta$-hydroxycodeinone series many of the derivatives are more potent than morphine and represent, with the exception of the Diels-Alder adducts of thebaine, the most potent compounds in the morphine-thebaine group. One series of compounds derived from the Diels-Alder adducts are the $14\alpha$-alkenylcodeinones (26; $R_1 = R_2 = 0$, $X = CH_2CH = CCH_2R$). They are obtained from alcohols of general structure (8) by hydrolysis with dilute acid. Catalytic reduction gives the potent $14\alpha$-alkyldihydrocodeinones (26; $R_1 = R_2 = 0$, $X = CH_2CH_2CHCH_3R$). As an extension to the range of available $14\alpha$-substituted codeinones the preparation of $N$-substituted $14\alpha$-aminocodeinones was a highly desirable objective.
Results and Discussion

The reaction of thebaine with nitrosyl chloride was reinvestigated by Bentley et al.\(^4\)\(^6\) as a possible means of introducing a nitrogen group at C-14. Unfortunately the reaction furnished the first example of electrophilic attack at C-7 and 7-oximinonepinone dimethyl ketal (24; \(R^1 = R^2 = \text{OMe}, XH = \text{NOH}\)) was isolated as the product. In the n.m.r. spectrum of the product the protons at C-8 and C-5 gave singlets and one ketal methoxy group gave a high field singlet because of shielding by the aromatic nucleus. The reaction of thebaine with nitrosoarenes was then investigated\(^6\) and the initially formed adducts (27) readily opened with dilute acid to produce 14-\(\text{N}\)-arylaminocodeinones (23; \(R^1 = R^2 = 0\), \(X = \text{NHAr}\)) - the first examples of \(\text{N}\)-substituted 14-aminocodeinones. If 1-chloro-1-nitrosocyclohexane is used as the dienophile under hydrolytic conditions 14-hydroxylamino-codeinone (23; \(R^1 = R^2 = 0\), \(X = \text{NHOH}\)) is obtained in excellent yield.\(^5\)\(^0\) A variety of reagents failed to convert the amino derivatives into the more useful parent 14-aminocodeinone. The 14-\(\text{N}\)-arylamino-compounds are readily rearranged with base to give phenols of general structure (28).\(^6\) The reaction of thebaine with ethyl azodicarboxylate\(^5\)\(^1\) gives, with 1 mole of the reagent \(\text{N-(NN-diethoxycarbonyl-hydrazinomethyl)}\)
(23)

(24)

(27)

(28)
northebaine (29) and 14, N-(NN'-diethoxycarbonyl-
hydrazomethyl)-norcodeine (30) with 2 moles. Acid
hydrolysis of (30) gives the 14-N-substituted com-
pound (23; R¹ = R² = O, X = NCOOEtNHCOOEt).

Nitration of thebaine was therefore considered as an
alternative means of introducing a nitrogen residue at
the C-14 position. Conventional nitrating agents could
not be used because thebaine undergoes rearrangement
with strong acids. Tetranitromethane has been used to
nitrate several natural products, e.g. skatole⁵² and
19-nortestosterone acetate⁵³, and it was considered
ideally suited for reaction with thebaine because of
its mild nature. Nitration of thebaine with tetra-
nitromethane in methanol at room temperature, like
bromination and chlorination, was found to occur at
C-14 to give 14-nitrocodeinone dimethyl ketal (23; R¹ =
R² = OMe, X = NO²) in rather low yield (25%). The bulk
of the thebaine was precipitated out of solution as the
bright yellow nitroform salt. Thus 1 mole of tetra-
nitromethane consumed 2 moles of thebaine. The reaction
was therefore repeated using different ratios of reagent
and thebaine. It was found that for 1 mole of thebaine
0.8 mole of tetranitromethane gave the same yield of
14-nitrocodeinone dimethyl ketal as did 1 mole, but
lower ratios gave less nitro ketal. After removal of
the nitroform salt the product was separated from
unreacted thebaine and a small amount of 14-nitrocodeinone by column chromatography and then recrystallised from alcohol to remove a small quantity of another impurity that was of similar polarity to the required product. Attempts to improve the yield were not successful. Salt formation could not be prevented by the addition of base, e.g. potassium and calcium carbonate and triethylamine, to the reaction mixture. The reaction was also found to work equally well in the dark and under oxygen free nitrogen. In contrast, when the reaction was repeated using ether or benzene instead of methanol as solvent the major product (excepting the nitroform salt) was identical to the minor impurity observed in the mother liquors from the recrystallisation of the 14-nitro ketal. Unfortunately the major product could not be separated from the minor impurity (14-nitro ketal) by t.l.c. in a wide variety of solvent systems on alumina, silica or basic silica plates and they co-crystallised when fractional crystallisation was attempted. The structure of the major product could not be ascertained from its spectra or reactions. Identification was hindered by the presence of the 14-nitro ketal. It seemed probable that the reaction in methanol proceeded by an ionic mechanism (unaffected by light or oxygen) whereas the reaction in benzene was free radical. The reaction using benzene as solvent was repeated with the addition
of a free radical initiator, benzoyl peroxide, when the time required for precipitate formation was reduced. Similarly a free radical trap, 2,6-di-t-butyl-p-cresol, delayed precipitate formation. Although this evidence cannot be regarded as conclusive it supported the suspected reaction mechanisms. Considerable confusion exists in the literature as to the part played by tetranitromethane in its reactions with olefines and both ionic and free radicle mechanisms have been proposed.54

14-Nitrocodeinone dimethyl ketal was easily identified as the major product from the reaction in methanol by its spectra. The olefinic signals in the n.m.r. spectrum occurred as a 2-proton singlet (τ 4.12), H-5 also gave a singlet (τ 4.96) and one methoxy group gave a high field (τ 6.95) singlet due to shielding by the double bond. The nitro group absorbed in the expected region (1546 cm.⁻¹) of the i.r. spectrum. The ketal was quantitatively hydrolysed with dilute acid to the enone in which the olefinic protons gave an AB quartet (τ 3.38 and 3.82, J 10 Hz, H-8 and H-7). In addition, the ring B protons were identified. The proton at C-9 (τ 5.92) gave a doublet being coupled (J 6 Hz) strongly only to the 10α-proton. The protons at C-10 were coupled to each other and thus H-10β gave a doublet (τ 6.50, J 18 Hz) and H-10α a quartet (τ 7.44, J 6 and 18 Hz). These values
were consistent with the dihedral angles measured from models and in good agreement with values obtained for ring B protons in other 14-substituted compounds. In the i.r. spectrum bands for both the carbonyl group (1690 cm⁻¹) and the nitro group (1548 cm⁻¹) confirmed the structure.

The reaction of dihydrothebaine (31; R = Me), prepared from thebaine by reduction with diimide, with tetranitromethane was also investigated. In this case nitration of the double bond was not observed and after chromatographic separation of unreacted starting material and dihydrocodeinone (22; R¹ = R² = O) the remaining product (5.0% yield) was concluded to be N-nitrosonordihydrothebaine (31; R = NO). The n.m.r. spectrum was similar to that of the starting material except for the absence of the N-methyl singlet and both the i.r. spectrum and analysis supported the structure. The reaction of tetranitromethane with tertiary amines is recorded in the literature and the products, N-nitroso compounds, are only formed in low yields. Because of the moderate yield from the reaction of thebaine with tetranitromethane an alternative nitrating agent was considered. Nitryl iodide has been used successfully by Hassner and co-workers to nitrate olefines. It is prepared in situ from silver nitrite and iodine and is claimed to react in several ways:

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(i) as nitryl iodide (NO$_2$I), i.e. a nitrating agent,
(ii) as iodonium nitrite (INO$_2$), i.e. an iodonating agent, and
(iii) by a free radical mechanism.

Reactions of thebaine with silver nitrite and iodine in chloroform: methanol (9:1) at room temperature did not give the 14-nitro ketal. The light sensitive product (75% yield) was identified mainly from the n.m.r. spectrum as 7$p$-iodoneopinone dimethyl ketal (24; $R^1 = R^2 = $OMe, $X = I$). The protons at C-7 and C-8 gave an AB quartet ($\tau$ 5.31 and 4.27) with a coupling constant (6 Hz) suggesting a $\beta$ configuration for the iodine. The proton at C-5 gave a singlet ($\tau$ 4.73) and one methoxy signal occurred as a high field ($\tau$ 7.06) singlet because of shielding by the aromatic nucleus. The recent preparation of 7$\alpha$- and 7$p$-hydroxyneopinone dimethyl ketal (24; $R^1 = R^2 = $OMe, $X = \alpha$- or $\beta$-OH) by Fleischhacker et al. from 14-bromocodeinone dimethyl ketal has confirmed the configuration assigned for the iodine. In the $\beta$-hydroxy epimer the coupling constant (6.5 Hz) is in good agreement with that of our iodide while the $\alpha$-epimer has a small coupling constant (1.5 Hz). The values are consistent with the dihedral angles measured on a Dreiding model. Thebaine was found to react with iodine alone to give the iodo ketal.
in equally good yield, but the reaction was accelerated by the addition of the silver salt. The iodo-compound was also obtained in lower yield from the reaction of thebaine with N-iodosuccinimide in methanol. 7β-
Iodoneopinone dimethyl ketal was resistant to mild acid hydrolysis and stronger acid caused decomposition. There was no reaction when water was substituted for methanol in the preparation and thus the parent iodo-ketone could not be obtained. The iodo ketal readily rearranged to 9-substituted indolinocodeinones with a wide variety of nucleophiles (see section 3). It was unaffected by sodium borohydride at room temperature and lithium aluminium hydride in ether under reflux gave a mixture of at least eight products the separation of which was not attempted. The iodide reacted with an excess of activated zinc dust to give an inseparable mixture of two products. The n.m.r. spectrum of the mixture showed that the major product, as expected, was thebaine.

To summarise the electrophilic reactions of thebaine; bromination, chlorination, hydroxylation and nitration give 14-substituted products, iodination and nitrosation give 7-substituted products. Factors affecting the site of electrophilic attack were therefore considered. Comparison of the nitration and iodination reactions indicated that the size of the
reagent was probably unimportant. The nitro group was more bulky than the iodo group therefore, on steric grounds alone, nitration at C-7 was more likely than at the more hindered C-14 position. Differences in the mechanistic type of the reactions (i.e., free radical or ionic) could be an important factor, but the precise nature of some of the reagents was not known although all were assumed to be ionic because of the reaction conditions. Product stability could account for the observed 7- or 14-substituted derivatives. In the nitrosation or iodination reaction attack could take place initially at C-14 followed by rearrangement to give the C-7 derivative. The reverse may also be true and in both cases the thermodynamically more stable isomer might be isolated. There are no examples of both a 7-substituted and a 14-substituted compound being isolated from an electrophilic attack on thebaine (but see below). Examples of 7- and 14-substituted isomeric compounds are known, e.g., 7- and 14-hydroxycodeinone dimethyl ketal. The 14-hydroxy ketal is obtained from electrophilic attack on thebaine but the 7-substituted derivative, as mentioned earlier, is prepared by solvolysis of 14-bromocodeinone dimethyl ketal.

Besides the size and nature of the reagent and product stability, salt formation appeared to play an
important role and was considered the most important factor. Bach et al.\textsuperscript{47} have recently reported that bromination of thebaine methoperchlorate gave predominantly 7-bromoneopinone dimethyl ketal methoperchlorate (24; R\textsuperscript{1} = R\textsuperscript{2} = OMe, X = Br, methoperchlorate salt). Presumably the additional substituent on nitrogen hindered attack at C-14. The bromination of thebaine hydrochloride was therefore investigated. Two methods of preparing 14-bromocodeinone dimethyl ketal (23; R\textsuperscript{1} = R\textsuperscript{2} = OMe, X = Br) from thebaine have been described. Fleischhacker's preparation\textsuperscript{40}, using N-bromoacetamide in methanol, was the preferred method while that of Rühl\textsuperscript{39} using bromine followed by sodium methoxide was found not to work. Four products were always obtained despite the use of a wide range of experimental conditions. After chromatographic separation only one product could be identified, namely 14-bromocodeinone (23; R\textsuperscript{1} = R\textsuperscript{2} = O, X = Br). One interesting feature of the n.m.r. spectrum of the bromo ketal was coupling (1 Hz) between H-5 and H-7. The results obtained for the bromination of thebaine with N-bromoacetamide in methanol in the presence of hydrochloric acid are given overleaf:
Notes (i) 1 mole of thebaine was used in all reactions.

(ii) hydrochloric acid was generated in situ by the addition of the correct quantity of acetyl chloride to the suspension of thebaine in methanol.

(iii) the reaction of preformed thebaine hydrochloride with N-bromoacetamide in methanol gave the same result as that with thebaine hydrochloride generated in situ.

(iv) the percentages of the products were determined from the n.m.r. spectrum of the total product mixture. The spectrum of 7-bromoneopinone dimethyl ketal was very similar to that of the 7-iodo-compound.
The effect of salt formation can clearly be seen from the table. Increasing acid concentration increased the percentage of 7-bromo-product. It was probable that the excess acid was causing breakdown of the brominating agent as illustrated by the reaction using $1\frac{1}{2}$ moles of N-bromoacetamide. The 7-bromo-compound was inseparable by t.l.c. from the other unknown product, but readily separable from the 14-bromo-component. Hence the reaction using equimolar quantities of reagents was repeated on a larger scale and the products separated by column chromatography, the 14-bromo ketal being the least polar component. The n.m.r. spectrum of the more polar component showed that it was obviously no longer the required 7-bromo-compound. The product was identified as 9α-hydroxyindolinocodeinone dimethyl ketal (32; $R^1 = R^2 = \text{OMe}$, $X = \text{OH}$) by comparison of the spectrum, melting point and mixed melting point with an authentic sample. The reaction was typical of the rearrangement reactions of the 7-iodo-compound (see section 3). The water present in the alumina was presumably responsible for the conversion. It was not possible to separate the bromo-isomers by fractional crystallisation.

14-Bromocodeinone ($23; R^1 = R^2 = 0, X = \text{Br}$) can be prepared by reaction of thebaine with N-bromosuccinimide in aqueous acetone. 35 In a
similar way 14-chlorocodeinone (23; R¹ = R² = O, X = Cl) was prepared using N-chlorosuccinimide. This method was superior to the literature preparation using iodobenzene dichloride. 36 When thebaine hydrochloride was treated with N-bromo­succinimide in aqueous acetone, only the 14-bromo­ketone was produced in low yield, the remainder of the product being unreacted starting material. Similarly, thebaine was recovered unchanged from treatment of thebaine hydrochloride with tetranitromethane. It had been hoped that 7-substituted neopinones would be obtained from these reactions but like the attempted preparation of 7-iodoneopinone mentioned above they were a complete failure. Salt formation may not be the complete explanation of attack at C-7 and the answer may be a combination of the factors discussed or some other unknown influence.

The reaction of thebaine with another pseudo­halogen, iodine azide (IN₃), was examined as a possible source of 14-iodocodeinone. Iodine azide was generated in situ from iodine monochloride and sodium azide. It was hoped that salt formation would not occur and the reagent is also claimed to react by an ionic mechanism.58,59 However the reaction did not proceed as anticipated and indolinocodeinone products were once again produced (the products are discussed in section 3). Halide exchange reactions
on the 14-bromo ketal (and enone) were also unsuccessful. Finally the reaction of thebaine with another pseudohalogen, iodine nitrate, generated from iodine monochloride and silver nitrate, was investigated. In this case only a tarry mixture of unidentifiable products was obtained. Both iodine azide\textsuperscript{58,59} and iodine nitrate\textsuperscript{60} have been successfully added to a variety of double bonds.

Only a few compounds in the morphine-thebaine group containing a fluoro substituent are known. Thebaine was therefore treated with trifluoromethyl hypofluorite ($\text{F}_3\text{COF}$) as a possible route to other fluoro derivatives. Trifluoromethyl hypofluorite, an electropositive fluorinating agent, has been used to fluorinate a variety of steroidal olefines\textsuperscript{61} and aromatic nuclei.\textsuperscript{62} Typical reactions with olefines are addition of the reagent to the double bond and addition of fluorine to the double bond. The difluoro compound is formed by breakdown of $\text{F}_3\text{CO}^-$ to carbonyl difluoride and fluoride ion. The reagent can be used in glass apparatus and is more stable and easier to handle than earlier fluorinating agents, but it has the disadvantage of reacting violently with some solvents, e.g. pyridine and oxygen containing solvents. Reaction with thebaine in alcohol free chloroform at $-40^\circ\text{C}$ gave only a salt of thebaine. Thebaine hydrochloride under the same
conditions gave several products (at least four) inseparable in quantity by p.l.c. The reaction with dihydrothebaine (31; \( R = \text{Me} \)) was found to be less complex but the products (only three) were again difficult to separate. Very small quantities were obtained but their identity could not be determined. In all cases the recovery of total products was only moderate (<50%). It seemed probable that aromatic fluorination was taking place and to test this dihydrocodeinone hydrochloride (22; \( R^1 = R^2 = 0, \) HCl salt) was treated with the reagent under the same conditions. Several products were produced and the n.m.r. spectrum of the total mixture showed a lack of aromatic protons; thus aromatic fluorination was possibly accounting for the large number of products. According to the literature, aromatic fluorination is usually carried out at a higher temperature (0°C) than fluorination of olefines (-80°C). The main problem was that the useful salts, e.g. the hydrochloride, of the alkaloids were only soluble in oxygenated solvents and chloroform (freezing point -61°C). The reaction of thebaine with trifluoromethyl hypofluorite at -80°C in methanol was therefore tried. On completion of the reaction the solution was strongly acidic and after work up a t.l.c. examination showed a large number of products. The addition of calcium oxide or
sodium fluoride to the reaction mixture tended to prevent product formation. However during a trial reaction using a temperature of 0°C and in the presence of calcium oxide a violent explosion occurred and as a result the work was abandoned.

The preparation of certain N-substituted 14-amino-compounds was discussed earlier, but the most useful and elusive parent, 14-aminocodeinone, could not be produced. 14-Nitrocodeinone dimethyl ketal was therefore examined as a precursor for the amino-enone. Reduction of the nitro group proved difficult. Catalytic hydrogenation over 10% palladium-charcoal gave only dihydrocodeinone dimethyl ketal (22; R¹ = R² = OMe), identified by hydrolysis to dihydrocodeinone. The 6-methoxy groups of this ketal gave a singlet in the n.m.r. spectrum (cf. the 14-substituted codeinone dimethyl ketaels). Similarly, 14-nitrocodeinone gave dihydrocodeinone (22; R¹ = R² = 0). Catalytic hydrogenation of 14-bromocodeinone also yields only dihydrocodeinone.³⁵ As expected, the 14-nitro ketal was unaffected by sodium borohydride and reduction with lithium aluminium hydride gave a mixture of several products, the separation of which was not attempted. The usual method of reducing nitro compounds with metal-mineral acid was not tried because after hydrolysis of the ketal function the reagent would
open the oxide bridge to give a phenol. Reduction was finally affected by refluxing the nitro ketal with an excess of zinc dust and ammonium chloride in methanol. In this case the mixture was too weakly acidic to hydrolyse the ketal function and hence phenol formation was prevented. The reduction could not be stopped at the intermediate nitroso and hydroxylamino stages since, using limited quantities of reagents, the observed product was a mixture of the amino ketal and unreacted starting material. Using neutral conditions, i.e. ammonium chloride omitted from the reaction mixture, the starting material was recovered unchanged. The structure of the amino ketal (23; R¹ = R² = OMe, X = NH₂), which proved difficult to crystallise, was confirmed from its spectra. The amino group was observed in both the i.r. (3470 and 3370 cm⁻¹) and the n.m.r. (τ 6.70, exchanged with D₂O) spectra. The protons at C-7 and C-8 gave an AB quartet (τ 4.02 and 4.34, J 10 Hz). H-5 gave a singlet and the ketal function gave the usual pattern. The highly crystalline 14-aminocodeinone (23; R¹ = R² = O, X = NH₂) was obtained on acid hydrolysis of the ketal and the spectra were consistent with this structure. The protons at C-7 and C-8 gave the expected AB quartet and in addition the two protons at C-10 were observed. The 10α proton gave a quartet (τ 7.25, J 6 and 19 Hz) and the 10β proton
a doublet (γ 6.74, J 19 Hz) while the H-9 signal was probably beneath the N-CH₃ singlet. These values were similar to those obtained for 14-nitrocodeinone. Unlike the 14-N-arylamino-compounds which undergo rearrangement with base the amino-enone was more stable. After prolonged treatment with sodium methoxide in methanol the only reaction appeared to be addition of methanol to the double bond.

A variety of amino derivatives were made. Acetylation of the amino group with acetic anhydride-pyridine at room temperature gave 14-N-acetylamino-codeinone (23; R¹ = R² = 0, X = NHCOCH₃). Cinnamoyl chloride gave the corresponding N-cinnamoyl derivative (23; R¹ = R² = 0, X = COCH = CPh) and benzyl chloroformate gave the N-benzyloxycarbonyl compound (23; R¹ = R² = 0, X = COOCH₂Ph). The N-cyanoamino-derivative (23; R¹ = R² = 0, X = NHCN) was produced by heating under reflux the amino-ketone and cyanogen bromide in ethanol free chloroform. The precipitated product gave, after basification, material identical with an authentic sample prepared by an entirely different route. The spectra of all the amino derivatives were consistent with the expected structures. Reduction of the amino-ketone to 14-aminocodeine (23; R¹ = OH, R² = H, X = NH₂) was accomplished in good yield with sodium borohydride. The n.m.r. spectrum exhibited the typical codeine pattern with a doublet for H-5.
Section 3  **THE INDOLINOCODEINES**

Introduction

Conroy\textsuperscript{35} reported that reduction of 14\textbeta{}-bromocodeinone (23; \( R^1 = R^2 = 0, \ X = \text{Br} \)) with sodium borohydride first afforded 14\textbeta{}-bromocodeine (23; \( R^1 = \text{OH}, \ R^2 = \text{H}, \ X = \text{Br} \)) which was further reduced with the same reagent to neopine (24; \( R^1 = \text{OH}, \ R^2 = \text{H}, \ X = \text{H} \)). The reduction was subsequently investigated by Okuda et al.\textsuperscript{63} who isolated and identified two additional products namely isoneopine (24; \( R^1 = \text{H}, \ R^2 = \text{OH}, \ X = \text{H} \)) and indolinocodeine (32; \( R^1 = \text{OH}, \ R^2 = \text{H}, \ X = \text{H} \)). Indolinocodeine, arising by a new skeletal rearrangement of the morphine structure, represented a new class of compound containing the hydroindole system which provides the generic name.

The structure was elucidated from its i.r. and n.m.r. spectra and various chemical transformations.\textsuperscript{63,64} Hofmann degradation of the methiodide yielded a methine base, which was identical with the benzoate of\textbeta{}-codeimethine (33) prepared from neopine. Silver carbonate oxidation yielded the corresponding \( \alpha{}\beta{} \)-unsaturated ketone (32; \( R^1 = R^2 = 0, \ X = \text{H} \)) and catalytic hydrogenation gave the dihydro compound (34; \( R^1 = \text{OH}, \ R^2 = \text{H}, \ X = \text{H} \)), which produced the dihydro ketone (34; \( R^1 = R^2 = 0, \ X = \text{H} \)) on Oppenauer oxidation. The oxide ring of the dihydro ketone was opened with zinc dust and ammonium chloride in
refluxing ethanol. The ketophenol (35) thus obtained differed from both cis and trans-dihydrothebaine (35; 14\( \beta \) H or 14\( \alpha \) H), indicating the absence of a proton at C-14. The olefinic protons of the enone (32; \( R^1 = R^2 = 0, X = H \)) gave an AB quartet in the n.m.r. spectrum. The Japanese workers thus concluded from this evidence that the ethanamine chain was linked to the 14-position. The orientation of the hydroxy group in indolino-codeine was assigned as \( \alpha \) on the basis of the high field n.m.r. absorption (\( \tau \) 8.51) of its acetate (32; \( R^1 = OAc, R^2 = H, X = H \)), the acetoxy group being shielded by the aromatic ring. The aziridinium cation (37) was proposed as the intermediate in the reaction, indolino-codeine arising by nucleophilic attack at the less hindered C-9\( \alpha \) position.

In a further paper a fourth product from the sodium borohydride reduction of 14\( \beta \)-bromocodeine was isolated (0.4%) and characterised as 9\( \alpha \)-methoxy-indolino-codeine (32; \( R^1 = OH, R^2 = H, X = OMe \)). The chemical shifts of the 5\( \beta \) (\( \tau \) 5.57, \( J_{6\beta} \) 4.5 Hz) and 6\( \beta \) protons (\( \tau \) 5.83, multiplet) were similar to those observed for indolino-codeine (\( \tau \) 5.50 and 5.70, \( J = 4.4 \) Hz). This pattern is similar to codeine but the coupling constants are slightly
smaller. The signals due to 7-H and 8-H were respectively a double doublet and a doublet again indicating the absence of a proton at C-14. The 9\(\beta\) proton gave a quartet (\(\tau 6.48\)) with coupling constants (9\(\beta\)-10\(\alpha\), 3.0 Hz, and 9\(\beta\)-10\(\beta\), 2.0 Hz) in good agreement with the values expected for the corresponding dihedral angles measured by a Dreiding model. This eliminated the other possible isomeric 14-substituted structures (23; 14\(\alpha\)- or \(\beta\)-O-methyl group). The Japanese workers were subsequently able to improve the yield (20\%) of the methoxy compound and prepare other 9-substituted derivatives by solvolysis of 14\(\beta\)-bromocodeine.\(^{66}\) In this way 9\(\alpha\)-methoxy, hydroxy, and acetoxy derivatives were obtained. The methanolysis reaction also gave 7\(\beta\)-methoxyneopine (24; \(R^1 = OH, R^2 = H, X = OMe\)) as a by-product. This contrasts with solvolysis reactions of 14-bromocodeinone dimethyl ketal when 7-substituted neopinones are the major products (see section 2). The indolino-codeine series of compounds were reconverted to the morphine series by solvolysis of the mesylate of 6-deoxy-9\(\alpha\)-hydroxyindolino-codeine (32; \(R^1 = R^2 = H, X = \text{mesyl}\)) producing 9\(\alpha\)- and 7\(\beta\)-methoxy-desoxyneopines (24 and 25; \(R^1 = R^2 = H, X = \text{OMe}\)).\(^{67}\)

Several naturally occurring alkaloids have been
isolated which contain a C-13 - C-14 ethanamine bridge, e.g. hasubanonine (38)\textsuperscript{68} and metaphanine (39)\textsuperscript{69} from \textit{Stephania japonica} and cephamaine (40) from \textit{Stephania cepharantha}.\textsuperscript{70} All of the known natural products are of opposite absolute configuration to the indolinocodeines and lack the C-4 - C-5 oxygen bridge. Hasubanonine and metaphanine have been correlated structurally with the indolinocodeines by conversion into compound (41), the enantiomer being prepared from dihydroindolinocodeinone (34; R\textsubscript{1} = R\textsubscript{2} = 0, X = H). Wolff-Kishner reduction gave desoxodihydroindolinocodeinone (42), which on catalytic hydrogenation followed by O-methylation with Rodinow's reagent yielded the required enantiomer.\textsuperscript{68}
Results and Discussion

As the first step in an attempt to relate 7β-iodoneopinone dimethyl ketal (24; R₁ = R₂ = OMe, X = I) with the known 7-oxoneopinone dimethyl ketal (24; R₁ = R₂ = OMe, XH = 0) it was treated with silver acetate in glacial acetic acid at room temperature overnight. The n.m.r. spectrum of the major product (33%), separated by chromatography, differed significantly from the expected 7β-acetoxy-derivative. Instead of the characteristic AB quartet observed for H-7 and H-8 in 7-substituted neopinones the spectrum contained a two-proton singlet (τ 4.17), a one-proton triplet (τ 4.86) and a one-proton singlet (τ 5.48). 9α-Acetoxy-indolinocodeinone dimethyl ketal (32; R₁ = R₂ = OMe, X = OAc) was considered the most likely product after examination and comparison of the spectrum with the other known 9-substituted indolinocodeines. The isomeric 14-acetoxycodeinone dimethyl ketal (23; R₁ = R₂ = OMe, X = OAc) was ruled out because of the presence of the triplet at relatively low field. The spectrum was interpreted as follows. The two proton singlet was due to the olefinic signals' coalescing, the other singlet was attributed to H-5 and the 9β proton was considered to give a triplet by coupling with both the C-10 protons.
In addition, one methoxy group of the ketal gave a high field (τ 7.05) singlet because of shielding by the double bond and the acetyl singlet was also at high field (τ 8.24) indicating shielding by the aromatic nucleus and thus suggesting an α configuration. Further evidence for the structure was obtained by the quantitative formation of an enone (32; \( R^1 = R^2 = OAc, X = OAc \)), τ 3.28 and 3.80 (AB quartet, J 11 Hz, H-7 and H-8) and 4.78 (double doublet, J 2.2 and 3.5 Hz, H-9β), on hydrolysis with cold dilute hydrochloric acid. For the 9β proton the coupling constants (9β-10α and 9β-10β) were in good agreement with the values expected from the corresponding dihedral angles measured from a Dreiding model and also agreed with the values obtained by the Japanese workers.65

Nucleophilic attack on the iodide leading to 9-substituted indolinocodeinones represented a new rearrangement reaction of the morphine alkaloids. Compounds of this type had previously been obtained from solvolytic reactions of 14-bromocodeine but yields were not very high (20%). Only oxygen substituents (OH, OMe, and OAc) had been introduced at C-9 and the stereochemistry at C-6 and C-9 was based on spectroscopic evidence. The following four objectives were therefore set out:
(i) to introduce nitrogen, carbon, sulphur, and halogen, in addition to oxygen, substituents at C-9,

(ii) to prepare the 9-keto-compound and thereby prove that the substituent was attached to C-9 and not C-10,

(iii) to prepare the 9,10-dehydro-compound thus proving that the nitrogen bridge was attached to C-14 and not C-9, and

(iv) to prove that the 9-substituent had the α and not the β configuration.

The preparation of the 9-keto-compound proved difficult. The acetoxy ketal (32; R1 = R2 = OMe, X = OAc) was quantitatively hydrolysed with base to give 9α-hydroxyindolinocodeinone dimethyl ketal (32; R1 = R2 = OMe, X = OH), which resisted Oppenauer oxidation. Hydrolysis of the ketal function with acid gave quantitatively the hydroxy-enone (32; R1 = R2 = O, X = OH), which was also unreactive towards both chromium trioxide and Pflederer-Moffat oxidation. The hydroxy-enone could not be prepared from the acetoxy-enone; base caused breakdown of the starting material. However acetylation of the hydroxy-enone gave the acetoxy-enone in good yield. Because the unsaturated 9α-hydroxy compounds could not be oxidised to the corresponding ketone,
9α-hydroxydihydroindolinocodeinone (34; R^1 = R^2 = 0, X = OH), prepared in excellent yield by catalytic hydrogenation of the enone, was used as an alternative starting material. Oppenauer oxidation using benzophenone and potassium t-butoxide gave the oily diketone (34; R^1 = R^2 = 0, XH = 0) in poor yield (10%). The compound could not be completely purified but the frequency (1706 cm\(^{-1}\)) for the carbonyl absorption in the i.r. spectrum confirmed a C-9 rather than a C-10 ketone and the n.m.r. spectrum was also simplified lacking both the 9β and hydroxy proton signals. For comparison, prometaphanine (43) gives the corresponding 10-ketone on manganese dioxide oxidation and the carbonyl absorption (1680 cm\(^{-1}\)) is in the expected region for an α,γ-unsaturated ketone. 71

9α-Acetoxydihydroindolinocodeinone (34; R^1 = R^2 = 0, X = OAc) prepared from both the acetoxyenone and the hydroxydihydro-compound was readily hydrolysed with base to give the 9α-hydroxydihydro-derivative showing that the conjugated system was responsible for the instability of the acetoxyenone in base. Sodium borohydride reduction of 9α-hydroxyindolinocodeinone gave in good yield 9α-hydroxyindolinocodeine (32; R^1 = OH, R^2 = H, X = OH), whose physical and spectroscopic properties

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were identical with those reported in the literature. The reduction, like that of codeinone derivatives, was stereospecific giving only one product. The above reactions are summarised in Scheme 1 (page 63). The reaction of the iodide with silver acetate in glacial acetic acid gave in addition to the 9α-acetoxy-derivative a small amount of the unknown isomeric 14β-acetoxycodeinone dimethyl ketal (23; \( R^1 = R^2 = \text{OMe}, X = \text{OAc} \)). The low yield was partly due to separation difficulties. The product was identified by the similarity of the n.m.r. spectrum with those of other 14-substituted codeinones and by acid hydrolysis to the well documented 14β-acetoxycodeinone (23; \( R^1 = R^2 = 0, X = \text{OAc} \)). Acetolysis of the iodide was also achieved in good yield using sodium acetate in aqueous dimethylformamide at room temperature. Prolonged treatment of 7β-iodoneopinone dimethyl ketal with sodium methoxide in methanol afforded (25%) \( \Delta^9 \)-indolinocodeinone dimethyl ketal (44; \( R^1 = R^2 = \text{OMe} \)). The proton signals for H-7 and H-8 occurred as an equivalent singlet (\( \tau 4.22 \)) while H-9 and H-10 gave an AB quartet (\( \tau 3.61 \) and 4.34, \( J 10 \text{ Hz} \)). Both the i.r. and u.v. spectra supported the styrene structure. The attachment of the nitrogen bridge was thus proved to be at
C-14 and not C-9. Acid hydrolysis as usual gave the corresponding enone (44; $R^1 = R^2 = 0$) the n.m.r. spectrum of which contained two AB quartets.

Reaction of the iodo-compound with sodium cyanide in aqueous dimethylformamide gave two products. The major (56% yield from the iodide) and least polar on t.l.c. was, as expected, $\beta\alpha$-cyano indolinocodeinone dimethyl ketal (32; $R^1 = R^2 = \text{OMe}$, $X = \text{CN}$), $\nu_{\text{max.}}$ 2238 cm$^{-1}$, while the minor component was identified as $\alpha\beta$-indolinocodeinone dimethyl ketal. It was possible that epimerisation at C-9 could have taken place during the course of the reaction because of the acidic nature of the $\beta\alpha$ proton. However no deuterium incorporation was observed when the reaction was repeated using dry dimethylformamide-deuterium oxide as solvent.

The cyano group was resistant to both acid hydrolysis (the ketal function was cleaved) and base hydrolysis, oxidation with hydroperoxide, and reduction with lithium triethoxyaluminium hydride. Reduction with lithium aluminium hydride gave the oily amino-derivative (32; $R^1 = R^2 = \text{OMe}$, $X = \text{CH}_2\text{NH}_2$).

In contrast to the reaction with sodium cyanide, $\alpha\beta$-isocyanoidolinocodeinone dimethyl ketal (32; $R^1 = R^2 = \text{OMe}$, $X = \text{NC}$), $\nu_{\text{max.}}$ 2140 cm$^{-1}$
was obtained as the major product (28%) on treatment of the iodide with silver cyanide in anhydrous acetone. The reactions of the iodide with cyanide thus satisfy the theory that use of silver ions promotes attack by the more electronegative atom of the ambident nucleophile. The isocyanoketal, the least polar component, was separated from the crude reaction mixture by column chromatography; the remainder of the mixture consisted of a large number of inseparable products. The formamidono-ene (32; R₁ = R₂ = 0, X = NHCHO), produced by acid hydrolysis of the isonitrile could not be further converted into the 9-amino-compound using more vigorous conditions. A side product of this reaction was 9α-methoxyindolocodeinone (32; R₁ = R₂ = 0, X = OMe), the ketal of which was also obtained from the iodide in low yield (4.3%) by refluxing with methanol. The 9-amino-ene was required for reduction to the 9-amino-alcohol to provide the possibility of linking the 6α and 9α positions and thus confirming the stereochemistry of both centres. An alternative route to the amino-alcohol was therefore devised.

Treatment of 7β-iodoneopinone dimethyl ketal with sodium acetate or sodium cyanide in aqueous dimethylformamide had given 9α-acetoxy or 9α-
cyanoidolinocodeinone dimethyl ketal in good yield. Treatment of the iodide with sodium azide in the same solvent gave 9α-azidoindolinocodeinone dimethyl ketal (32; R₁ = R² = OMe, X = N₃), ν_max 2105 cm⁻¹, in equally good yield (59%). The minor and more polar component was identified as 7α-azidoneopinone dimethyl ketal by comparison of the n.m.r. spectrum with those of other 7-substituted neopinones, by the presence of an azide group, ν_max 2105 cm⁻¹, and by analysis as the crystalline picrate. 9α-Azidoindolinocodeinone dimethyl ketal was converted into the 9-amino-compound with an excess of lithium aluminium hydride in ether under reflux. The product, 9α-aminoindolinocodeinone dimethyl ketal (32; R₁ = R² = OMe, X = NH₂), on formylation with acetic anhydride and formic acid gave the same formamide-derivative derived from acid hydrolysis of the 9α-isocyanoidolinocodeinone dimethyl ketal. No identifiable product was obtained from the acid hydrolysis of the amino-ketal. Acid hydrolysis of the azido-ketal gave the expected enone (32; R₁ = R² = O, X = N₃) which on reduction with lithium aluminium hydride yielded a mixture of two inseparable compounds. From the spectra of the total product one component appeared to be the required amino-6α-alcohol (32; R₁ = OH, R² = H, X = NH₂)
and the other the 6β epimer. This result was surprising in view of earlier work on the reduction of codeinone derivatives when the reaction always proceeded stereospecifically to give only 6α products.\textsuperscript{72}

The problem was overcome by reducing the azido-ketone with sodium borohydride to give only the 6α alcohol (32; $R^1 = \text{OH}, R^2 = \text{H}, X = \text{N}_3$) and then conversion of the azido group into the amino group with lithium aluminium hydride. The n.m.r. spectrum of the azido-alcohol was interpreted as follows. The proton at C-5 gave a doublet ($\tau 5.56$, $J_{6\beta} 4.0$ Hz, cf., codeine), H-6 a multiplet which simplified to a double doublet on deuteration ($\tau 5.84$, $J_{\text{OH}} 10$, $J_{6\beta} 4.0$ and $J_7 6.0$ Hz), H-7 a quartet ($\tau 3.61$, $J_{6\beta} 6.0$ and $J_8 10.0$ Hz), and H-8 a doublet ($\tau 4.05$, $J_7 10$ Hz). The spectrum of the amino-alcohol was almost identical and that of the 9α-hydroxy-alcohol (mentioned above) was similar. The coupling constants were in good agreement with the values expected from the observed (Dreiding model) dihedral angles and with the values quoted by the Japanese workers.\textsuperscript{65,66}

Acetylation of the amino-alcohol with acetic anhydride-pyridine at room temperature overnight afforded a mixture of the $N$-acetyl-derivative (32; $R^1 = \text{OH}, R^2 = \text{H}, R^3 = \text{NHAc}$) and the diacetate (32; $R^1 = \text{OAc}, R^2 = \text{H}, R^3 = \text{NHAc}$). After work-up with
base only the N-acetyl compound remained. Under
more vigorous conditions, refluxing for three hours,
the diacetate was produced. The n.m.r. spectra of the
acetates were very complicated. The diacetate re-
tained a doublet for H-5 (τ 5.44, J_{6β} 5 Hz) and as
expected a quartet for H-6β appeared at lower field.
The olefinic pattern was not interpretable. The
monoacetate possessed two groups of complex signals.
One group (τ 3.42-4.05) arose from H-7, H-8 and
N-H, the other (τ 5.40-5.80) from H-5, H-6β and
H-9β. In addition H-5 gave a singlet. The acetyla-
tion reaction showed that it was possible to prefer-
tentially attach groups to the amino function. A
Dreiding model confirmed that bridging or group
transfer was easily possible between the 6α and 9α
positions and the formamido álcohol (32; R^1 = OH,
R^2 = H, X = NHCHO) was initially considered for
this purpose. In acid solution it was hoped that
a cyclic intermediate would be formed resulting in
the transfer of the formyl group from C-9 to C-6.

Reduction of the formamido-enone with sodium
borohydride gave a mixture of two products. After
separation, the major product appeared to be the
6β álcohol, i.e. 9α-formylandinoindolinoisocodeine
(32; R^1 = H, R^2 = OH, X = NHCHO) and the minor pro-
duct the required álcohol. The n.m.r. spectrum of
the major alcohol showed H-5 to absorb as a doublet (\( \tau 5.72, J_{6\alpha} 8.0 \text{ Hz} \)) and the olefinic protons as an equivalent singlet. The coupling constant (5\( \beta \)-6\( \alpha \)) was similar in value (8.5 Hz) to that obtained by the Japanese workers for 6\( \beta \)-chloro-compounds.\(^6\)\(^7\) The difference observed in coupling constants for H-5\( \beta \) between the isocodeine and indolinoisocodeine systems is due to different ring shapes, although similar values are obtained for codeine and indolinoisocodeine derivatives. It was not possible to assign a unique conformation to ring C for the alcohols from the n.m.r. spectra. From the coupling constants the ring shape appeared to be dependent on the substituents at C-9 and C-6, i.e. a bad interaction caused a change of conformation. The situation was further confused by the possibility of ring B's existing in two conformations. 9\( \alpha \)-Formylaminoin dolinoisocodeine (32; \( R^1 = \text{OH}, R^2 = \text{H}, X = \text{NHCHO} \)) was however prepared by formylation of the amino-alcohol and was identical to the minor component from the reduction of the formamido-enone. Transfer of the formyl group with acid catalysis was not observed despite several attempts under varying conditions. Cyclisation of the \( N \)-methoxycarbonyl compound (32; \( R^1 = \text{OH}, R^2 = \text{H}, R^3 = \text{NCOOCH}3 \)) was considered an alternative procedure. This type of reaction has been used by
Rapoport\textsuperscript{73} to join a 10\(\beta\)-hydroxy group to an N-methoxycarbonyl group in 10\(\beta\)-hydroxy-N-methoxycarbonylnorcocaine (45). The N-methoxycarbonyl derivative, prepared from the amino-alcohol with an excess of methyl chloroformate, was only obtained in moderate yield because the reaction could not be forced to completion. Attempts to cyclise the product with sodium methoxide in benzene or xylene failed. Attempts to link the 6\(\alpha\) and 9\(\alpha\) positions were therefore unsuccessful, but the \(\alpha\)-orientation of 9-substituents appears well established by n.m.r. spectroscopy. The above reactions are summarised in Scheme 2 (page 72).

The reaction of thebaine with iodine azide in dry acetonitrile or dimethylformamide was referred to in the previous section (see page 44). With equimolar quantities of reactants two products were formed in low yield and proved very difficult to separate by p.l.c. The least polar component could not be obtained pure but was always contaminated with some of the more polar material. The i.r. spectra on each of the products showed two azido groups and the n.m.r. spectra resembled that of 9\(\alpha\)-azidoindolinocodeinone dimethyl ketal but showed only one 6-methoxy signal. Because the 6-methoxy signal of the impure component was at relatively
Scheme 2
high field (τ 6.85), indicating a β orientation, it was tentatively assigned the structure 6α, 9α-
-diazidoindolinoisocodeine methyl ether (32; R¹ = N₂, R² = OMe, X = N₂). The methoxy signal of the pure
compound was in the normal position (τ 6.38) suggesting the structure 6β, 9α-diazidoindolino-
codeine methyl ether (32; R¹ = OMe, R² = N₂, X = N₂). The products were thus isomeric at C-6 and both
compounds when treated with dilute acid gave the same enone, identical in physical properties to
9α-azidoadindolinoisocodeinone. No satisfactory analysis on the pure component could be obtained (a common
difficulty with polyazido-compounds) and accurate mass measurement was not possible because the com-
 pound was too unstable in the mass spectrometer to give a molecular ion or any suitable ion at lower
m/e values. The products presumably arise by prior formation of 7β-iodo-6-azido-neopine and -isoneopine
methyl ethers followed by rearrangement to the 9-
azidoindolinoisocodeinone structure. When an excess
of reagent was used a third and major product was formed. The structure of this compound was not
determined.

The preparation of a 9α-Ο-mesyl derivative was reported by Abe et al. The possibility thus ex-
isted of obtaining 9β-substituents by SN₂ reactions
on the mesylate. In accord with the original work the \(\alpha\)-\(\gamma\)-tosyl-derivative could not be prepared but the hydroxy-enone reacted with mesyl chloride to give the \(\alpha\)-chloro-compound (32; \(R^1 = R^2 = 0, X = Cl\)) rather than the mesylate. The product was identified as the chloro compound from the mass spectrum. The n.m.r. spectra of the product also provided the best example of the pattern for the two C-10 protons. A Dreiding model showed that the dihedral angles between protons at 9-10\(\alpha\) and 9-10\(\beta\) were approximately equal. Thus H-9 gave a double-doublet (almost a triplet, \(\tau 5.90, J \approx 3.5 \text{ Hz}\)), H-10\(\alpha\) a quartet (\(\tau 6.55, J 3.5 \text{ and } 15 \text{ Hz}\)) and H-10\(\beta\) a similar quartet (\(\tau 7.15, J 3.5 \text{ and } 15 \text{ Hz}\)). These values were, as expected from models, different from those of 14-substituted codeinones. The so called "mesylate" reported by the earlier workers was not characterised but merely isolated as an unstable intermediate and may therefore also have been a chloro-compound.

Having fortuitously introduced a halogen substituent at C-9 the only other type of substituent we required, to complete our proposed range of derivatives, was a sulphur containing residue. Obligingly the iodo-compound with potassium thiocyanate in aqueous dimethylformamide gave \(\alpha\)-thiocyanatoindolinocodeinone dimethyl ketal (32; \(R^1 = R^2 = OMe, X = SCN\)), \(\nu_{\text{max}}\).
2145 cm$^{-1}$, in rather low yield (10%).

In order to provide access to other 9-substituted derivatives or improve yields of existing compounds a variety of other nucleophilic reactions were carried out on the iodide. Attempts to introduce fluorine in both aqueous and non-aqueous solvents were unsuccessful. Treatment of the iodide with potassium fluoride in aqueous dimethylformamide gave the 9α-hydroxycompound as the major product while, in dry dimethylformamide, the styrene ketal was obtained. The hydroxy ketal was also isolated as the major product from reactions with sodium chloride, potassium cyanate and sodium nitrite in aqueous dimethylformamide. Silver nitrite in acetone on the other hand gave a mixture of 9α-nitritoindolinocodeinone dimethyl ketal (32; $R_1 = R_2 =$ OMe, $X =$ ONO) and the hydroxy ketal. The yield of the nitrite was very low mainly because it was readily converted into the hydroxy ketal during isolation. In all the above reactions leading to the 9α-hydroxy ketal yields were lower than in the preparation via the 9α-acetoxy ketal, but the number of stages was less. The styrene ketal was obtained as the major product from the reaction of the iodide with sodamide in dry dimethylformamide. This reaction afforded both an improvement in yield (30%) and separation of the product compared with the
previous method. Sodium hydroxide in dimethylformamide
gave an inseparable mixture of the styrene ketal and
9α-dimethylaminooindolino codeinone dimethyl ketal \((32; R^1 = R^2 = OMe, X = NMe_2)\). The latter compound was
identified from the n.m.r. spectrum of the reaction
mixture and had arisen from the breakdown of the solv­
ent with strong base. The structure was confirmed
by its preparation free from the styrene ketal by
treatment of the starting material with dimethylamine
in dimethylformamide. Finally, the iodide was re­
covered unchanged after refluxing with anhydrous
potassium iodide in acetone for several hours.

Viebbeck et al. reported\(^4\) that methanalysis of
14-bromocodeinone dimethyl ketal \((23; R^1 = R^2 = OMe, \ X = Br)\) in the presence of 1 equivalent of sodium
carbonate gave a mixture of 7-methoxyneopinone di­
methyl ketal \((24; R^1 = R^2 = X = OMe)\) and 14-methoxy­
codeinone dimethyl ketal \((23; R^1 = R^2 = X = OMe)\).
The products, inseparable on t.l.c., were separated
by refluxing the mixture in ether with methyl iodide
when the 7-methoxy-compound was quaternised and pre­
cipitated out of solution while the 14-methoxy­
derivative remained in solution as the free base.
The structure of both compounds was then based on
the products of Hofmann degradation which were ex­
amined by u.v. spectroscopy. In addition, the 14-
methoxy ketal was hydrolysed to the corresponding enone with strong acid. The melting points quoted for both the 14-methoxy ketal and enone were identical to the values obtained in the present work for 9α-methoxyindolinocodeinone dimethyl ketal and the parent enone. Solvolysis of 14-bromocodeinone dimethyl ketal with methanol-sodium carbonate was therefore reinvestigated. The reaction was repeated under similar conditions and the melting point, mixed melting point and the n.m.r. spectrum of the so-called 14-methoxy ketal were found to be identical with those of the 9α-methoxy ketal. Quaternisation of the 9α-methoxy ketal was probably prevented because of the proximity of the 6α-methoxy group to the nitrogen atom. Solvolysis of the 14-bromo ketal therefore gave a rearranged 9α-methoxy product and not the 14-substituted codeinone as stated in the literature. Moreover, solvolysis of 7-iodoneopinone dimethyl ketal under the same conditions gave the same yield of the 9α-methoxy ketal. The reaction also provided the first example of indolinocodeinones being obtained by solvolysis of the 14-bromo ketal. Previously only 14-bromocodeine (23; \(R^1 = \text{OH}, R^2 = \text{H}, X = \text{Br}\)) had been used as the precursor. Confirmation of the structure of 7-methoxyneopinone dimethyl ketal was not possible because of separation difficulties.
The Japanese workers proposed the following mechanism (see Scheme 3, page 80) for the formation of indolinocodeines from 14-bromocodeine (46; R\(^1\) = OH, R\(^2\) = H). Ionisation of bromine gives a C-14 cation (47; R\(^1\) = OH, R\(^2\) = H). Because the lone pair of the nitrogen atom and a vacant orbital at C-14 in the cation are located in a 1,3 diaxial relation then ready formation of a cyclic cation (48; R\(^1\) = OH, R\(^2\) = H) is expected. Nucleophilic attack at the least hindered C-9\(^ω\) position of the cyclic cation gives the 9\(^ω\)-substituted indolinocodeines (32; R\(^1\) = OH, R\(^2\) = H). It seemed reasonable that the conversion of 7\(^β\)-iodoneopinone dimethyl ketal (49) into 9- substituted indolinocodeinone dimethyl ketals (32; R\(^1\) = R\(^2\) = OMe) involved a similar intermediate (48; R\(^1\) = R\(^2\) = OMe). In this case initial removal of halogen was not necessary and a concerted mechanism to give the intermediate cation was possible, although a silver salt could assist in removal of halogen. This type of aziridinium intermediate would also account for the production of the styrene ketal and 7\(^β\)-azidoneopinone dimethyl ketal, since it was stereochemically unlikely that the 7-azide could arise from a direct SN\(_2\) displacement on the starting material. The 9\(^ω\)-chloro-compound referred to earlier was probably produced via a similar intermediate (48; R\(^1\) =
SCHEME 3
and this would account for the retention of configuration at C-9. In contrast, $\text{I}^\text{4-p}$-acetoxy-codeinone dimethyl ketal, isolated from the reaction of the iodo-compound with silver acetate, may arise from a cyclic intermediate involving the silver acetate, since attack on the aziridinium cation at C-14 would be expected to give a $\text{I}^\text{4-p}$- derivative. The existence of the intermediate was verified by reacting the iodide with silver perchlorate in benzene, i.e. under nonsolvolytic conditions. Immediately after filtration of the precipitated silver iodide the n.m.r. spectrum of the product was determined. The N-Me signal had moved to lower field merging with one of the 6-methoxy signals and the usual pattern for H-7 and H-8 in 7-substituted neopinones disappeared and was replaced by another AB quartet at lower field and typical of a 7,8 double bond. The aziridinium perchlorate was only moderately stable and could not be crystallised. The same intermediate was however obtained from $\text{I}^\text{4-p}$-bromocodeinone dimethyl ketal (46; $R^1 = R^2 = \text{OMe}$) and silver perchlorate. The isolated aziridinium cation gave a mixture of 9$\text{M}$-cyanoindolinocodeinone dimethyl ketal and the styrene ketal when treated with sodium cyanide in aqueous dimethylformamide and with sodium acetate in the same solvent gave the
usual 9α-acetoxy ketal as the major product. The aziridinium salt therefore had the properties required of the proposed intermediate. A similar cation has been proposed as an intermediate in the biosynthesis of the hasubanonine alkaloids.74
Experiments with animals usually give a fair guide to the potency of a drug in man but marked discrepancies sometimes occur, e.g. nalorphine is inactive in some animals as an analgesic but is as active as morphine in man. For some compounds, particularly those of intermediate or weak potency compared with morphine, the results may represent their depressant effects on the central nervous system (CNS) and not their analgesic actions. This can be checked by the use of an analgesic antagonist when the action of the compound should be reduced or abolished. The determination of analgesia involves giving groups of animals graded doses of the drug under test and, after a suitable time interval, determining the response of each animal to a stimulus. Dose-response curves are constructed and the dose producing analgesia in 50% of the animals is found (ED$_{50}$ value) and compared with that of a reference drug (e.g. morphine).

Two methods have been used to determine the analgesic activity of some of the compounds prepared in the present work. They are the Hendershot and Forsaith method (H. and F.)$^{76}$, which is used for weak analgesics and the Tail Pressure Test (T.P.)$^{77}$ used for more potent analgesics. The intraperitoneal
(i.p.) injection of mice with an aqueous solution of 2-phenyl-1,4-benzoquinone elicits a response (writhing) which is antagonised by the weaker analgesic agents. This provides the basis of the H. and F. test. Thus groups of animals are injected with different doses of the drug under test and some 25 min. later a benzoquinone solution is injected. The number of stretches (writhes) occurring in a given time is noted and compared with that of a control group. In the T.P. test the animal is injected with the drug and pressure is applied to the tail until the animal struggles and then squeaks. The animal is considered analgesed when its pain threshold is at least twice that of the mean control value. In both methods ED$_{50}$ values are determined and compared with those of reference compounds. The results are dependent upon the route of administration of the drug.

Morphine antagonist action is determined by injecting, at the same time but at different sites, morphine sulphate and the drug under test. After a suitable time interval the response to a stimulus is observed, e.g. the animal's tail is dipped into water at 55°C. Animals which do not respond are analgesed while those that do respond (in the example cited those that withdraw their tails before 5 seconds)
are not analgesed. Hence from a suitable graph the ED$_{50}$ for antagonism is obtained.

The 14-substituted codeinones along with derivatives of the Diels-Alder adducts of thebaine offer the most potent analgesics in the morphine-thebaine group. It was therefore of considerable importance to determine the analgesic activity of some of the 14-$N$-substituted compounds which had been prepared. The few 14-$N$-substituted derivatives that had been made earlier did show some analgesic activity, e.g., 14-hydroxylaminocodeinone hydrochloride had an ED$_{50}$ value (subcutaneous, s.c.) of 7 mg./Kg. (T.P.).

The results for 14-nitrocodeinone and some of the compounds derived from 14-aminocodeinone are given in the table at the end of this section. 14-Nitrocodeinone itself was inactive at low doses and toxic at higher doses. A more general CNS screen did not reveal any useful properties; the compound was inactive as a morphine antagonist. The parent amino-enone was, as expected, only of low activity while the $N$-acetyl compound was of similar potency to codeine and the $N$-cinnamoyl derivative 40 times as active as morphine. By comparison, in the corresponding 14-hydroxycodeinone series the parent compound is toxic, the $O$-acetyl derivative is 4 times and the $O$-cinnamoyl derivative 177 times as active as morphine.
These values were obtained from a tail-clip test and the compounds were given subcutaneously, but even so it is apparent that the cinnamoyl compound was highly active in both series.

Because of the large number of compounds available in the morphine group of alkaloids activity can often be predicted with some certainty. The structure-activity relationships are generally as follows: 80

(i) substitution in the aromatic ring—decreased activity.
(ii) conversion of the 3-0-methyl group into a 3-hydroxy group—increased activity.
(iii) fission of the ether ring—decreased activity.
(iv) hydrogenation of the 7,8 double bond—increased activity.
(v) a 6-keto group is desirable, although 6-CH₂ and 6-CH₂alkyl are equally active. 6-OH, -OR, and -OCOR groups cause decreased activity (the β isomer is usually more active than the α isomer).
(vi) an N-Me group gives optimum activity and N-H, N-alkyl (other than methyl) and N⁺-R₂, decreased activity. N-Allyl and N-cyclopropylmethyl groups cause morphine antagonism.

Thus the 14-H-substituted codeinones offer plenty of scope for structural modification in an attempt to
provide a useful analgesic. Demethylation of the 3-methoxy group would almost certainly markedly increase the potency as may reduction of the 7,8 double bond. Many 14-\(\text{N}\)-substituted derivatives could be made and the possibility of preparing 1'-disubstituted derivatives, i.e. 14-\(\text{N}\)R\(_2\), exists. Antagonists could probably be made in the usual way by conversion of the \(\text{N}\)-methyl group into \(\text{N}\)-allyl or \(\text{N}\)-cyclopropylmethyl, but there is the possibility of retaining the \(\text{N}\)-methyl group and attaching the allyl residue to the 14 position, i.e. of preparing 14-\(\text{N}\)-allylaminocodeinone (23; \(R_1 = R_2 = 0\), \(X = \text{NHCH}_2\text{CH} = \text{CH}_2\)).

In a series of patents certain indolinocodeine derivatives are claimed to possess analgesic and antitussive activity. Most compounds covered by the patents contain either a hydroxy group at the 6\(\alpha\) position or a halogen at the 6\(\beta\) position and there is no specific mention of 9\(\alpha\)-substituted derivatives. Coverage is also extended to include certain 7,8-dihydro substances and compounds containing a free phenolic group at the 3 position. It was therefore desirable to test certain of the 9\(\alpha\)-substituted indolinocodeinones, although it was unlikely that useful activity would be found because a C-9 to C-13 ethanamine bridge is considered essential for high activity. As can be seen from the table few compounds

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possessed any analgesic activity and even the most potent compounds, $9\omega$-acetoxyindolino-codeinone dimethyl ketal and the parent enone, were appreciably weaker than codeine. It should be noted that conversion of ketal to ketone made little difference to the activity. The acetoxy-ketone was completely inactive in a more general CNS screen. Because of the lack of activity it was not possible to extend the structure-activity relationship for the morphine alkaloids to the indolino-codeinone group. It would appear that the indolino-codeinones are of little value as analgesics or CNS active compounds.
<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>TEST</th>
<th>ROUTE</th>
<th>ED&lt;sub&gt;50&lt;/sub&gt; mg./Kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulphate (reference)</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>0.640 P&lt;sub&gt;95&lt;/sub&gt; 0.460-0.820</td>
</tr>
<tr>
<td>Codeine phosphate (reference)</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>5.6 P&lt;sub&gt;95&lt;/sub&gt; 3.2-8.0</td>
</tr>
<tr>
<td>Morphine sulphate (reference)</td>
<td>T.P.</td>
<td>s.c.</td>
<td>2.6 P&lt;sub&gt;95&lt;/sub&gt; 1.52-4.42</td>
</tr>
<tr>
<td>Codeine phosphate (reference)</td>
<td>T.P.</td>
<td>s.c.</td>
<td>13.5 P&lt;sub&gt;95&lt;/sub&gt; 11.3-16.2</td>
</tr>
<tr>
<td>14β-Nitrocodeinone</td>
<td>T.P.</td>
<td>i.p.</td>
<td>&gt;100</td>
</tr>
<tr>
<td>14β-Nitrocodeinone</td>
<td>H. and F.</td>
<td>p.o.</td>
<td>&gt;50 toxic at 100 mg./Kg.</td>
</tr>
<tr>
<td>14β-Aminocodeinone</td>
<td>H. and F.</td>
<td>p.o.</td>
<td>46 P&lt;sub&gt;95&lt;/sub&gt; 20-106</td>
</tr>
<tr>
<td>14β-Aminocodeinone</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>7 P&lt;sub&gt;95&lt;/sub&gt; 2.9-16.8</td>
</tr>
<tr>
<td>14β-N-Acetylamino codeinone</td>
<td>H. and F.</td>
<td>p.o.</td>
<td>11.5 P&lt;sub&gt;95&lt;/sub&gt; 4-33.4</td>
</tr>
<tr>
<td>14β-N-Acetylamino codeinone</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>4.5 P&lt;sub&gt;95&lt;/sub&gt; 1.96-10.35</td>
</tr>
<tr>
<td>14β-N-Cinnamoylamino codeinone</td>
<td>T.P.</td>
<td>i.p.</td>
<td>0.055 P&lt;sub&gt;95&lt;/sub&gt; 0.025-0.121</td>
</tr>
<tr>
<td>9α-Acetoxyindolinocodeinone dimethyl ketal</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>36 P&lt;sub&gt;95&lt;/sub&gt; 18.9-68.4</td>
</tr>
<tr>
<td>9α-Acetoxyindolinocodeinone</td>
<td>H. and F.</td>
<td>p.o.</td>
<td>28 P&lt;sub&gt;95&lt;/sub&gt; 14.0-56.0</td>
</tr>
<tr>
<td>Δ&lt;sup&gt;9&lt;/sup&gt;-Indolinocodeinone hydrochloride</td>
<td>H. and F.</td>
<td>s.c.</td>
<td>~100</td>
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</table>

continued
<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>TEST</th>
<th>ROUTE</th>
<th>ED$_{50}$ mg./Kg.</th>
</tr>
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<tbody>
<tr>
<td>9α-Hydroxyindolinocodeinone</td>
<td>H. and F.</td>
<td>s.c.</td>
<td>&gt;100</td>
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<tr>
<td>9α-Hydroxydihydroindolinocodeinone</td>
<td>H. and F.</td>
<td>s.c.</td>
<td>&gt;100</td>
</tr>
<tr>
<td>9α-Hydroxyindolinocodeine</td>
<td>H. and F.</td>
<td>s.c.</td>
<td>&gt;100</td>
</tr>
<tr>
<td>9α-Azidoindolinocodeinone dimethyl ketal</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>&gt;100</td>
</tr>
<tr>
<td>9α-Azidoindolinocodeinone</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>&gt;100</td>
</tr>
<tr>
<td>9α-Formylaminoindolinocodeinone</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>&gt;100</td>
</tr>
<tr>
<td>9α-Cyanoindolinocodeinone</td>
<td>H. and F.</td>
<td>i.p.</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Key:— H. and F. Hendershot and Forsaith method  
T.P. Tail Pressure test  
i.p. intraperitoneal administration  
s.c. subcutaneous administration  
p.o. parenterally administered  
P$_{95}$ 95% confidence limits
EXPERIMENTAL

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Ultraviolet spectra were obtained with a Unicam SP 800 spectrophotometer, infra-red spectra with either a Perkin-Elmer 237 or 257 spectrophotometer, n.m.r. spectra (60 MHz) with a Perkin-Elmer R-10 spectrometer, mass spectra with an A.E.I. M.S. 12 spectrometer and optical rotations with a Bendix automatic polarimeter. Unless otherwise specified, ultraviolet spectra were measured in methanol, infra-red spectra in chloroform, n.m.r. spectra in deuterochloroform using tetramethylsilane as internal standard and optical rotations in chloroform. Thin layer chromatograms were produced on alumina (0.25 mm. layer, Merck GF254) using a Dragendorf spray to develop the plate, which usually gave orange coloured spots. Although RF values are quoted they should only be regarded as approximate. Preparative layer chromatograms were also produced on alumina (0.50 mm. layer, Merck PF254). Neutral alumina ("Camag", grade III) was used for column chromatography. The solvents used were usually re-distilled and dried.
Dihydrothebaine-\(\beta\)\(^{11}\) (9). - Clean, thin slices of sodium (5.12 g.) were added to a stirred suspension of thebaine (32.0 g.) in liquid ammonia (320 ml.). After approximately 1 hour the transitory orange colour was finally replaced by a yellow-blue colour. The excess of sodium was destroyed by the addition of a few drops of alcohol and the solution was cautiously poured into cold water (350 ml.). A small amount of precipitate was formed (unreacted thebaine) and was filtered off under vacuum. Addition of solid carbon dioxide to the filtrate precipitated the phenolic base, which was then dissolved in ether (1½ l.). The extract was washed well to remove ammonia, dried (MgSO\(_4\)) and evaporated to give a pale pink crystalline residue. Recrystallisation from ethyl acetate-petroleum ether (60:80) gave dihydrothebaine-\(\beta\) (31.0 g., 96%) as white crystals, m.p. 151-153°C, (Lit.\(^{11}\) m.p. 154°C), \(R_f\) 0.30 (benzene-ethyl acetate, 4:1), \(\nu_{\text{max.}}\) 3510 (phenolic OH), 1708 and 1663 cm\(^{-1}\) (1,4-diene).

\(\beta\)-Acetyldihydrothebaine-\(\beta\)\(^{10}\) (9; \(\beta\)-acetyl). - Dihydrothebaine-\(\beta\) (31.0 g.) in dry pyridine (110 ml.) and acetic anhydride (19.2 ml.) was left at 0°C for 2 hours and then at room temperature overnight. The solvent was evaporated under reduced pressure and the residue shaken with sodium hydrogen carbonate and
extracted with chloroform. The extracts were dried (MgSO₄) and evaporated to give a red-brown syrup, which was chromatographed on alumina (1 Kg.). Elution with benzene-ethyl acetate (4:1) gave the desired O-acetate as an oil which did not crystallise (29.2 g., 83%), Rf 0.55 (benzene-ethyl acetate, 4:1), ν max. 1768 (O-acetate), 1705 and 1665 cm⁻¹ (1,4-diene).

Salutaridine.¹⁰ (10). - Freshly sublimed selenium dioxide (10.2 g.) in ethanol (30 ml.) and O-acetyl-dihydrothebaine-δ (29.2 g.) in peroxide free dioxan (500 ml.) were heated under reflux for 8 hours. Selenium (4.8 g.) was filtered off and the solvent evaporated in vacuo. The residue was treated with charcoal (10 g.) in refluxing benzene (400 ml.) and the resulting clarified solution filtered and evaporated. This residue in chloroform (400 ml.) was shaken with manganese dioxide (120 g., prepared by the method of Mancera et al.¹²) for 30 minutes at room temperature and then filtered through Celite and evaporated. The remaining brown material was heated under reflux in ethanol (240 ml.) containing yellow ammonium sulphide solution (8 ml.) for 2½ hours. After filtration through Celite the cooled solution was diluted with ethanol (160 ml.) and treated with 2N-sodium hydroxide solution (120 ml.) at room temperature overnight. The ethanol was
evaporated and the residue in water (400 ml.) washed with ether. The phenolic diene, precipitated by addition of excess solid carbon dioxide, was then extracted with chloroform (2 l.). The extract was dried (MgSO$_4$), evaporated and the residue chromatographed over alumina. Elution with benzene-ethyl acetate (1:1) gave salutaridine, which recrystallised from ethyl acetate as white crystals (4.0 g., 11.9% yield from thebaine), m.p. 198-199° (Lit. 197-198°), R$_f$ 0.41 (chloroform), $\nu_{\text{max}}$ 3540 (phenolic OH), 1673, 1643 and 1622 cm$^{-1}$ (dienone), $\tau$ 2.33 (1H, s, H-5), 3.30 (2H, s, aromatic), 3.53 (1H, s, OH, exchanges with D$_2$O), 3.60 (1H, s, H-8), 6.08 (3H, s, 3-OCH$_3$), 6.22 (3H, s, 6-OCH$_3$) and 7.55 (3H, s, N-CH$_3$).

7-Methylsalutaridinols-I and-II. (11 and 12; $R = \text{CH}_3$). - Methyl lithium was prepared by the standard procedure from methyl iodide and lithium metal and the strength of the solution was estimated by titration against standard acid. An ethereal solution of methyl lithium (1.1M., 3 ml.) was added to a solution of salutaridine (0.700 g.) in dried, redistilled tetrahydrofuran (60 ml.) and the mixture was heated under reflux for 9 hours with the addition of two further quantities (2 ml.) of methyl lithium after 3 and 6 hours. The solvents were removed under
reduced pressure and the residue was dissolved in water, neutralised with solid carbon dioxide and extracted with chloroform (2 x 50 ml.). The extract was dried (MgSO₄), evaporated and the residue (0.750 g.) chromatographed on alumina (40 g.). Elution with chloroform gave an inseparable mixture of 7-methylsalutaridinol-II and unreacted salutaridine (0.494 g.) and 7-methylsalutaridinol-I (0.100 g., 13.7%) as a pure component. Alcohol-I could not be crystallised, Rₚ 0.04 (chloroform), λ_max. 278 nm. (1850), ν_max. 3610 (OH), 3540 (OH), 1708 and 1660 cm⁻¹ (1,4-diene), τ 3.35 (2H, s, aromatic), 3.76 (1H, s, H-5), 4.31 (1H, s, H-8), 6.13 (3H, s, 3-OCH₃), 6.30 (3H, s, 6-OCH₃), 7.58 (3H, s, N-CH₃) and 8.65 (3H, s, 7-CH₃) m/e 343 (M+), 328, 326, 325, 312, 311 and 310.

The inseparable mixture was dissolved in methanol (50 ml.) and treated with sodium borohydride (1.062 g.) at 0°C with stirring. After 2 hours at 0°C and 2 hours at room temperature the solvent was evaporated and the residue shaken with water and chloroform. The chloroform extract was dried (MgSO₄) evaporated and the residue chromatographed on alumina (25 g.). Elution with chloroform afforded crystalline 7-methylsalutaridinol-II (0.310 g.) and salutaridinols -I and -II as separate components. 7-Methylsalutaridinol-II was recrystallised with difficulty from
benzene as fine white needles (0.17 g., 23%), m.p. 124-125°C, R F 0.26 (chloroform), \( \lambda_{\text{max}} \) 287 nm. (2430) and (\( \text{CF}_3 \text{COOH/H}_2\text{SO}_4 \), 2% v/v) 419 nm. (10,100), \( \nu_{\max} \) 3590 (OH), 3530 (OH), 1703 and 1659 cm\(^{-1}\) (1,4 diene), T 3.36 (2H, s, aromatic), 3.68 (1H, s, H-5), 4.35 (1H, s, H-8), 6.16 (3H, s, 3-OCH\(_3\)), 6.36 (3H, s, 6-OCH\(_3\)), 7.63 (3H, s, N-CH\(_3\)) and 8.52 (3H, s, 7-CH\(_3\)), m/e 343 (M\(^+\)), 328, 326, 325, 312, 311 and 310. (Accurate mass measured 343.1775. \( \text{C}_{20}\text{H}_{25}\text{N} \text{O}_4 \) requires 343.1784).

Salutaridinol-II was obtained as an oil while salutaridinol-I gave white crystals from ethyl acetate m.p. 223-225°C (Lit.\(^{10}\) m.p. 223-225°C), \( \lambda_{\text{max}} \) 288 nm. (2275) and (\( \text{CF}_3 \text{COOH/H}_2\text{SO}_4 \), 2% v/v) 420 nm. (12,300).

7-Phenysalutaridinols-I and -II (11 and 12; R = Ph) were similarly obtained from salutaridine (164 mg.) and phenyl lithium, but in this case all the starting material was consumed and the sodium borohydride reduction was not necessary. 7-Phenylsalutaridinol-I was obtained as an oil which would not crystallise (20 mg., 9.4%), R F 0.06 (chloroform), \( \lambda_{\text{max}} \) 283 nm. (3080), \( \nu_{\max} \) 3600 (OH), 3540 (OH), 1703 and 1662 cm\(^{-1}\) (1,4 diene), T 2.6-2.95 (5H, m, 7-phenyl), 3.05-3.40 (2H, m, aromatic), 3.60 (1H, s, H-5), 4.32 (1H, s, H-8), 6.12 (3H, s, 3-OCH\(_3\)), 6.42 (3H, s, 6-OCH\(_3\)) and 7.58 (3H, s, N-CH\(_3\)).

7-Phenylsalutaridinol-II (142 mg., 70%) was re-
crystallised from benzene several times to give a white crystalline solvate, m.p. 193-193.5°C, \( R_f \) 0.46 (chloroform), \( \lambda_{\text{max}} \) 288 nm. (1950) and (CF\(_3\)COOH/H\(_2\)SO\(_4\), 2% v/v) 399 (8860) and 430 nm. (9600), \( \psi_{\text{max}} \) 3595 (OH), 3540 (OH), 1703 and 1662 cm\(^{-1}\) (1,4-diene), \( \tau \) 2.5-2.8 (6H, m, H-5 and 7-phenyl), 3.36 (2H, s, aromatic), 4.42 (1H, s, H-8), 6.16 (3H, s, 3-OCH\(_3\)), 6.32 (3H, s, 6-OCH\(_3\)) and 7.70 (3H, s, N-CH\(_3\)), m/e 405 (M\(^+\)), 390, 388, 387, 374, 373 and 372. (Found: C, 75.82; H, 6.85; N, 3.19. \( C_{25}H_{27}NO_4 \) requires C, 75.84; H, 6.76; N, 3.15\%).

**6-Desoxy-6β-chlorocodeine.**\(^{15} \) (17; \( R^1 = H, R^2 = Cl \) - Thionyl chloride (64 ml., purified by distillation from quinoline) was added slowly with intermittent shaking to anhydrous codeine (5.20 g.) with cooling in ice. The mixture was allowed to stand at room temperature for 1 hour. The excess thionyl chloride was removed rapidly under vacuum to produce a yellow syrup, which was dissolved in ice-water (1 l.) and the resulting solution was neutralised with sodium carbonate and extracted with ether. The extract was dried (MgSO\(_4\)) and evaporated to yield a white crystalline product (4.55 g.), which was a mixture of three compounds. The mixture was separated by column chromatography on alumina (250 g.) using benzene-chloroform (1:1) as solvent.
6-Desoxy-6\textsuperscript{\textgreek{p}}-chlorocodeine (2.40 g., 46\%) and 8-desoxy 6\textsuperscript{\textgreek{p}}-chloropseudocodeine (0.27 g., 5.1\%) were obtained as pure components, while the third product, 6-desoxy-1, 6\textsuperscript{\textgreek{p}}-dichlorocodeine, was mixed with some 6-desoxy-6\textsuperscript{\textgreek{p}}-chlorocodeine. Separation of the latter mixture (0.41 g.) was achieved by repeated p.l.c. using benzene-chloroform (1:1) as solvent. The very low yield of dichloro compound (0.038 g.) indicated the difficulty of separation. 6-Desoxy-6\textsuperscript{\textgreek{p}}-chlorocodeine recrystallised from methanol as glassy prisms, m.p. 151-152\(^\circ\)C (Lit. 15 m.p. 151-153\(^\circ\)C), \(R_F\) 0.72 (benzene-chloroform, 1:1), \(\tau\) 3.38 (2H, s, aromatic), 4.02 (1H, m, \(J_8\) 10, \(J_6\)\(\alpha\) 6 and \(J_{14}\) 2 Hz, H-7), 4.38 (1H, q, \(J_7\) 10 and \(J_{14}\) 2 Hz, H-8), 4.96 (1H, s, H-5), 5.48 (1H, d, \(J_6\) 6 Hz, H-6), 6.18 (3H, s, 3-0CH\(_3\)) and 7.56 (3H, s, N-CH\(_3\)). 8-Desoxy-8\textsuperscript{\textgreek{p}}-chloropseudocodeine was obtained as an oil which did not crystallise, \(R_F\) 0.51 (benzene-chloroform 1:1), \(\tau\) 3.30 (2H, s, aromatic), 4.0-4.3 (2H, m, H-6 and H-7), 4.98 (1H, q, \(J_6\) 3.0 and \(J_7\) 1.5 Hz, H-5), 6.03 (1H, m, H-8), 6.14 (3H, s, 3-0CH\(_3\)), 6.45 (1H, m, H-9) and 7.56 (3H, s, N-CH\(_3\)). 6-Desoxy-1,6\textsuperscript{\textgreek{p}}-dichlorocodeine recrystallised from petroleum-ether (40:60) as white crystals, m.p. 115-115.5\(^\circ\)C, \(R_F\) 0.80 (benzene-chloroform, 1:1), \(\tau\) 3.30 (1H, s, H-2), 4.02 (1H, m, H-7), 4.40 (1H, q, \(J_7\) 10 and \(J_{14}\) 2 Hz, H-8), 4.98 (1H, s, H-5), 5.50 (1H, d, \(J_6\) 6 Hz, H-6), 6.18 (3H, s, 3-0CH\(_3\)) and
7.56 (3H, s, N-CH₃), m/e 355, 353, 351 (all M⁺), 318 and 316.

6-Chlorodesoxycodine-A (20) - Potassium t-pentoxide (0.400 g., prepared from potassium metal and t-amyl alcohol) was added to a stirred solution of 6-desoxy-6p-chlorocodeine (0.935 g.) in dry benzene (50 ml.) contained in a dry, carbon dioxide free nitrogen atmosphere. The mixture was heated under reflux for four hours. The solvent was evaporated, water was added to the residue and the resulting solution was neutralised with solid carbon dioxide and extracted with chloroform (2 x 25 ml.). The extract was dried (MgSO₄) and evaporated to give a brownish residue (1.069 g.). Column chromatography on alumina (75 g.) eluting with benzene-chloroform (1:1) gave the major product, 6-chlorodesoxycodine-A, as an oil which darkened considerably on standing for several days (0.350 g., 37%), Rf 0.42 (benzene-chloroform, 1:1), λ_max 279 nm. (4350), υ_max 3540 cm⁻¹ (phenolic OH), τ 3.34 and 3.42 (2H, ABq, J 8 Hz aromatics), 3.34-3.42 (1H, obscured by aromatics, H-5), 4.05-4.35 (2H, m, H-7 and H-8), 6.20 (3H, s, 3-OCH₃) and 7.62 (3H, s, N-CH₃), m/e 319, 317 (M⁺), 302, 289, 282 and 178 (Accurate mass measured 317.1187. C₁₈H₂₀Cl₁₈NO₂ requires 317.1183).

6-Chlorodesoxycodine-A picrate was obtained as
yellow crystals from ethanol, m.p. 148-149°C (decomposes) (Found: C, 52.89; H, 4.29; N, 10.41. 

C_{18}H_{20}ClNO_2⋅C_6H_3N_3O_7 requires C, 52.70; H, 4.21; N, 10.25%).

6-Chlorodesoxycodeine-A acetate (20; O-acetylated) was obtained as an oil from 6-chlorodesoxycodeine-A in the usual manner, R_p 0.49 (benzene-chloroform, 1:1),  

\[ \text{\textit{UV}}_{\text{max}} \text{1765 cm}^{-1} (\text{O-acetyl}), \text{\textit{MS}} 3.20 (2\text{H}, \text{s}, \text{aromatic}), 3.88 (1\text{H}, \text{s broad}, \text{H-5}), 4.05-4.38 (2\text{H}, \text{m}, \text{H-7 and H-8}), 6.28 (3\text{H}, \text{s}, 3-\text{OCH}_3), 7.62 (3\text{H}, \text{s}, \text{N-CH}_3) \text{and} 7.70 (3\text{H}, \text{s}, \text{CH}_3\text{CO}).

Codeine Tosylate \textsuperscript{33} (17; R^1 = OTs, R^2 = H). - An ice cold solution of tosyl chloride (2.44 g.) in pyridine (2.1 ml.) was added to a solution of anhydrous codeine (3.49 g.) in pyridine (3.5 ml.) at 0°C. The mixture was maintained at 0°C for 4 hours, poured into iced-water and stirred rapidly. Addition of conc. ammonium hydroxide solution gave a pink precipitate which was filtered off, washed thoroughly with water and dried under vacuum over phosphorus pentoxide. Recrystallisation from methyl ethyl ketone gave pink crystals of codeine tosylate (4.85 g., 92%), m.p. 120-121°C (Lit.\textsuperscript{33} m.p. 121-121.5°C), \textit{MS} 2.10 and 2.61 (4\text{H}, \text{ABq}, \text{tosyl group}), 3.38 (2\text{H}, \text{s}, \text{aromatic}), 4.30-4.64 (2\text{H}, \text{m}, \text{H-7 and H-8}), 4.65-4.80 (1\text{H}, \text{m}, \text{H-6\text{p}}), 5.10 (1\text{H}, \text{s}, \text{H-5}), 6.18 (3\text{H}, \text{s}, 3-\text{OCH}_3), 7.48
(3H, s, -CH₃) and 7.56 (3H, s, -CH₃).

Isocodeine Acetate. (17; R¹ = H, R² = OAc). -
Cetyl trimethyl ammonium bromide (4.0 g.) was dissolved in ethanol and added to a suspension of silver acetate (1.8 g.) in ethanol (20 ml.). The mixture was shaken for a few hours in the absence of light and filtered through Celite to remove silver bromide. The ethanol was evaporated to yield a yellowish residue, cetyl trimethyl ammonium acetate, which gave a negative silver nitrate test for halogen, \( \nu_{\text{max}} \ 1575 \text{ cm}^{-1} \) (acetate). The reagent (4.28 g.) in dry benzene (20 ml.) was added to a solution of codeine tosylate (4.78 g.) in dry benzene (20 ml.) and the mixture was allowed to shake at room temperature for 6 hours. Water (50 ml.) was added to the mixture and the organic layer separated (by centrifuging) and washed with water (2 x 50 ml.). The solvent was evaporated and the residue dissolved in chloroform was percolated through alumina to remove polar material. Evaporation of the solvent gave isocodeine acetate (3.10 g., impure) as a viscous oil which did not crystallise, \( R_F \ 0.60 \) (benzene-chloroform, 1:3), \( \nu_{\text{max}} \ 1740 \text{ cm}^{-1} \) (acetate), \( \tau \ 3.40 \) and 3.46 (2H, ABq, \( J \ 8.5 \text{ Hz} \), aromatics), 4.06 (1H, m, H-7), 4.40 (1H, q, \( J \ 7.10 \text{ Hz and J} \ 14 \ 2 \text{ Hz, H-8}) \), 4.86 (1H, d, \( J \ 6 \text{ Hz, H-6}) \), 5.25 (1H, s, H-5), 6.23 (3H, s, 3-CH₃), 7.62 (3H, s, N-CH₃) and 8.02 (3H, s, CH₂CO).
Isocodeine. (17; \( R^1 = H, R^2 = \text{OH} \)). - Isocodeine acetate (3.10 g., impure) was dissolved in ethanol (75 ml.) - water (15 ml.) and 2N-sodium hydroxide (38 ml.) was added. The solution was shaken at room temperature for 18 hours, neutralised with solid carbon dioxide, evaporated to dryness and the residue dissolved in chloroform - water. The chloroform layer was separated, dried (MgSO\(_4\)) and chromatographed over alumina (100 g.). Elution with chloroform gave isocodeine, which recrystallised from ethyl acetate as white crystals (1.75 g., 55% from codeine tosylate, 50% from codeine), m.p. 172\(^\circ\)C (Lit\(^\text{14}\) m.p. 171-172\(^\circ\)C), \( R_F \) 0.12 (chloroform), \( \tau \) 3.38 and 3.50 (2H, ABq, J 8 Hz, aromatics), 4.08 (1H, m, H-7), 4.45 (1H, q, J\(_7\) 10 and J\(_{14}\) 2 Hz, H-8), 5.25 (1H, s, H-5), 5.82 (1H, d, J 6 Hz, H-6), 6.20 (3H, s, 3-OCH\(_3\)), 6.29 (1H, s, OH, exchanges with D\(_2\)O) and 7.60 (3H, s, N-CH\(_3\)).

Catalytic hydrogenation. - The following general procedure was used for catalytic hydrogenations. The compound was dissolved in the minimum amount of methanol and hydrogenated at atmospheric pressure over a 10% palladium-charcoal catalyst. When the required volume of hydrogen had been consumed the catalyst was removed by filtration through Celite and the filtrate evaporated to give the dihydro compound.
Dihydrocodeine. (22; $R^1 = \text{OH}$, $R^2 = \text{H}$). - Anhydrous codeine (1.21 g.) gave dihydrocodeine as an oil which was crystallised with difficulty from water (0.80 g., 65%), white crystals m.p. 110-111°C (Lit. m.p. 112-113°C), $R_F$ 0.40 (chloroform, cf.: codeine = 0.34), $\tau$ 3.32 and 3.38 (2H, ABq, J 8 Hz, aromatics), 5.45 (1H, d, J 5 Hz, H-5), 6.18 (3H, s, 3-0CH$_3$), 6.38 (1H, s, OH, exchanges with D$_2$O) and 7.65 (3H, s, N-CH$_3$).

Dihydroisocodeine. (22; $R^1 = \text{H}$, $R^2 = \text{OH}$). - Isocodeine (0.598 g.) gave crystalline dihydroisocodeine (0.452 g., 76%), m.p. 205-206°C (from absolute alcohol; Lit. m.p. 199-200°C), $R_F$ 0.02 (chloroform), $\tau$ 3.38 (2H, s, aromatic), 5.68 (1H, d, J 6 Hz, H-5), 6.18 (3H, s, 3-0CH$_3$) and 7.64 (3H, s, N-CH$_3$).

$N$-(2-Chloro-1,1,2-trifluoroethyl)-diethylamine. 22 The reaction was carried out in a pressure vessel (300 ml. capacity and made of "Monel"). Dry, re-distilled diethylamine (6.86 g.) was placed in the vessel which was cooled to -78°C and evacuated. Chlorotrifluoroethylene (18 g., excess) was added and the pressure vessel was sealed and placed in a large volume water-bath. After 72 hours the excess gas was vented and the contents of the vessel were rapidly transferred to a distillation apparatus taking care to reduce exposure to the air to a minimum. Distilla-
tion through a Vigreux column produced N-(2-chloro-1, 1,2-trifluoroethyl)-diethylamine (10.7 g., 60%) as a colourless liquid which fumed in air, b.p. 30°C (5.0-5.5 mm. Hg), (Lit.\textsuperscript{22} b.p. 32-33°C, 5.5-6.0 mm. Hg).

6-Desoxy-6β-fluorocodeine.\textsuperscript{21} (17; R\textsuperscript{1} = H, R\textsuperscript{2} = F).

- N-(2-chloro-1,1,2-trifluoroethyl)-diethylamine (2.1 ml.) was added to dichloromethane (6 ml.) containing methanol (0.17 ml.). The solution was kept at 25°C for 30 minutes and then added to a cold solution (5°C) of anhydrous codeine (0.99 g.) in dichloromethane (13 ml.). The mixture was maintained at 0°C for 16 hours, ice-water was added and the organic phase separated and extracted with water (2 x 20 ml.). The aqueous extracts were combined, washed with dichloromethane, neutralised with sodium hydrogen carbonate solution and extracted with chloroform (2 x 25 ml.). The extract was dried (MgSO\textsubscript{4}), and evaporated to give a yellowish oil (0.57 g.) which crystallised on standing. The product, 6-desoxy-6β-fluorocodeine, recrystallised from aqueous methanol as white crystals (0.35 g., 35%), m.p. 138-140°C (Lit.\textsuperscript{21} m.p. 141-143°C), R\textsubscript{F} 0.73 (chloroform), τ 3.36 and 3.42 (2H, ABq, J 8 Hz, aromatics), 4.05-4.23 (2H, m, H-7 and H-8), 5.08 (1H, q, J\textsubscript{F} 48 and J\textsubscript{7} 6 Hz, H-6α), 5.10 (1H, d, J\textsubscript{F} 18 Hz, H-5), 6.18 (3H, s, 3-OCH\textsubscript{3}) and 7.58 (3H, s, N-CH\textsubscript{3}), m/e 301 (M\textsuperscript{+}) and 286.
8-Desoxy-8β-fluoropseudocodeine. (19; R₁ = H, R² = F). - Isocodeine (1.36 g.) when treated with the fluorinating reagent in a similar manner gave a yellowish oil (0.73 g.) which was dissolved in a small quantity of methanol. Water was added and the crystalline product which separated out on standing, a mixture of two compounds, was filtered off (0.1850 g.) and dried under vacuum. Separation of the mixture was achieved on p.l.c. over alumina eluting with chloroform. 8-Desoxy-8β-fluoropseudocodeine was obtained as white crystals (0.0700 g., 5.6%), m.p. 144-146°C (from methanol), Rₚ 0.71 (chloroform), 7 3.36 (2H, s, aromatic), 3.85-4.22 (2H, m, H-6 and H-7), 5.00 (1H, m, J₆ 3 Hz, H-5), 5.54 (1H, m, J₅ 50 and J₁₄ 10 Hz, H-8), 6.19 (3H, s, 3-CH₃), 6.42 (1H, m, H-9), and 7.58 (3H, s, N-CH₃), m/e 301 (M⁺) and 286 (Found: C, 71.30; H, 6.80; N, 4.81. C₁₈H₂₀FNO₂ requires C, 71.74; H 6.96; N, 4.65%).

6-Desoxy-6α-fluorodihydrocodeine. (22; R₁ = H, R² = F). - 6-Desoxy-6α-fluorocodeine (0.2002 g.) was hydrogenated in the above manner using methanol containing a small amount of N-hydrochloric acid. The product, 6-desoxy-6α-fluorodihydrocodeine, was obtained as yellowish crystals (0.1897 g.) which readily re-crystallised from methanol-water to give white crystals (0.1780 g., 89%), m.p. 173-175°C, Rₚ 0.61 (chloroform), 7 3.34 and 3.39 (2H, ABq, J 8 Hz, aromatics), 5.20-5.42
(1H, m, H-6α), 5.66 (1H, d, J 6 Hz, H-5), 6.23
(3H, s, 3-OCH₃) and 7.62 (3H, s, N-CH₃), m/e 303 (M⁺)
and 288.

No satisfactory F¹⁹ spectra could be obtained
on any of the fluoro derivatives because of insufficient
quantities of compounds.

14α-Nitrocodeinone Dimethyl Ketal. (23; R¹ = R² =
OCH₃, X = NO₂). - Tetranitromethane (3.68 g.) was
added dropwise to a solution of thebaine (5.84 g.)
in methanol (200 ml.) and the resulting dark brown
mixture was stirred at room temperature for 6 hours;
after approximately 30 min. a bulky yellow crystalline
precipitate appeared. The precipitate (4.70 g.) of
thebaine nitroform salt was filtered off and the
solution cautiously evaporated to dryness under re-
duced pressure. The residue was treated with benzene-
chloroform (1:1) and any undissolved material again
filtered off. The filtrate was subject to column
chromatography over alumina (200 g.). Elution with
benzene-chloroform (1:1) afforded a white crystalline
product, which on recrystallisation from alcohol
yielded 14α-nitrocodeinone dimethyl ketal as long,
white needles (1.67 g., 24%), m.p. 227-227.5°C, Rₚ 0.75
(cf. thebaine 0.45, benzene-chloroform, 1:1), [α]D
-91° (C 0.55), υ max. 1546 cm⁻¹ (NO₂), τ 3.37 and 3.47
(2H, ABq, J 8 Hz, aromatics), 4.12 (2H, s, H-7 and H-8),

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4.96 (1H, s, H-5), 6.16 (3H, s, 3-OCH₃), 6.55 (3H, s, 6-OCH₃), 6.95 (3H, s, 6-OCH₂) and 7.58 (3H, s, N-CH₃), m/e 388 (M⁺), 342, 310 and 278 (Found: C, 62.00; H, 6.51; N, 7.26. C₂₀H₂₄N₂O₆ requires C, 61.84; H, 6.23; N, 7.21%). The mother liquors contained mainly a second, unidentified nitration product. Further elution of the column with benzene-chloroform (1:1) yielded a small quantity of 14α-nitrocodeinone (Rᶠ 0.68).

**Acid Hydrolysis of the Ketal Group.** - The following general procedure illustrates the method used to hydrolyse a ketal group to a ketone group. The ketal was suspended in water, 2N-hydrochloric acid (excess) was added and the resulting solution (effected with warming if necessary) was allowed to stand at room temperature for 1 hour. The solution was basified with sodium hydrogen carbonate solution and extracted with several portions of chloroform. The extracts were combined, dried (MgSO₄) and evaporated down under reduced pressure to give usually the crystalline ketone in virtually quantitative yield.

1α-Nitrocodeinone (23; R¹ = R² = O, X = NO₂) was obtained as pale lemon plates by the above method and was identical to the minor product obtained above from the nitration of thebaine, m.p. 172.5-173°C, Rᶠ 0.68 (chloroform), \( [\alpha]D^0 + 196^\circ \) (C 0.612), \( \nu \) max.
1690 (conjugated C=O) and 1548 cm$^{-1}$ (NO$_2$), $\tau$ 3.32 (2H, s, aromatic), 3.38 and 3.82 (2H, ABq, J 10 Hz, H-7 and H-8), 4.86 (1H, s, H-5), 5.92 (1H, d, J$_{10\alpha}$ 6 Hz, H-9), 6.18 (3H, s, 3-CH$_3$), 6.50 (1H, d, J$_{10\alpha}$ 18 Hz, H-10$\beta$), 7.44 (1H, q, J$_9$ 6 and J$_{10\beta}$ 18 Hz, H-10$\alpha$) and 7.60 (3H, s, N-CH$_3$), m/e 342 (M$^+$) 295 and 253 (Found: C, 63.10; H, 5.30; N, 7.88. C$_{18}$H$_{16}$N$_2$O$_5$ requires C, 63.15; H, 5.30; N, 8.18%).

**Dihydrothebaine**.55 (31; R = CH$_3$). - Hydrazine hydrate (100%, 30 ml.) was added to a solution of thebaine (3.0 g.) in warm methanol (150 ml.). The mixture was warmed for 48 hours at 65-70°C whilst oxygen was bubbled through the solution at a steady rate. The reaction mixture was evaporated down under reduced pressure until a white crystalline precipitate appeared. After dilution with an equal volume of water it was stored at 0°C for 18 hours. The white crystalline solid was filtered off under vacuum (2.20 g.), washed with a small amount of water-methanol (20:1) and recrystallised from methanol. Dihydrothebaine was obtained as slightly greyish crystals (2.00 g., 66%), m.p. 163-164°C (Lit.55 m.p. 160-163°C), $R_F$ 0.30 (benzene-chloroform, 1:1), $\nu_{max.}$ 1668 cm$^{-1}$ (enol ether), $\tau$ 3.32 and 3.38 (2H, ABq, J 8 Hz, aromatics), 5.18-5.40
(2H, m, H-5 and H-7), 6.18 (3H, s, 3-OCH₃), 6.54 (3H, s, 6-OCH₃) and 7.58 (3H, s, N-CH₃).

**Dihydrocodeinone.** (22; R¹ = R² = 0). - Dihydrocodeinone (0.821 g.) was hydrolysed with conc. hydrochloric acid by heating on a steam bath for a few minutes. The product was obtained by basification with ammonia until a precipitate was formed. The white crystalline precipitate was filtered off under vacuum, washed liberally with cold water and finally recrystallised from industrial alcohol. Dihydrocodeinone was obtained as white crystals (0.482 g., 61%), m.p. 196-198°C (Lit.¹⁴ m.p. 197-198°C), Rₚ 0.07 (benzene-chloroform, 1:1), νₘₐₓ. 1726 cm⁻¹ (C = O), τ3.32 (2H, s, aromatic), 5.36 (1H, s, H-5), 6.10 (3H, s, 3-OCH₃) and 7.58 (3H, s, N-CH₃).

**N-Nitrosonordihydrothebaine.** (31; R = NO). - Dihydrothebaine (1.50 g.) was nitrated using a similar method to the nitration of thebaine. The crude reaction mixture (three components) was separated by column chromatography over alumina (100 g.) eluting with benzene-chloroform (1:1). The least polar component was identified as N-nitrosonordihydrothebaine and the second and third fractions as unreacted starting material and dihydrocodeinone respectively. N-nitrosonordihydrothebaine was obtained as off-white crystals from methanol (0.0865 g., 5.0%).
m.p. 223-225°C, Rf 0.63 (benzene-chloroform, 1:1), 
\(\lambda_{max} 3460 \ (0.261 \text{ in } \text{CHCl}_3) \ \nu_{max} 1668 \text{ cm}^{-1}\)
(enol ether), \(\tau 3.27 \text{ and } 3.36 \ (2\text{H, } \text{ABq, } J 8 \text{ Hz, aromatics}),
5.08-5.40 \ (2\text{H, } \text{m, } H-5 \text{ and } H-7), 6.16 \ (3\text{H, } s, \ 3-\text{OCH}_3) \text{ and }
6.52 \ (3\text{H, } s, \ 6-\text{OCH}_3), m/e 328 \ (M^+) \text{ and } 293 \ (\text{Found: } 
C, 65.50; H, 6.09; N, 8.38. } \text{C}_{18}H_{20}N_2O_4 \text{ requires } 
C, 65.84; H, 6.14; N, 8.53%).

**Catalytic Hydrogenation of 14β-Nitrocodineone Dimethyl Ketal.** - Catalytic hydrogenation of the nitro ketal (95 mg.) gave a mixture of two products which were separated by column chromatography over alumina (20 g.) eluting with benzene-chloroform (1:1). The i.r. and n.m.r. spectra of the least polar component showed a mixture of two compounds which were probably unreacted starting material and 14β-nitrodihydrocodeinone dimethyl ketal. The mixture could not be resolved on t.l.c. The more polar product (19 mg., 23%), dihydrocodeinone dimethyl ketal, was obtained as an oil, which did not crystallise, \(\tau 3.30 \text{ and } 3.40 \ (2\text{H, } \text{ABq, } J 8 \text{ Hz, aromatics}),
5.54 \ (1\text{H, } s, \ H-5), 6.12 \ (3\text{H, } s, \ 3-\text{OCH}_3), 6.74
(6\text{H, } s, \ 6(-\text{OCH}_3)_2) \text{ and } 7.60 \ (3\text{H, } s, \ N-\text{CH}_3).

Because the product could not be crystallised it was converted into dihydrocodeinone, m.p. and mixed m.p. 195-196°C, with identical physical properties to an authentic sample.
Catalytic Hydrogenation of 14β-Nitrocodeinone. -

Catalytic hydrogenation of the nitro-enone (100 mg.) under acidic conditions gave after basification a mixture of two compounds. The least polar component, separated by column chromatography over alumina (20 g.) eluting with chloroform, was identified as dihydrocodeinone, m.p. and mixed m.p. 195-196°C, with identical physical properties to an authentic sample.
14α-Aminocodeinone Dimethyl Ketal. (23; \( R^1 = R^2 = \text{OCH}_3 \), \( X = \text{NH}_2 \)). – 14α-Nitrocodeinone dimethyl ketal (1.61 g.) was dissolved in hot methanol (200 ml.) and ammonium chloride (2.50 g.) and zinc powder (2.50 g.) were added. The mixture was heated under reflux with vigorous stirring for 1 hour, filtered whilst still hot and the filtrate evaporated to dryness under reduced pressure. The residue was partitioned between water and chloroform and the chloroform layer separated, dried (\( \text{MgSO}_4 \)) and percolated through alumina to remove any polar material. Elution with chloroform and evaporation of solvent yielded 14α-aminocodeinone dimethyl ketal as an oil (1.17 g., 79%) which crystallised with some difficulty, from methanol, as colourless needles, m.p. 133-134°C, \( R_f \) 0.75 (chloroform), \( \angle \alpha_\beta \) -173° (C 0.548), \( \nu \) max. \( 3470 \) and \( 3370 \text{ cm}^{-1} \) (\( \text{NH}_2 \)), \( \tau \) 3.36 and 3.44 (2H, ABq, J 8 Hz, aromatics), 4.02 (1H, d, J 10 Hz, H-8), 4.34 (1H, dd, J 1 and 10 Hz, H-7), 5.28 (1H, d, J 1 Hz, H-5), 6.15 (3H, s, 3-OCH\(_3\)), 6.55 (3H, s, 6-OCH\(_3\)), 6.70 (2H, s, \text{NH}_2, \text{exchanges with D}_2\text{O}), 6.79 (3H, s, 3-OCH\(_3\)) and 7.60 (3H, s, N-CH\(_3\)), m/e 358 (M\(^+\)), 343 and 327 (Accurate mass measured 358.1897. \( \text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4 \) requires 358.1893).

14α-Aminocodeinone (23; \( R^1 = R^2 = 0 \), \( X = \text{NH}_2 \)) was obtained as a white crystalline compound, which was recrystallised from methanol, m.p. 193-194°C,
R_f 0.50 (chloroform), [α]_D° -191.5° (C 0.339), ν_{max.} 3360 and 3290 (NH₂), 1682 cm⁻¹ (conjugated C = O), γ3.26 and 3.95 (2H, ABq, J 10 Hz, H-7 and H-8), 3.34 (2H, s, aromatic), 5.28 (1H, s, H-5), 6.19 (3H, s, 3-OCH₃), 6.74 (1H, d, J 10₁ 19 Hz, H-10β), 7.25 (1H, q, J 10β 19 Hz and J 9 6 Hz, H-10α), 7.60 (3H, s, N-CH₃) and 7.61 (2H, s, NH₂, exchanges with D₂O), m/e 312 (M⁺), 295 and 255 (Found: C, 68.99; H, 6.45; N, 9.04. C₁₈H₂₀N₂O₃ requires C, 69.21; H, 6.45; N, 8.97%).

14β-N-Acetylanaminocodeinone. (23; R¹ = R² = 0, X = NHCOCH₃). - Acetic anhydride (1 ml.) was added to a solution of 14β-aminocodeinone (0.1640 g.) in dry pyridine (2 ml.). The mixture was allowed to stand at room temperature for 12 hours, and then evaporated to dryness under reduced pressure. The residue was shaken with sodium hydrogen carbonate solution and extracted with chloroform (2 x 10 ml.). The extract was dried (MgSO₄) and evaporated to dryness to yield 14β-N-acetylanaminocodeinone as white crystals (0.1740 g., 94%), m.p. 257.5-258°C from methanol, R_f 0.58 (chloroform), [α]_D° +99° (C 0.354), ν_{max.} 3370 (broad, NH) and 1695 cm⁻¹ (broad, CH₃CO and conjugated C=O), γ2.96 (1H, s, NH, exchanges with D₂O-CD₂COOD), 3.34 (2H, s, aromatic), 3.78 and 3.83 (2H, ABq, J 10 Hz, H-7 and H-8), 5.09 (1H, s, H-5), 6.20 (3H, s, 3-OCH₃), 113
6.75 (1H, d, \( J_{10\alpha} \) 18 Hz, H-10\( \beta \)), 6.88 (1H, d, \( J_{10\alpha} \) 6 Hz, H-9), 7.56 (1H, q, \( J_{10\beta} \) 18 and J\( \beta \) 6 Hz, H-10\( \beta \)), 7.59 (3H, s, N-CH\(_3\)) and 8.18 (3H, s, CH\(_3\)CO), m/e 354 (M\( ^{+} \)), 339, 311 and 295 (Found: C, 67.68; H, 6.58; N, 7.98. C\(_{20}\)H\(_{22}\)N\(_2\)O\(_4\) requires C, 67.78; H, 6.26; N, 7.91%).

14\( \phi \)-N-Cinnamoylaminocodeinone. (23; \( R^1 = R^2 = 0, X = \text{NHCOCH} = \text{CHPh} \)) was similarly prepared by adding a solution of cinnamoyl chloride (excess) in carbon tetrachloride to the aminoketone in pyridine at 0°C. The product was recrystallised from methanol as slightly coloured crystals, m.p. 229-230°C, \( R_F \) 0.80 (chloroform), \( \alpha_D \) +188° (C 0.392), \( \lambda_{\text{max.}} \) 280 nm. (35,700), \( \nu_{\text{max.}} \) 3350 (broad, NH), 1695 (C = O, conjugated), 1670 (C = O conjugated), 1632 (C = C) and 1578 cm\(^{-1}\) (aromatic further conjugated), \( \tau \) 2.39 and 3.45 (2H, ABq, J 18 Hz, olefinic), 2.66 (5H, m, aromatic), 3.36 (2H, s, aromatic H-1 and H-2), 3.75 (2H, s, H-7 and H-8), 4.96 (1H, s, H-5), 6.22 (3H, s, 3-CH\(_3\)) and 7.56 (3H, s, N-CH\(_3\)), m/e 442 (M\(^{+} \)), 311 and 295 (Found: C, 72.29; H, 6.00; N, 6.22. C\(_{27}\)H\(_{26}\)N\(_2\)O\(_4\).\( \frac{1}{4}\)CH\(_3\)OH requires C, 72.03; H, 6.16; N, 6.11%).

14\( \phi \)-N-Benzoyloxy carbonylaminocodeinone (23; \( R^1 = R^2 = 0, X = \text{NHCOOCH}_2\text{Ph} \)) was similarly prepared by heating under reflux the aminoketone in chloroform with benzyl chloroformate (excess) for 15 minutes. The product was recrystallised from methanol as
colourless needles, m.p. 219-222°C, Rf 0.85 (chloroform), vmax. 3350 (broad, NH), 1720 (COOCH2Ph) and 1693 cm⁻¹ (conjugated C =O), τ 2.64 (5H, s, aromatic), 3.35 (2H, s, aromatic H-1 and H-2), 3.52 (1H, s, NH), 3.81 (2H, s, OCH2Ph), 5.11 (1H, s, H-5), 6.22 (3H, s, 3-OCH3), 6.78 (1H, d, J₁₀α 18 Hz, H-10β), 7.02 (1H, d, J₁₀α 6 Hz, H-9), 7.62 (1H, q, J₁₀β 18 and J₉ 6 Hz, H-10α) and 7.65 (3H, s, N-CH2), m/e 446 (M⁺) and 339 (Found: C, 68.78; H, 5.90; N, 5.86. C₂₆H₂₆O₅N₂·¾CH₂OH requires C, 68.81; H, 6.10; N, 5.60%).

**14β-N-Cyanoaminocodeinone.** (23; R¹ = R² = 0, X = NHCON). - Cyanogen bromide (150 mg.) was added to a solution of 14β-aminocodeinone (90 mg.) in chloroform (20 ml., ethanol free) and the mixture was refluxed for 15 minutes. The resulting precipitate was filtered off and dissolved in water with gentle heating. The solution was basified with aqueous sodium hydrogen carbonate and extracted with chloroform (2 x 15 ml.). The extracts were dried (MgSO₄) and evaporated to give an oil which crystallised on addition of methanol. Recrystallisation gave material (0.0510 g., 53%), m.p. 201-202°C identical with an authentic sample (mixed m.p. 201°C) prepared by Mr P. Horsewood by a different route, Rf 0.52 (chloroform), vmax. 3190 (very broad, NH), 2220 (CN) and 1690 cm⁻¹ (conjugated C =O), τ 3.29
(2H, s, aromatic), 3.48 and 3.65 (2H, ABq, J 10 Hz, H-7 and H-8), 5.06 (1H, s, H-5), 6.16 (3H, s, 3-0CH₃), 6.72 (1H, d, J₁₀α 18 Hz, H-10β), 6.94 (1H, d, J₁₀α 6 Hz, H-9), 7.49 (1H, q, J₁₀β 18 Hz and J₉ 6 Hz, H-10α) and 7.59 (3H, s, N-CH₃), m/e 337 (M⁺), 312 and 296.

14β-Aminocodeine. (23; R¹ = OH, R² = H, X = NH₂). - Sodium borohydride (0.150 g.) was added to a solution of 14β-aminocodeinone (0.0890 g.) in methanol (50 ml.). The mixture was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue partitioned between water and chloroform. The chloroform extract was dried (MgSO₄) and evaporated to dryness under reduced pressure to yield 14β-aminocodeine as white crystals (0.0660 g., 74%), m.p. 185-186°C from methanol, Rₚ 0.27 (chloroform), τ 3.40 (2H, s, aromatic), 4.20 (1H, m, H-7), 4.58 (1H, dd, J₆β 2 and J₇ 9 Hz, H-8), 5.09 (1H, d, J 6 Hz, H-5), 5.36 (1H, m, H-6), 6.20 (3H, s, 3-0CH₃), 6.83 (1H, d, J₁₀α 19 Hz, H-10β), 7.38 (1H, q, J₉ 6 and J₁₀β 19 Hz, H-10α), 7.54 (2H, s, NH₂, exchanges with D₂O) and 7.64 (3H, s, N-CH₃), m/e 314 (M⁺) and 297 (Found: C, 68.82; H, 7.20; N, 8.87. C₁₈H₂₂N₂O₃ requires C, 68.77; H, 7.05; N, 8.91%).

7β-Iodoneopinone Dimethyl Ketal. (24; R¹ = R² = 0CH₃, X = I). - A mixture of silver nitrite (1.49 g.) and
iodine (4.91 g.) were stirred together vigourously in chloroform (60 ml., ethanol free)-methanol (6 ml.) for 30 minutes under dry nitrogen. A solution of thebaine (1.50 g.) in chloroform (6 ml.) was added and the mixture stirred for a further 5 hours. The insoluble silver salts were filtered off and the solution was washed with (i) two portions of sodium meta-bisulphite solution and (ii) two portions of saturated sodium chloride solution. After drying (MgSO₄), the solution was evaporated to small bulk and percolated through alumina (chloroform as solvent) to remove coloured impurities. Evaporation of solvent yielded an oily product (1.80 g., 80%) which crystallised slowly on standing. Recrystallisation from methanol gave 7β-iodoneopinone dimethyl ketal as light sensitive, colourless crystals, m.p. 144-147°C, Rf 0.61 (benzene-chloroform, 1:1), T 3.36 and 3.46 (2H, ABq, J 8 Hz, aromatics), 4.27 and 5.31 (2H, ABq, J 6 Hz, H-8 and H-7), 4.73 (1H, s, H-5), 6.16 (3H, s, 3-OCH₃), 6.55 (3H, s, 6-OCH₃), 7.06 (3H, s, 6-OCH₃) and 7.53 (3H, s, N-CH₃), m/e (M⁺) not observed, 342 (M⁺-iodine), 310 and 278 (Found: C, 51.21; H, 5.66; N, 3.26. C₂₀H₂₄INO₄ requires C, 51.18; H, 5.15; N, 2.98%).

14β-Bromocodeinone Dimethyl Ketal. ⁴⁰ (23; R¹ = R² = OCH₃, X = Br). A solution of N-bromoacetamide
(2.143 g.) in methanol (7½ ml.) was added to a suspension of thebaine (4.665 g.) in methanol (50 ml.). The mixture was shaken violently for 10 minutes. After approximately two minutes the thebaine dissolved and the product precipitated out several minutes later. The mixture was stored at 0°C for 3 hours. The crystalline precipitate was filtered off under vacuum and washed with a small amount of cold methanol. Recrystallisation from methanol gave 14β-bromocodeinone dimethyl ketal as colourless needles (2.50 g., 40%) m.p. 161-163°C (Lit., m.p. 160-162°C), R_f 0.75 (benzene-chloroform, 1:1), T 3.34 and 3.44 (2H, ABq, J 8 Hz, aromatic), 4.00 (1H, d, J 10 Hz, H-8), 4.38 (1H, dd, J_5 1 and J_8 10 Hz, H-7), 5.31 (1H, d, J 1 Hz, H-5), 6.12 (3H, s, 3-OCH₃), 6.54 (3H, s, 6-OCH₃), 6.81 (3H, s, 6-OCH₃) and 7.55 (3H, s, N-CH₃).

14β-Halocodeinone (23; R¹ = R² = 0, X = Br or Cl).

Thebaine (1.245 g., 4 mmole) was suspended in acetone-water (2:1, 4 ml.) and a solution of N-halosuccinimide (4.2 mmole, halo = chloro or bromo) in acetone-water (2:1, 8 ml.) was added with mechanical stirring over a period of 10 minutes. The temperature was maintained at 15-18°C during addition and thereafter for 10 minutes. Water (20 ml.) was added over a period of 20 minutes with vigorous stirring and the product started to crystallise out. The stirring was continued for 1 hour at 20°C and then for a
further 2 hours at 0°C. The product was filtered off under vacuum, sucked dry, washed with water (25 ml.) and recrystallised from methanol (60-65% yield).

14β-Chlorocodeinone was obtained as long white needles, m.p. 181.5-182.5°C, Rf 0.56 (benzene-chloroform, 1:1), $\nu_{max}$, 1688 cm⁻¹ (conjugated C = O), $\tau$ 3.14 and 3.97 (2H, ABq, J 10 Hz, H-7 and H-8), 3.33 (2H, s, aromatic), 5.34 (1H, s, H-5), 6.18 (3H, s, 3-OCH₃) and 7.54 (3H, s, N-CH₃) m/e 333, 331 (M⁺) and 296.

14β-Bromocodeinone was obtained as fine, yellow crystals with an ill-defined melting point, Rf 0.55 (benzene-chloroform, 1:1), $\nu_{max}$, 1685 cm⁻¹ (conjugated C = O), $\tau$ 3.04 and 4.06 (2H, ABq, J 10 Hz, H-7 and H-8), 3.33 (2H, s, aromatic), 5.41 (1H, s, H-5), 6.16 (3H, s, 3-OCH₃), 6.72 (1H, d, J₁₀α 18 Hz, H-10β), 6.72 (1H, d, J₁₀α 6 Hz, H-9), 7.40 (1H, q, J₂ 6 and J₁₀β 18 Hz, H-10α) and 7.54 (3H, s, N-CH₃).

N.B. Reaction of thebaine with N-iodosuccinimide (Organic Syntheses preparation 84) in methanol gave a mixture of unreacted starting material and 7β-iodoneopinone dimethyl ketal.

Reaction of Thebaine with N-Bromoacetamide in the Presence of Acid. - Acetyl chloride (0.0685 ml., ≈1 mole) was added to a suspension of thebaine (0.30 g., ≈1 mole) in methanol (25 ml.) - all the thebaine dissolved. N-Bromoacetamide (0.132 g., ≈1 mole) in
methanol (2 ml.) was added and the mixture was shaken for 3 hours. The solvent was evaporated, water was added to the residue and the resulting solution was basified with sodium hydrogen carbonate solution. The solution was extracted with chloroform (2 x 25 ml.), the extracts were combined, dried (MgSO₄) and evaporated to dryness. The n.m.r. spectrum of the residue was then obtained, from which the ratio of products was determined \( \beta \)-bromoneopinone dimethyl ketal (54%) and \( \beta \)-bromocodeinone dimethyl ketal (46%). The reaction was repeated using different quantities of reagents (see Results and Discussion, Section 2). The n.m.r. spectrum of \( \beta \)-bromoneopinone dimethyl ketal, deduced by subtraction of the 14-bromo ketal signals, was as follows: 3.32 and 3.42 (2H, ABq, J 8 Hz, aromatic), 4.20 and 5.49 (2H, ABq, J 6 Hz, H-8 and H-7), 4.84 (1H, s, H-5), 6.16 (3H, s, 3-OCH₃), 6.54 (3H, s, 6-OCH₃), 7.02 (3H, s, 6-OCH₃) and 7.57 (3H, s, N-CH₃). Attempted separation of the \( \beta \)-bromo-compound and the \( \alpha \) isomer by column chromatography was not successful. The \( \beta \)-bromo-compound was converted into \( \beta \)-hydroxyindoindolino-codeinone dimethyl ketal. Thebaine hydrochloride and N-bromoacetamide gave a similar ratio of products i.e. \( \beta \) (50%) and \( \alpha \) (50%).

Reaction of Thebaine Hydrochloride with Trifluoromethyl Hypofluorite (F₃COF).
CAUTION. The reagent reacts (or explodes) with grease, mercury, benzene, pyridine and oxygen containing solvents. All manipulations involving the reagent were therefore performed behind a safety screen. Although some reactions were successfully carried out in methanol a violent explosion occurred on one occasion.

The apparatus consisted of a two necked flask fitted with a gas inlet tube (sufficiently long to bubble gas through the solution) connected via a three-way tap to (i) the reagent cylinder and (ii) a dry, carbon dioxide and oxygen free nitrogen supply. A bubbler containing either dry chloroform or dry carbon tetrachloride was used as the gas outlet. The apparatus was rigorously dried before assembly and all connections were made with PVC tubing.

A solution of thebaine hydrochloride in dry chloroform (chloroform-methanol, 9:1 or methanol) was placed in the flask and nitrogen was bubbled through for several hours to displace the air from the apparatus. The solution was then stirred, cooled (0°C, -40°C or -80°C, depending on solvent) and the nitrogen supply stopped. The reagent was slowly bubbled through the solution until it was detected in the outlet gas stream (using starch-iodide paper) when the flow was stopped and nitrogen was again bubbled through to flush out the excess gas. The solution was allowed to warm up
to room temperature, the solvent was evaporated off and the residue was partitioned between 2N-sodium hydroxide solution and chloroform. The chloroform layer was separated, dried (MgSO₄) and evaporated down. Partial separation of the residue (a mixture of at least four compounds) was achieved by firstly column chromatography and secondly p.l.c. using benzene-chloroform (1:1) as solvent. No component was obtained sufficiently pure in the quantity required for its identification.

Identical reactions were carried out on the following starting materials: thebaine, dihydrothebaine, dihydrothebaine hydrochloride and dihydrocodeine hydrochloride. Thebaine gave mainly a salt (probably thebaine hydrofluoride) but the products obtained from the other starting materials could not be separated.

9α-Acetoxyindolinocodeinone Dimethyl Ketal. (32; \( R^1 = R^2 = OCH_3 \), \( X = CH_3COO \)). Silver acetate (0.725 g.) was added to a solution of 7p-iodoneopinone dimethyl ketal (1.8010 g.) in glacial acetic acid (25 ml.) and the mixture was stirred for 12 hours in the absence of light. The insoluble salts were filtered off and the acetic acid was neutralised with sodium hydrogen carbonate solution. The aqueous solution was extracted with chloroform (2 x 50 ml.), the extracts were dried (MgSO₄) and evaporated (1.6570 g.). The residue was chromatographed over alumina (100 g.) to give crystalline
9α-acetoxyindolinocodeinone dimethyl ketal as the least polar component on elution with benzene-chloroform (1:1). The acetoxy ketal was obtained as white crystals from methanol (0.5060 g., 33%), m.p. 123-124.5°C, Rf 0.74 (benzene-chloroform, 1:1), \[\beta_d^0 = 77^\circ \ (C 1.33), \nu_{\text{max.}} 1723 \text{ cm}^{-1} \ (\text{acetate}), \tau 3.38 \text{ and } 3.46 \ (2H, \text{ ABq, } J 8 \text{ Hz, aromatic}) \], 4.17 (2H, s, H-7 and H-8), 4.86 (1H, t, J 2.7 Hz, H-9), 5.48 (1H, s, H-5), 6.12 (3H, s, 3-0CH₃), 6.52 (3H, s, 6-0CH₃), 7.05 (3H, s, 6-0CH₃), 7.52 (3H, s, N-CH₃) and 8.24 (3H, s, CH₃CO); m/e 401 (M⁺), 386, 370, 358 and 342 (Found: C, 65.80; H, 6.76; N, 3.51. C₂₂H₂₇NO₆ requires C, 65.82; H, 6.78; N, 3.49%). Further elution of the column yielded an impure substance (0.0660 g.), the major component of which was separated by p.l.c. on alumina (eluting with benzene-chloroform, 1:1). The pure component, 14β-acetoxycodeinone dimethyl ketal, was obtained as white crystals (0.0310 g.), m.p. 184-186°C (from methanol), Rf 0.68 (benzene-chloroform, 1:1), \[\nu_{\text{max.}} 1722 \text{ cm}^{-1} \ (\text{acetate}), \tau 3.39 \text{ and } 3.49 \ (2H, \text{ ABq, } J 8 \text{ Hz, aromatics}), 3.80 \ (1H, \text{ d, } J 10 \text{ Hz, H-8}), 4.34 \ (1H, \text{ dd, } J 1 \text{ and } 10 \text{ Hz, H-7}), 5.30 \ (1H, \text{ d, } J 1 \text{ Hz, H-5}), 6.01 \ (1H, \text{ d, } J 6 \text{ Hz, H-9}), 6.16 \ (3H, \text{ s, } 3-0CH₃), 6.58 \ (3H, \text{ s, } 6-0CH₃), 6.91 \ (3H, \text{ s, } 6-0CH₃), 7.68 \ (3H, \text{ s, N-CH₃}) \text{ and } 7.94 \ (3H, \text{ s, CH₃CO}), \text{ m/e } 401 \ (\text{M}^+) \text{ 370 and 358} \ (\text{Found: C, 66.12; H, 6.52; N, 3.48. C₂₂H₂₇NO₆ \text{ requires C, 65.82;}}})
14β-Acetoxycodeinone \( (23; R^1 = R^2 = 0, X = \text{CH}_3\text{COO}) \) was obtained as colourless crystals from methanol, m.p. 182-183°C (Lit. \( 14 \) m.p. 185°C), \( R_f \) 0.58 (benzene-chloroform, 1:1), \( V_{\text{max.}} \) 1732 (acetate) and 1690 cm\(^{-1} \) (conjugated \( \text{C}=\text{O} \)), \( \tau \) 2.91 and 3.90 (2H, ABq, \( J \) 10 Hz, H-7 and H-8), 3.34 (2H, s, aromatic), 5.27 (1H, s, H-5), 5.93 (1H, d, \( J \) 6 Hz, H-9), 6.18 (3H, s, 3-\( \text{OCH}_3 \)), 7.61 (3H, s, N-\( \text{CH}_3 \)) and 7.93 (3H, s, \( \text{CH}_3\text{CO} \)).

Alternative Preparation of 9β-Acetoxyindolino-codeinone Dimethyl Ketal. - The following method is typical of that used for reactions of 7β-iodoneopinone dimethyl ketal with nucleophiles using aqueous dimethylformamide as solvent.

A solution of sodium acetate (1.00 g., large excess) in water (5 ml.) was added to a solution of 7β-iodoneopinone dimethyl ketal (1.80 g.) in dimethylformamide (30 ml.). The mixture was stirred at room temperature for 12 hours, poured into water (150 ml.) and extracted with ether (2 x 100 ml.). The ethereal extract was washed thoroughly with sodium chloride solution, dried (\( \text{MgSO}_4 \)) and evaporated. The residue was chromatographed on alumina (75 g.). Elution with benzene-chloroform (1:1) gave the 9β-acetoxyketal (0.80 g., 52%) as white crystals identical to material prepared above. No 14-substituted products were
obtained.

9\(\alpha\)-Acetoxyindolinocodineinone (32; \(R^1 = R^2 = 0, X = CH_3COO\)) was obtained as white crystals from aqueous methanol m.p. 137-138°C, \(R_f 0.50\) (benzene-chloroform, 1:1), \(\nu_{\text{max.}}\) 1724 (acetate) and 1702 cm\(^{-1}\) (conjugated \(C = O\)), \(\tau\) 3.28 and 3.80 (2H, ABq, J 10 Hz, H-7 and H-8), 3.36 (2H, s, aromatic), 4.78 (1H, dd, J 2.2 and 3.5 Hz, H-9\(\beta\)), 5.27 (1H, s, H-5), 6.12 (3H, s, 3-OCH\(_3\)), 7.40 (3H, s, N-CH\(_3\)) and 8.32 (3H, s, CH\(_2\)CO), m/e 355 (M\(^+\)), 313, 296, 295 and 285 (Found: C, 67.53; H, 6.21; N, 3.81. \(C_{20}H_{21}NO_5\) requires C, 67.59; H, 5.96; N, 3.94%).

9\(\alpha\)-Hydroxyindolinocodineinone Dimethyl Ketal. (32; \(R^1 = R^2 = OCH_3, X = OH\)). - The acetoxy ketal (3.20 g.) was dissolved in industrial alcohol-water (45 ml., 8:1) and 2N-sodium hydroxide (5 ml.) was added. The mixture was allowed to stand at room temperature for 12 hours, the aqueous solvent was evaporated off, water was added to the residue and the resulting solution was neutralised with solid carbon dioxide. The neutral solution was extracted with chloroform (2 x 100 ml.); the extracts were dried (Na\(_2\)SO\(_4\)) and evaporated to yield an oil which crystallised on standing (2.84 g., 98%). The product, 9\(\alpha\)-hydroxyindolinocodineinone dimethyl ketal was recrystallised from aqueous methanol, m.p. 118.5-119.5°C, \(R_f 0.61\) (benzene-chloroform, 1:1),
$\Delta \nu_D +108^o$ (C 0.623), $\nu_{\text{max}}$ 3490 cm$^{-1}$ (broad, OH),
$\tau$ 3.34 (2H, s, aromatic), 3.90 and 4.03
(2H, ABq, $J$ 10 Hz, H-7 and H-8), 5.46 (1H, s, H-5),
6.14 (3H, s, 3-OCH$_3$), 6.48 (3H, s, 6-OCH$_3$), 7.03
(3H, s, 6-OCH$_3$) and 7.54 (3H, s, N-CH$_3$), m/e 359 (M$^+$),
344 and 327 (Found: C, 66.55; H, 7.15; N, 3.93.
C$_{20}$H$_{25}$N$_2$O$_5$ requires C, 66.83; H, 7.01; N, 3.90%)

$\beta$-Hydroxyindolinocodeinone (32; $R^1 = R^2 = 0$,
X = OH) was obtained as colourless needles from
methanol, m.p. 209-211°C, $R_f$ 0.12 (benzene-chloroform,
1:1), $\Delta \nu_D +92^o$ (C 0.858), $\nu_{\text{max}}$ 3570 (OH) and
1695 cm$^{-1}$ (conjugated C=O),
$\tau$ 3.12 and 3.78
(2H, ABq, $J$ 10 Hz, H-7 and H-8), 3.32 (2H, s, aromatic),
5.30 (1H, s, H-5), 6.14 (3H, s, 3-OCH$_3$), 7.46
(3H, s, N-CH$_3$) and 8.70 (1H, broad, OH, exchanges
with D$_2$O), m/e 313 (M$^+$), 296, 285 and 284 (Found:
C, 68.83; H, 6.15; N, 4.64. C$_{18}$H$_{19}$N$_2$O$_4$ requires
C, 68.99; H, 6.11; N, 4.47%)

Acetylation of $\beta$-Hydroxyindolinocodeinone. -
$\beta$-Hydroxyindolinocodeinone (0.0800 g.) was acetylated
in the usual manner with acetic anhydride in pyridine
to give $\beta$-acetoxyindolinocodeinone as a white
crystalline product (0.0800 g., 88%, m.p. and mixed
m.p. 137-138°C).

$\beta$-Hydroxydihydroindolinocodeinone. (34; $R^1 = R^2 = 0$,
X = OH). - The hydroxy-enone (0.3040g.) was
hydrogenated to give the corresponding dihydro com-

pound as a colourless oil which crystallised slowly
on standing (0.2880 g., 94%). Recrystallisation
from methanol gave colourless needles m.p. 168-169°C,
R_f 0.60 (chloroform, cf: 9α-hydroxyindolinocodeinone
0.45), \( \Delta \approx 0.001 \) (C 0.673), \( \nu_{\text{max}} \) 3360 (broad, OH)
and 1730 cm\(^{-1} \) (C = O), \( \tau \) 3.39 (2H, s, aromatic),
5.28 (1H, s, H-5), 5.64 (1H, dd, J 6.5 and 8.5 Hz, H-9b),
6.15 (3H, s, 3-OCH\(_3\)) and 7.45 (3H, s, N-CH\(_3\)), m/e
315 (M\(^+\)), 297 and 287 (Accurate mass measured 315.1475.
C\(_{18}\)H\(_{21}\)N\(_2\)O\(_4\) requires 315.1470).

9α-Acetoxydihydroindolinocodeinone. (34; \( R^1 = R^2 = 0 \), X = CH\(_3\)COO). - The acetoxy-enone (0.1840 g.) was
hydrogenated to give the corresponding dihydro com-
pound as an oil which could not be crystallised
(0.1330 g., 72%), R_f 0.50 (benzene-chloroform, 1:1),
\( \nu_{\text{max}} \) 1735 cm\(^{-1} \) (broad, acetate and C = O), \( \tau \) 3.37
and 3.46 (2H, ABq, J 8 Hz, aromatics), 4.58
(1H, dd, J 6.5 and 8.5 Hz, H-9b), 5.30 (1H, s, H-5),
6.15 (3H, s, 3-OCH\(_3\)), 7.60 (3H, s, N-CH\(_3\)) and 8.01
(3H, s, CH\(_3\)CO). m/e 357 (M\(^+\)), 328, 314 and 298.

9α-Acetoxydihydroindolinocodeinone Picrate.
Yellow crystals from methanol, \( \Delta \approx 0.001 \) (C 0.456)
(Found: C, 53.00; H, 4.75; N, 9.50. C\(_{20}\)H\(_{23}\)N\(_2\)O\(_5\).C\(_6\)H\(_5\)N\(_3\)O\(_7\)
requires C, 53.24; H, 4.47; N, 9.55%).

Base Hydrolysis of 9α-Acetoxydihydroindolinocodeinone.

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- The acetoxydihydro-ketone (0.0280 g.) was hydrolysed with 2N-sodium hydroxide to give the corresponding 9α-hydroxydihydro-ketone (0.0190 g., 80%, m.p. and mixed m.p. 167-168°C).

**Acetylation of 9α-Hydroxydihydroindolinocodeinone.** - The hydroxydihydro-ketone (0.0905 g.) was acetylated with acetic anhydride-pyridine to give the corresponding acetoxydihydro-ketone (0.0855 g., 83%) as an oil with identical physical properties to the above sample.

**9-Ketodihydroindolinocodeinone.** (34; R¹ = R² = XH = 0). - Dry benzene (20 ml.) and small pieces of potassium (0.5 g.) were added to t-butanol (7 ml.), which had been previously dried by refluxing over sodium and then distilled directly into the reaction flask. The mixture was heated under reflux until all the potassium dissolved, the reflux condenser was replaced by a Vigreux column and with stirring the excess t-butanol was distilled off as the benzene azeotrope, more benzene was added as necessary to keep the potassium t-butoxide in solution. When the boiling point reached 79°C and remained constant for 20 ml. of distillate the column was replaced by a reflux condenser, the system was flushed with nitrogen and a solution of 9α-hydroxydihydroindolinocodeinone (0.4195 g.) and benzophenone (2.0500 g.) in dry benzene
(15 ml.) was added. The mixture was heated under reflux in a nitrogen atmosphere for 2½ hours, cooled, and 2N-hydrochloric acid (40 ml.) added. The benzene layer was separated and extracted with hydrochloric acid (2 x 40 ml.). The aqueous extracts were combined, washed with ether (2 x 40 ml.) and basified with conc. sodium hydroxide solution. The basic solution was extracted with chloroform (2 x 25 ml.) and the extracts were dried (MgSO₄) and evaporated to dryness (0.3150 g.). A t.l.c. examination showed the presence of some starting material which was separated from the required product by chromatography over alumina (30 g.). 9-Ketodihydroindolinocodeinone was obtained as an oil (0.0420 g., 10%) which would not crystallise, Rf 0.66 (benzene-chloroform, 1:1), V_max 1735 (C = 0) and 1708 cm⁻¹ (C = 0), τ 3.26 and 3.36 (2H, ABq, J 8 Hz, aromatics), 5.21 (1H, s, H-5), 6.08 (3H, s, 3-0CH₂) and 7.37 (3H, s, N-CH₂), m/e no (M⁺) observed, 296, 285 and 256.

9α-Hydroxyindolinocodeine. (32; R¹ = OH, R² = H, X = OH). - Sodium borohydride (0.2500 g.) was added with stirring to a solution of 9α-acetoxyindolinocodeinone (0.1000 g.) in methanol (6 ml.) at 0°C. The mixture was kept at 0°C for 2 hours and room temperature for 2 hours. The solvent was evaporated off and the residue was shaken with 2N-sodium
hydroxide solution (5 ml.) for 3 hours. The aqueous solution was extracted with chloroform (2 x 15 ml.), the extracts were dried and evaporated down to give 9α-hydroxyindolinocodeine (0.0730 g., 82%). Recrystallisation from aqueous acetone gave white crystals, m.p. 185-1870C, $\alpha D +158^\circ$ (C 0.332 in EtOH). (Lit. values: m.p. 193-1950C, $\alpha D + 159^\circ$), $R_F$ 0.38 (chloroform, blue-black spot), $\nu_{\text{max}}$ 3575 (OH) and 3380 cm$^{-1}$ (OH), $\tau$ 3.35 (2H, s, aromatic), 3.85 (1H, q, J 6 and 10 Hz, H-7), 3.90 (1H, d, J 10 Hz, H-8), 5.55 (1H, d, J 5 Hz, H-5), 5.70 (1H, m, H-6β), 6.17 (3H, s, 3-OCH$_3$), 7.25 (1H, s, OH, exchanges with D$_2$O) and 7.53 (3H, s, N-OCH$_3$), m/e 315 (M$^+$), 297, 286 and 269.

Sodium borohydride reduction of 9α-hydroxyindolincodcinone also gave 9α-hydroxyindolinocodeine with identical physical properties to the above product.

$\alpha^9$-Indolinocodeinone Dimethyl Ketal. (44; R$^1$ = R$^2$ = OCH$_3$). - Sodium methoxide was added to a solution of 7β-iodoneopinone dimethyl ketal (1,0640 g.) in methanol (40 ml.) and the mixture was allowed to stand at room temperature for 96 hours. The methanol was evaporated off, water was added to the residue and the solution was extracted with chloroform (2 x 25 ml.). The combined extracts were dried (MgSO$_4$) and evaporated to give a colourless oil. The oil, a mixture of
several products, was subject to p.l.c. (eluting with benzene-chloroform, 1:1) to give pure $\Delta^9$-indolinocodeinone dimethyl ketal as a colourless oil which did not crystallise (0.1910 g., 25%), $R_F$ 0.57 (benzene-chloroform, 1:1), $\nu_{\max}$ 1578 cm$^{-1}$ (aromatic, further conjugated), $\tau$ 3.42 (2H, s, aromatic), 3.61 and 4.34 (2H, ABq, J 10 Hz, H-10 and H-9), 4.22 (2H, s, H-7 and H-8), 5.21 (1H, s, H-5), 6.12 (3H, s, 3-OCH$_3$), 6.66 (3H, s, 6-OCH$_3$), 6.89 (3H, s, 6-OCH$_3$) and 7.56 (3H, s, N-CH$_3$), m/e 341 (M$^+$), 326, 310, 301 and 298 (Accurate mass measured 341.1628. C$_{20}$H$_{23}$NO$_4$ requires 341.1627).

Alternative method. - Sodamide (1.00 g.) was added to a stirred solution of the iodide (0.9370 g.) in dry dimethylformamide (40 ml.). The mixture was stirred for 12 hours and then poured cautiously into water. The aqueous solution was extracted with ether (2 x 50 ml.), the extracts were combined and washed with saturated sodium chloride solution. The ether extract was dried (MgSO$_4$) and evaporated down to give an oily residue (0.5260 g.). Chromatography of the residue over alumina (90 g.) using benzene-chloroform (2:3) as solvent gave $\Delta^9$-indolinocodeinone dimethyl ketal as an oil (0.1760 g., 26%), which had identical physical properties to the sample prepared above.
\( \Delta^9 \)-Indolinocodeinone \((44; R_1 = R_2 = 0)\) was obtained as an oil, which again did not crystallise, \( R_F 0.29 \) (benzene-chloroform, 1:1), \( \nu_{\text{max}} \) 1685 (conjugated \( \text{C} = 0 \)) and 1573 cm\(^{-1}\) (aromatic further conjugated), \( \tau \) 3.37 (2H, s, aromatic), 3.39 and 3.95 (2H, ABq, J 10 Hz, H-10 and H-9), 3.39 and 4.21 (2H, ABq, J 10 Hz, H-8 and H-7), 5.17 (1H, s, H-5), 6.15 (3H, s, 3-\( \text{OCH}_3 \)) and 7.50 (3H, s, N-\( \text{CH}_3 \)).

Addition of \( \text{C}_6\text{D}_6 \) separated the superimposed signals at \( \tau \) 3.39 to give \( \tau \) 3.50 and 4.05 (2H, ABq, J 10 Hz, H-10 and H-9), 3.58 and 4.34 (2H, ABq, J 10 Hz, H-8 and H-7); m/e 295 (M\(^+\)), 280, 267 and 266 (Accurate mass measured 295.1215. \( \text{C}_{18}\text{H}_{17}\text{NO}_3 \) requires 295.1208).

\( \Delta^9 \)-Indolinocodeinone Hydrochloride was obtained as very fine white crystals darkening above 120°C, \( \lambda_{\text{max}} \) 273 (7300), 305 (5050) and 314.5 nm (4650). Addition of 1 drop of base gave \( \lambda_{\text{max}} \) 273 (7150), 302.5 (4250) and 314 nm (4000). No satisfactory analysis could be obtained.

\( \omega \)-Cyanoindolinocodeinone Dimethyl Ketal \((32; R_1 = R_2 = \text{OCH}_3, X = \text{CN})\). - The iodoketal \((1.0010 \text{ g.})\) was treated with sodium cyanide \((0.60 \text{ g.})\) in aqueous dimethylformamide according to the general method.

The residue obtained \((0.5620 \text{ g.})\) was chromatographed over alumina \((40 \text{ g.})\). Elution with benzene-chloroform
(1:1) gave \(\alpha\)-cyanoindolinocodeinone dimethyl ketal as white crystals (0.4410 g., 56%), m.p. 157.5-158.5°C from methanol, \(R_F\) 0.90 (benzene-chloroform, 1:3), \(\gamma\) \(\alpha\) \(\beta\) \(\gamma\) 7 \(+47^\circ\) (C 0.953), \(\nu_{max}\) 2238 cm\(^{-1}\) (weak, CN), \(\tau\) 3.32 (2H, s, aromatic), 4.01 (2H, s, H-7 and H-8), 5.47 (1H, s, H-5), 6.13 (3H, s, 3-0CH\(_3\)), 6.50 (3H, s, 6-0CH\(_3\)), 6.96 (3H, s, 6-0CH\(_3\)) and 7.60 (3H, s, N-CH\(_3\)), m/e 368 (M\(^+\)), 352 and 337 (Found: C, 69.01; H, 7.01; N, 7.50. \(C_{21}H_{24}N_2O_4\) requires C, 68.46; H, 6.57; N, 7.60%). Further elution of the column with the same solvent gave a small amount (0.0210 g.) of pure \(\Delta^9\)-indolinocodeinone dimethyl ketal.

\(\alpha\)-Cyanoindolinocodeinone \((32; R^1 = R^2 = 0, X = \text{CN})\) was obtained as colourless crystals from methanol m.p. 218-220°C, \(R_F\) 0.60 (benzene-chloroform, 1:3), \(\nu_{max}\) 2238 (weak, CN) and 1705 cm\(^{-1}\) (conjugated C = 0), \(\tau\) 3.18 and 3.68 (2H, ABq, \(J\) 10 Hz, H-7 and H-8), 3.24 (2H, s, aromatic), 5.28 (1H, s, H-5), 6.11 (3H, s, 3-0CH\(_3\)) and 7.45 (3H, s, N-CH\(_3\)), m/e 322 (M\(^+\)) and 293 (Found: C, 70.40; H, 5.84; N, 8.69. \(C_{19}H_{18}N_2O_3\) requires C, 70.79; H, 5.63; N, 8.69%).

\(\omega\)-Aminomethylindolinocodeinone Dimethyl Ketal \((32; R^1 = R^2 = \text{OCH}_3, X = \text{CH}_2\text{NH}_2)\). - The cyanoketal (0.1970 g.) in ether (15 ml.) was added to a stirred suspension of lithium aluminium hydride (0.1100 g.)
in ether (10 ml.). After stirring for 1 hour the excess reducing agent was destroyed by careful addition of water. The ether layer was separated and the aqueous layer was extracted with a further portion of ether. The combined ethereal extracts were washed with saturated sodium chloride solution, dried (MgSO₄) and evaporated down to give an oil (0.1360 g., 68%), which resisted crystallisation, Rₚ 0.02 (benzene-chloroform, 1:1), T 3.39 (2H, s, aromatic), 4.94 and 4.15 (2H, ABq, J 10 Hz, H-7 and H-8), 5.50 (1H, s, H-5), 6.14 (3H, s, 3-0CH₃), 6.51 (3H, s, 6-0CH₃), 7.04 (3H, s, 6-0CH₃), 7.53 (3H, s, N-CH₃) and 8.35 (2H, broad, s, NH₂, exchanges with D₂O), m/e (M⁺) not observed, 332, 297 and 295.

9α-Isocyanoindolinocodeinone Dimethyl Ketal. (32; R¹ = R² = OCH₃, X = NC). - Silver cyanide (0.50 g.) was added to a solution of 7β-iodoneopinone dimethyl ketal (1.6675 g.) in dry acetone (40 ml.). The mixture was stirred for 12 hours in the absence of light, the insoluble material was filtered off under vacuum and the filtrate was evaporated. Methanol was added to the residue and the insoluble material was again filtered off and washed several times with hot methanol. The filtrate and washings were combined and evaporated (1.2480 g.). The residue on chromatography over alumina (85 g., eluting with benzene-
chloroform, 1:1) gave \( \alpha \)-isocyanooindolinocodeinone dimethyl ketal, the least polar component, as an oil which rapidly crystallised (0.3655 g., 28%). The product was recrystallised from methanol, m.p. 152-153°C, \( R_F \) 0.80 (benzene-chloroform, 1:1), \( \nu_{\text{max}} \) 2140 cm\(^{-1}\) (NO), \( \tau \) 3.32 (2H, s, aromatic), 3.98 and 4.08 (2H, ABq, J 10 Hz, H-7 and H-8), 5.47 (1H, s, H-5), 6.12 (3H, s, 3-OCH\(_3\)), 6.50 (3H, s, 6-OCH\(_3\)), 6.96 (3H, s, 6-OCH\(_3\)) and 7.58 (3H, s, N-CH\(_3\)), m/e 368 (M\(^+\)), 353, 337 and 293 (Found: C, 68.43; H, 6.50; N, 7.60. \( \text{C}_{21}\text{H}_{24}\text{N}_{2}\text{O}_{4} \) requires C, 68.46; H, 6.57; N, 7.60%).

Further elution of the column afforded complex mixtures of other products none of which could be separated into its constituent components.

\( \alpha \)-Formylaminoindolinocodeinone. (32; \( R_1 = R_2 = 0 \), \( X = \text{NHCHO} \)). - Acid hydrolysis in the usual manner of \( \alpha \)-isocyanooindolinocodeinone dimethyl ketal (0.3100 g.) gave a mixture of two products. Separation was affected by chromatography over alumina (30 g.) eluting with benzene-chloroform (1:1). The minor (0.0200 g.) and least polar component was identified as \( \alpha \)-methoxyindolinocodeinone by comparison with an authentic sample (for preparation see later).

\( \alpha \)-Formylaminoindolinocodeinone was obtained as the more polar product (0.2470 g., 87%) forming colourless needles from methanol, m.p. 227.5-228°C, \( R_F \) 0.25
(benzene-chloroform, 1:1), $\nu_{\text{max.}}$ 3420 (NH) 1705-1680 cm$^{-1}$
(broad, CHO and conjugated C = O), $\tau$ 2.23 (1H, broad s, CHO), 3.15 and 3.85 (2H, ABq, J 10 Hz, H-7 and H-8), 3.31 (2H, s, aromatic), 4.86 (1H, m, NH, exchanges on addition of $D_2O-CD_3COOD$), 5.33 (1H, s, H-5), 6.15 (3H, s, 3-OCH$_3$) and 7.36 (3H, s, N-CH$_3$), m/e 340 ($M^+$), 311, 295 and 280 (Found: C, 66.94; H, 6.30; N, 8.12. C$_{19}$H$_{20}$N$_2$O$_4$ requires C, 67.04; H, 5.92; N, 8.23%).

$\gamma$-Azidoindoloincodineone Dimethyl Ketal. (32; $R^1 = R^2 = OCH_3$, $X = N_2$). - $\gamma$-Iodoneopinone dimethyl ketal (1.700 g.) on treatment with sodium azide (1.50 g.) in aqueous dimethylformamide gave an oil, which rapidly crystallised and consisted of two components (1.252 g.). Chromatography over alumina (100 g., benzene-chloroform, 1:1) gave the azido ketal as white crystals, m.p. 115-116°C from methanol, $R_\text{T}$ 0.74 (benzene-chloroform, 1:1), $\nu_{\text{max.}}$ 2105 cm$^{-1}$
(N$_2$), $\tau$ 3.34 (2H, s, aromatic), 4.05 (2H, s, H-7 and H-8), 5.48 (1H, s, H-5), 6.12 (3H, s, 3-OCH$_3$), 6.27 (1H, t, J 2.6 Hz, H-9$\beta$), 6.49 (3H, s, 6-OCH$_3$) and 7.56 (3H, s, N-CH$_3$), m/e ($M^+$) not observed, 356, 329, 314 and 298 (Found: C, 62.44; H, 6.31; N, 14.60. C$_{20}$H$_{24}$N$_4$O$_4$ requires C, 62.48; H, 6.29; N, 14.58%).

Further elution of the column with the same solvent gave $\gamma$-azidoneopinone dimethyl ketal (24; $R^1 = R^2 = OMe$, $X = N_2$), which was obtained as an oil.
and which did not crystallise, \( R_f \) 0.64 (benzene-chloroform, 1:1), \( \nu_{\max} \) 2105 cm\(^{-1}\) (\( N_3 \)), \( \tau \) 3.34 and 3.44 (2H, ABq, J 8 Hz, aromatics), 4.40 and 5.95 (2H, ABq, J 6 Hz, H-8 and H-7), 5.17 (1H, s, H-5), 6.15 (3H, s, 3-OC\( \text{H}_3 \)), 6.50 (3H, s, 6-OC\( \text{H}_3 \)), 7.02 (3H, s, 6-OC\( \text{H}_3 \)) and 7.57 (3H, s, N-CH\( \text{N}_3 \)), m/e 384 (M\(^+\)), 341, 314, 310 and 298. 2-Azidoneopinone Picrate. - Yellow crystals from methanol, m.p. 169-170°C (Found: C, 51.24; H, 4.84; N, 16.24. \( C_{20}H_{24}N_4O_4\cdot C_6H_3N_3O_7 \) requires C, 50.90; H, 4.44; N, 15.98%).

9\( \beta \)-Azidoneopinone. (32; \( R_1 = R_2 = 0, X = N_3 \), - Colourless needles from methanol, m.p. 124-125°C, \( R_f \) 0.43 (benzene-chloroform, 1:1): \( \nu_{\max} \) 2100 (\( N_3 \)) and 1702 cm\(^{-1}\) (conjugated C = 0), \( \tau \) 3.20 and 3.76 (2H, ABq, J 10 Hz, H-7 and H-8), 3.28 (2H, s, aromatic), 5.28 (1H, s, H-5), 6.14 (3H, s, 3-OC\( \text{H}_3 \)) and 7.49 (3H, s, N-CH\( \text{N}_3 \)), m/e (M\(^+\)) not observed, 309, 283 and 254 (Found: C, 63.60; H, 5.51; N, 16.54). \( C_{18}H_{18}N_4O_3 \) requires C, 63.89; H, 5.36; N, 16.56%.

Reaction of Thebaine with Iodine Azide. - Iodine monochloride (0.915 g.) in dry and redistilled acetonitrile (or dimethylformamide, 5 ml.) was added drop-wise to a stirred slurry of sodium azide (0.750 g.) in acetonitrile (or dimethylformamide, 25 ml.) at -20°C. The mixture was stirred for 10 minutes. A slurry of thebaine (1.500 g.) in acetonitrile (10 ml.) was added
to the preformed reagent and the mixture was allowed
to warm up to room temperature and then stirred for a
further 14 hours. The red-brown product was poured
into water (125 ml.) and a small amount of chloroform
was added. The product was then extracted with ether
(2 x 50 ml.). The addition of chloroform prevented
large quantities of insoluble tar being precipitated
out by the ether. The combined ether extracts were
washed with (i) sodium meta-bisulphite solution and
(ii) water, dried (MgSO₄) and evaporated down (0.5640 g.).
The product, a mixture of two components, was per-
colated over alumina and then subjected to p.l.c.
Development of the plates with benzene (twice)
afforded two epimeric diazido ketals. The least
polar component, \(6\alpha,9\alpha\text{-diazidoindolinoisocodeine} \)
methyl ether \((32; R^1 = N_3, R^2 = OCH_3, X = N_3)\), was
obtained as an impure oil (26 mg.) being contaminated
with other material, \(R_F 0.78 \) (benzene-chloroform,
1:1), \(v_{\text{max.}} 2105 \) (broad, \(N_3\)), \(\tau 6.10 \) (3H, s, 3-OCH₃),
6.85 (3H, s, 6β-OCH₃) and 7.44 (3H, s, N-CH₃), other
proton signals were obscured by impurities. The
more polar component, \(6\beta,9\alpha\text{-diazidoindolinoisocodeine} \)
methyl ether \((32; R^1 = OCH_3, R^2 = X = N_3)\), was obtained
as colourless crystals, m.p. 108-110°C from methanol
(33 mg.), \(R_F 0.74 \) (benzene-chloroform, 1:1), \(v_{\text{max.}}
2100 \) (broad, \(N_3\)), \(\tau 3.25 \) (2H, s, aromatic), 3.91
(2H, s, H-7 and H-8), 5.45 (1H, s, H-5), 6.09
(3H, s, 3-OCH₃), 6.38 (3H, s, 6α-OCH₃) and 7.54
(3H, s, N-CH₃), m/e (M⁺) not observed, 340, 325 and
298. No satisfactory analysis could be obtained.

When the reaction was investigated using an ex­
cess of the reagent (1N₃) a third and major product
of unknown constitution was obtained.

Acid hydrolysis of either epimer separately
gave 9α-azidoindolinocodeinone with identical physical
properties to a reference sample.

9α-Aminoindolinocodeinone Dimethyl Ketal. (32;
R¹ = R² = OCH₃, X = NH₂). - 9α-Azidoindolinocodeinone
dimethyl ketal (0.6420 g.) in dry ether (20 ml.) was
added to a suspension of lithium aluminium hydride
(0.6720 g.) in ether (40 ml.). The mixture was
stirred and heated under reflux for 3 hours. The
excess reducing agent was destroyed by cautious
addition of ether saturated with water. The organic
layer was separated and the aqueous layer was ex­
tracted with ether (25 ml.). The combined extracts
were washed with saturated sodium chloride solution,
dried (MgSO₄) and evaporated to give a colourless
oil (0.4380 g., 74%). The product, 9α-aminoindolino­
codeinone dimethyl ketal, was crystallised and re­
crystallised from ether, white crystals m.p. 123-124°C,
Rₚ 0.08 (benzene-chloroform, 1:1), [α]D + 89° (c 0.505)
\( \nu_{\text{max.}} \) 3370 and 3300 cm\(^{-1}\) (weak, \( \text{NH}_2 \)), \( \tau \) 3.35
(2H, s, aromatic), 3.98 (2H, s, H-7 and H-8), 5.47
(1H, s, H-5), 6.12 (3H, s, 3-0CH\(_3\)), 6.48 (3H, s, 6-0CH\(_3\)),
7.04 (3H, s, 6-0CH\(_3\)), 7.53 (3H, s, N-0CH\(_3\)) and 8.50
(2H, s, \( \text{NH}_2 \), exchanges with D\(_2\)O), m/e 358 (M\(^+\), weak),
343 and 326 (Found: C, 67.11; H, 7.29; N, 7.95.
C\(_{20}\)H\(_{26}\)N\(_2\)O\(_4\) requires C, 67.02; H, 7.31; N, 7.82%).

**Formylation of 9α-Aminoindolino-codeinone Dimethyl Ketal.** Based on the formylation procedure of Sheehan and Yang. 85 - The amino ketal (0.1835 g.) was dissolved in formic acid (98%, 10 ml.) and acetic anhydride (4 ml.) was added slowly and dropwise with stirring under nitrogen at a rate to maintain a temperature of 50-55°C, external heating was supplied by an oil bath. After the addition was complete the mixture was stirred for 1 hour at room temperature. Ice was added, the solution was neutralised with sodium hydrogen carbonate solution and extracted with chloroform (2 x 25 ml.). The extracts were dried (MgSO\(_4\)) and evaporated to give crystalline 9α-formylaminoindolino-codeinone (0.1430 g., 82%), m.p. and mixed m.p. 226°C, physical properties identical to an authentic sample.

**9α-Azidoindolino-codeine.** (32; \( R^1 = \text{OH}, R^2 = \text{H}, X = \text{N}_3 \)). - See preparation of 14β-aminocodeine for experimental details. Thus the azido-enone (0.6500 g.) on reduction with a large excess of sodium borohydride
gave white crystals of 9α-azidoindolinocodeine (0.5470 g., 85%), m.p. 171-172°C from methanol, Rf 0.60 (benzene-chloroform, 1:1, black spot with Dragendorf reagent), νmax. 3455 (broad, OH) and 2100 cm⁻¹ (N₂), τ 3.32 (2H, s, aromatic), 3.61 (1H, q, J 6 and 10 Hz, H-7), 4.05 (1H, d, J 10 Hz, H-8), 5.56 (1H, d, J 4 Hz, H-5), 5.82 (1H, m, H-6), simplifies to a dd on addition of D₂O), 6.14 (3H, s, 3-OCH₃), 6.76 (1H, q, J 3 and 18 Hz, H-10α), 7.24 (1H, q, J 3 and 18 Hz, H-10β), 7.57 (3H, s, N-CH₃) and 7.75 (1H, broad s, OH, exchanges with D₂O), m/e (M⁺) not observed, 285 and 256 (Found: C, 63.50; H, 6.24; N, 16.54. C₁₈H₂₀N₄O₃ requires C, 63.51; H, 5.92; N, 16.46%).

9α-Aminindoindolinocodeine. (32; R₁ = OH, R₂ = H, X = NH₂) - See preparation of 9α-aminoindolinocodeine dimethyl ketal for experimental details. Thus the 9α-azido-alcohol (1.90 g.) in ether (500 ml.) on reduction with lithium aluminium hydride (2.10 g.) in ether (100 ml.) gave an oily product (0.8230 g.) which contained some starting material. The 9α-amino-alcohol was obtained pure by chromatography over alumina (80 g., benzene-chloroform, 1:3). The product was recrystallised from methanol (0.5380 g., 31%), m.p. 232-234°C, Rf 0.15 (benzene-chloroform, 1:1, black spot), τ 3.39 (2H, s, aromatic), 3.58 (1H, q, J 6 and 10 Hz, H-7), 4.01 (1H, d, J 10 Hz, H-8), 5.58 (1H, d, J 4 Hz, H-5), 5.85 (1H, dd, J 4 and 6 Hz, H-6),
6.10 (3H, s, 3-OCH$_3$), 7.55 (3H, s, N-CH$_3$) and 7.78 (2H, s, NH$_2$, exchanges with D$_2$O), m/e 314 (M$^+$, weak) and 296 (Found: C, 68.78; H, 7.18; N, 8.86. C$_{18}$H$_{23}$N$_2$O$_3$ requires C, 68.77; H, 7.05; N, 8.91%).

9α-Acetylaminoindolinocodeine. (32; R$^1$ = OH, R$_2$ = H, X = NHCOCH$_3$). - Acetic anhydride (0.4 ml.) was added to a solution of the amino-alcohol (0.0960 g.) in dry pyridine (4 ml.) and the solution was allowed to stand at room temperature for 12 hours. The solvent was removed under reduced pressure, the residue was dissolved in ethanol-water (10 ml., 1:1) and 2N-sodium hydroxide was added. The mixture was shaken for 4 hours at room temperature, the solvent was evaporated off, water was added to the residue which was extracted with chloroform (2 x 15 ml.). The extracts were dried (MgSO$_4$) and evaporated down to give 9α-acetylaminoindolinocodeine as an oil which rapidly crystallised (0.0850 g., 80%), white needles from methanol m.p. 241-242°C, $\alpha$$_D$ +210° (C 0.442), R$_F$ 0.34 (chloroform, cf. 9α-aminocodeine 0.15), $\nu$$_{max}$ 3340 (broad, CH and NH) 1660 and 1540 cm$^{-1}$ (amide), $\tau$ 3.27 (2H, s, aromatic), 3.42-4.05 (3H, m, H-7, H-8 and NH, NH exchanges with D$_2$O-CD$_3$COOD), 5.40-5.80 (3H, m, H-5, H-6$,^p$, H-9$^p$), 6.19 (3H, s, 3-OCH$_3$), 7.48 (3H, s, N-CH$_3$) and 8.39 (3H, s, CH$_2$CO), m/e 356 (M$^+$), 313 and 297 (Found: C, 67.21; H, 6.98; N, 7.80.)
C20H24N2O4 requires C, 67.39; H, 6.79; N, 7.86%.

9α-Acetylaminoinolinocodine Acetate. (32; R1 = CH3COO, R2 = H, X = NHCOCH3). - Acetic anhydride (1 ml.) was added to a solution of the amino-alcohol (0.0500 g.) in pyridine (2 ml.) and the mixture was heated under reflux for 3 hours. The solvent was evaporated off, the residue was dissolved in water and the resulting solution was neutralised with sodium hydrogen carbonate solution and extracted with chloroform (2 x 15 ml.). The extracts were dried (MgSO4) and evaporated to give a colourless oil which would not crystallise (0.0540 g., 85%), Rf 0.70 (chloroform), Vmax. 3420 (NH), 1748 (acetate), 1668 and 1535 cm⁻¹ (amide), δ 3.32 (2H, s, aromatic), 3.75 (1H, q, J 1 and 10 Hz, H-7), 4.05 (1H, d, J 10 Hz, H-8), 4.22 (1H, q, J 1 and 5 Hz, H-6β), 4.78 (1H, m, NH, exchanges with D2O-CD3COOD), 5.44 (1H, d, J 5 Hz, H-5), 6.12 (3H, s, 3-0CH3), 7.46 (3H, s, N-CH3), 8.35 (3H, s, CH3CO) and 8.40 (3H, s, CH2CO), m/e 398 (M+), 383, 355, 339 and 338 (Accurate mass measured 398.1841. C22H26N2O5 requires 398.1842). The picrate was also an oil, which resisted crystallisation.

9α-Formylaminoinolinocodeine. (32; R1 = OH, R2 = H, X = NHCHO). - The amino-alcohol (0.1030 g.) was formylated according to the above procedure for
9α-aminoindolinocodeinone dimethyl ketal. Base was necessary during work up to hydrolyse O-esters (see preparation of N-acetyl compound). The crystalline residue (0.0880 g.) was columned over alumina (20 g., chloroform as solvent) to separate it into its two constituents. The formyl-alcohol, the least polar component, was obtained as white crystals from methanol (0.0280 g., 25%) m.p. 257-259°C, Rf 0.35 (chloroform), $\nu_{\text{max.}}$ 3340 (NH), and 1675 cm$^{-1}$ (CHO), 7.23 (1H, broad s, CHO), 3.34 (2H, s, aromatic), 3.52-4.06 (3H, m, H-7, H-8 and N-H), 5.42-5.74 (3H, m, H-5, H-6 and H-9), 6.17 (3H, s, 3-CH$_3$), and 7.50 (3H, s, N-CH$_3$), m/e 342 ($M^+$), 324 313 and 297.

Reduction of 9α-Formylaminoindolinocodeinone. - See preparation of 14β-aminocodeine for experimental details. The N-formyl ketone (0.2470 g.) on reduction with excess sodium borohydride gave an oil which was a mixture of two compounds. Partial separation was achieved by chromatography over alumina (30 g.). Elution with chloroform gave a mixture of the most polar and least polar compounds (0.0790 g.) and a pure sample of the most polar component (0.0650 g.). The inseparable mixture was subjected to p.l.c. on alumina (chloroform as solvent) to give a further quantity (0.0210 g.) of the most
polar component and a pure sample of the faster running compound (0.0110 g.). The more polar compound had identical physical properties to 9α-formylaminoindolinocodeine. The epimer and major product, 9α-formylaminoindolinoisocodeine, was obtained as white crystals (0.0860 g., 35%), m.p. 268–270°C from methanol, R f 0.13 (chloroform, both epimers gave blue-black spots), V max. 3420 (broad, NH and OH) and 1685 cm⁻¹ (CHO), τ 2.15 (1H, broad s, CHO), 3.30 (2H, s, aromatic), 4.16 (2H, s, H-7 and H-8), 5.72 (1H, d, J 8 Hz, H-5), 6.14 (3H, s, 3-OCH₃) and 7.47 (3H, s, N-CH₃), m/e 342 (M⁺), 325, 324, 313, 298 and 297. No satisfactory analysis could be obtained.

9α-Methoxycarbonylaminoindolinocodeine. (32; R¹ = OH, R² = H, X = NHCOOCH₃). - A large excess of methyl chloroformate (3 μl.) was added to a solution of the amino-alcohol (0.1350 g.) in methanol (10 ml.). The mixture was allowed to stand at room temperature for 24 hours. The solvent was evaporated, water was added to the residue, which was neutralised with sodium hydrogen carbonate solution and extracted with chloroform (2 x 15 ml.). The extracts were dried (MgSO₄) and evaporated. The product was columned over alumina (12 g., eluting with chloroform) to remove traces of unreacted starting material. The
N-methoxycarbonyl alcohol was obtained as an oil, which resisted crystallisation (0.0940 g., 59%), Rf 0.90 (chloroform, black spot), $\nu_{\text{max}}$ 3340 (broad, NH and OH), 1708 and 1530 cm$^{-1}$, $\tau$ 3.35 (2H, s, aromatic), 3.76-4.14 (2H, m, H-7 and H-8), 4.45 (1H, m, NH exchanges slowly with D$_2$O-CD$_3$COOD), 5.44-6.06 (3H, m, H-5, H-6$^\beta$, H-9$^\beta$), 6.23 (3H, s, 3-OCH$_3$), 6.52 (3H, s, COOCH$_3$) and 7.48 (3H, s, N-CH$_3$), m/e 372 (M$^+$), 354, 343 and 313.

9α-Methoxycarbonylaminopindolinocodeine picrate was obtained as yellow crystals from methanol, m.p. 207-210°C (Found: C, 51.71; H, 4.80; N, 11.90. C$_{20}$H$_{24}$N$_2$O$_5$.C$_6$H$_3$N$_3$O$_7$ requires C, 51.91; H, 4.52; N, 11.64%).

9α-Chloroindolinocodeinone. (32; $R^1 = R^2 = 0$, X = Cl). - A chilled solution of mesyl chloride (0.2 ml.) in pyridine (0.5 ml.) was added to a solution of 9α-hydroxyindolinocodeinone (0.3770 g.) in pyridine (1.5 ml.) at 0°C. The mixture was allowed to remain at 0°C for 1 hour with intermittent shaking and then stood at room temperature overnight. The red solution was poured into iced water (40 ml.) and basified cautiously with ammonium hydroxide solution. The aqueous solution was extracted with ethyl acetate (2 x 40 ml.), the extracts were combined and washed with water, dried (MgSO$_4$) and evaporated down (0.2790 g.).
The residue was percolated through alumina using chloroform as solvent. Evaporation of solvent gave 9α-chloroindolinocodeinone (0.1320 g., 33%) as colourless needles from methanol, m.p. 116-120°C, R\textsubscript{F} 0.60 (benzene-chloroform, 1:1), \( \nu_{\text{max}} \) 1702 cm\(^{-1}\) (conjugated C = O), \( \tau \) 3.26 and 3.76 (2H, ABq, J 10 Hz, H-7 and H-8), 3.30 (2H, s, aromatic), 5.26 (1H, s, H-5), 5.68 (1H, dd, J 2.7 and 3.3 Hz, H-9β), 6.12 (3H, s, 3-OCH\(_3\)), 6.55 (1H, q, J 2.7 and 15 Hz, H-10α), 7.15 (1H, q, J 3.1 and 15 Hz, H-10β) and 7.44 (3H, s, N-CH\(_3\)), m/e 333, 331 (M\(^+\)), 296, 283, 268 and 254 (Accurate mass measured 296.1291. \( C_{18}H_{18}NO_3 \) requires 296.1287).

9α-Thiocyanatoindolinocodeinone Dimethyl Ketal. (32; \( R^1 = R^2 = \text{OCH}_3 \), \( X = \text{SCN} \)). - Obtained by treatment of 7β-iodoneopinone dimethyl ketal (1.6870 g.) with potassium thiocyanate (2.0 g.) in aqueous dimethylformamide using the general procedure. The residue (0.9030 g.) was chromatographed over alumina (100 g.). Elution with benzene-chloroform (2:3) gave the thiocyanate as white crystals (0.1480 g., 10%), m.p. 171-172°C from methanol, R\textsubscript{F} 0.47 (benzene-chloroform, 1:1), \( \nu_{\text{max}} \) 2145 cm\(^{-1}\) (SCN), \( \tau \) 3.29 (2H, s, aromatic), 3.96 (2H, s, H-7 and H-8), 5.46 (1H, s, H-5), 6.09 (3H, s, 3-OCH\(_3\)), 6.50 (3H, s, 6-OCH\(_3\)), 7.00 (3H, s, 6-OCH\(_3\)) and 7.51 (3H, s, N-CH\(_3\)), m/e 400 (M\(^+\)), 371, 344 and 312 (Found: C, 63.15; H, 6.24; N, 6.86.)
C$_{21}$H$_{24}$N$_2$O$_4$S requires C, 62.99; H, 6.04; N, 7.00%.

9α-Nitritoindolinocodeinone Dimethyl Ketal. (32; R$^1$ = R$^2$ = OCH$_3$, X = ONO). - Silver nitrite (2.0 g., freshly prepared) was added to a solution of 7β-ido-neopinone dimethyl ketal (1.7300 g.) in dry acetone (50 ml.). The mixture was stirred for 12 hours, the insoluble material was filtered off and the filtrate was evaporated (1.300 g.). The residue, a mixture of two compounds, was chromatographed over alumina (100 g.).

9α-Nitritoindolinocodeinone dimethyl ketal (0.2050 g.) was eluted first with benzene-chloroform (1:1), but was contaminated with the more polar component, 9α-hydroxyindolinocodeinone dimethyl ketal. The mixture was recolumned over alumina (30 g.) to give a small quantity of crystalline nitrito ketal (0.0370 g.). Because the nitrito ketal was unstable on chromatography and recrystallisation caused further decomposition it was not further purified, R$_F$ 0.74 (benzene-chloroform, 1:1), $\lambda_{max}$ 281.5, $\upsilon_{max}$ 1628 cm$^{-1}$ (ONO), τ 3.32 (2H, s, aromatic), 4.06 (2H, s, H-7 and H-8), 4.66 (1H, t, J 3.5 Hz, H-9β), 5.45 (1H, s, H-5), 6.10 (3H, s, 3-OCH$_3$), 6.50 (3H, s, 6-OCH$_3$), 7.02 (3H, s, 6-OCH$_3$) and 7.47 (3H, s, N-CH$_3$), m/e 388 (M$^+$), 373, 358, 342 and 327. The product could not be obtained sufficiently pure for analysis.

9α-Dimethylaminoindolinocodeinone Dimethyl Ketal.
Anhydrous dimethylamine (5 ml.) was added to a chilled solution of 7β-iodoneopinone dimethyl ketal (0.7650 g.) in dry dimethylformamide. The mixture was stored at 0°C for 12 hours and then allowed to warm up to room temperature. After pouring into water (150 ml.), the aqueous solution was extracted with ether (2 x 100 ml.) and the ethereal extracts were washed with (i) two portions of water and (ii) two portions of saturated sodium chloride solution. The extract was dried (MgSO₄) and evaporated to give an oily residue (0.6610 g.), which was chromatographed over alumina (50 g.). Elution with benzene-chloroform (1:1) gave 9α-dimethylaminoindolinocodeinone dimethyl ketal as an oil (0.1650 g., 26%), which did not crystallise, Rf 0.58 (benzene-chloroform, 1:1), τ 3.34 (2H, s, aromatic), 3.92 and 4.16 (2H, ABq, J 10 Hz, H-7 and H-8), 5.43 (1H, s, H-5), 6.08 (3H, s, 3-OCH₃), 6.48 (3H, s, 6-OCH₃), 6.99 (3H, s, 6-OCH₃), 7.54 (3H, s, N-CH₂) and 8.08 (6H, s, N-(CH₃)₂), m/e 386 (M⁺), 371, 355 and 342.

9α-Dimethylaminoindolinocodeinone dimethyl ketal picrate was obtained as yellow crystals from methanol (Found: C, 54.89; H, 5.38; N, 11.31. C₂₂H₂₀N₂O₄·C₆H₃N₃O₇ requires C, 54.63; H, 5.40; N, 11.33%).

Other Reactions of 7β-Iodoneopinone Dimethyl Ketal. - The following reactions summarised in the table were also carried out. The products were separated by chromatography over alumina and were identical with
reference samples.

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<td>24</td>
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</table>

* products were inseparable in this case.

9α-Methoxyindolinocodeinone Dimethyl Ketal (32; \( R^1 = R^2 = X = \text{OCH}_3 \)). - A solution of 7β-iodoneopinone dimethyl ketal (0.9250 g.) in methanol (40 ml.) was heated under reflux for 8 hours. The methanol was evaporated off and the residue (0.8350 g.) was dissolved in benzene-chloroform (1:1) and subject to chromatography over alumina (100 g.). Elution with benzene-chloroform (1:1) gave the 9α-methoxy ketal as a pure crystalline component (0.0320 g., 4.3%).
m.p. 104-104.5°C from methanol, Rf 0.78 (benzene-chloroform, 1:1), $\alpha_7^D +98^\circ$ (C 0.586), $r$ 3.35 (2H, s, aromatic), 4.00 and 4.18 (2H, ABq, J 10 Hz, H-7 and H-8), 5.46 (1H, s, H-5), 6.10 (3H, s, 3-0CH$_3$), 6.50 (3H, s, 6-0CH$_3$), 6.91 (3H, s, 6-0CH$_3$), 7.07 (3H, s, 9α-0CH$_3$) and 7.53 (3H, s, N-CH$_3$), m/e 373 (M$^+$), 358 and 342 (Found: C, 67.45; H, 7.05; N, 4.13. C$_{21}$H$_{27}$NO$_5$ requires C, 67.6; H, 7.29; N, 3.75%).

9α-Methoxyindolinocodeinone. (32; $R^1 = R^2 = 0$, X = OCH$_3$). - Obtained as white crystals from methanol, m.p. 158.5-159.5°C, Rf 0.35 (benzene-chloroform, 1:1), $\alpha_7^D +104^\circ$ (C 0.865), $\nu$ max. 1695 cm$^{-1}$ (conjugated C = O), $r$ 3.22 and 3.81 (2H, ABq, J 10.8 Hz, H-7 and H-8), 3.34 (2H, s, aromatic), 5.32 (1H, s, H-5), 6.14 (3H, s, 3-0CH$_3$), 6.45 (1H, t, J 2.6 Hz, H-9β), 6.94 (3H, s, 9α-0CH$_3$) and 7.44 (3H, s, N-CH$_3$), m/e 327 (M$^+$), 312, 298 and 296 (Found: C, 69.97; H, 6.43; N, 4.31. C$_{19}$H$_{21}$NO$_4$ requires C, 69.70; H, 6.47; N, 4.28%).

9α-Methoxyindolinocodeinone Dimethyl Ketal. - Alternative methods based on the methanolysis of 14-bromocodeinone dimethyl ketal by Heinisch et al.$^{44}$

(i) From 7β-iodoneopinone dimethyl ketal: The iodo ketal (1.451 g.) was dissolved in methanol (50 ml.) and sodium carbonate (164 mg., previously heated at 150°C for 2 hours) was added. The mixture was heated
under reflux for 12 hours, the solvent was evaporated and the residue was treated with several portions of hot ether. The ethereal solution was washed with water, dried (MgSO₄) and methyl iodide (1 ml.) was added. The mixture was refluxed for 4 hours; after approximately 5 mins. an oily whitish precipitate was formed which crystallised on scratching. The precipitate was filtered off and the filtrate was evaporated to give an oil, 9α-methoxyindolinocodeinone dimethyl ketal, which crystallised on addition of methanol (0.3110 g., 27%), m.p. and mixed m.p. 104°C.

(ii) From 14β-bromocodeinone dimethyl ketal:
The 14β-bromo ketal (0.4850 g.) under identical conditions also gave 9α-methoxyindolinocodeinone dimethyl ketal (0.0920 g., 21%), m.p. and mixed m.p. 104°C.

Aziridinium Perchlorate. (48; R¹ = R² = OCH₃, perchlorate salt).

(i) From 7β-iodoneopinone dimethyl ketal: A solution of silver perchlorate (0.7000 g.) in benzene (30 ml.) was added to a stirred solution of 7β-iodoneopinone dimethyl ketal (1.5810 g.) in benzene (20 ml.). The mixture was stirred vigorously for 2 mins. and then filtered through Celite to remove the precipitated silver iodide. The filtrate was evaporated to give the aziridinium perchlorate as a white foam (0.4800 g., 32%), 3.28 (2H, s, aromatic), 3.58
and 3.96 (2H, ABq, J 10.5 Hz, H-7 and H-8), 5.06 (1H, s, H-5), 6.20 (3H, s, 3-OCH₃), 6.60 (3H, s, 6-OCH₃), 6.60 (3H, N⁺-CH₃) and 6.94 (3H, s, 6-OCH₃).

(ii) From 14β-bromocodeinone dimethyl ketal:
The bromo ketal (1.9300 g.) was treated with AgClO₄ (1 equivalent) in an identical reaction. The same aziridinium perchlorate (0.7100 g., 35%) was obtained as a white foam.

The aziridinium perchlorate could not be crystallised from a variety of solvents.

Reaction of the Aziridinium Perchlorate with Sodium Acetate. - A solution of sodium acetate (0.50 g.) in water (5 ml.) was added to a solution of the aziridinium cation (0.4800 g.) in dimethylformamide (25 ml.). The mixture was stirred at room temperature for 12 hours, poured into water (100 ml.) and the solution was extracted with ether (2 x 50 ml.). The extracts were combined, washed with water and saturated sodium chloride solution, dried (MgSO₄) and evaporated (0.1810 g.). The partially crystalline residue was chromatographed over alumina (25 g.) to give 9α-indolino acetoxycodeinone dimethyl ketal as white crystals on elution with benzene-chloroform (1:1). The product was recrystallised from methanol m.p. and mixed m.p. 123-123.5°C, identical with a reference sample.

Reaction of the Aziridinium Perchlorate with
Sodium Cyanide. - In an analogous experiment the aziridinium salt (0.7100 g.) was reacted with sodium cyanide (0.60 g.) in aqueous dimethylformamide. Chromatography of the residue (0.3500 g.) over alumina (35 g.) afforded 9d-cyanoindolinocodeinone dimethyl ketal (0.2030 g., 34%) on elution with benzene-chloroform (2:3). The product was recrystallised from methanol, m.p. and mixed m.p. 157-158°C, identical to a reference sample. Further elution of the column yielded a small quantity of $\Delta^9$-indolinocodeinone dimethyl ketal with identical physical properties to a reference sample.
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