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14-HYDROXYCODEINE AND DERIVATIVES.

A C K N O W L E D G M E N T S

The author records his sincere thanks to Dr. F. S. Spring, F.R.S., and Dr. G. T. Newbold for their sustained advice, interest, and encouragement; to Professor P. L. Pauson for his helpful supervision during the later stages of this work; and to Messrs. T. and H. Smith Ltd., Edinburgh, for the gift of alkaloids.

OBJECTIVE

The object of this work was to prepare a series of 14-substituted codeine derivatives for pharmacological study using the natural product thebaine as starting material. Thebaine is easily converted into 14-hydroxy-codeinone and the preparation of 14-substituted codeine derivatives from this compound presented interesting problems of reaction mechanism and stereochemistry as well as providing compounds of considerable interest as analgesics.

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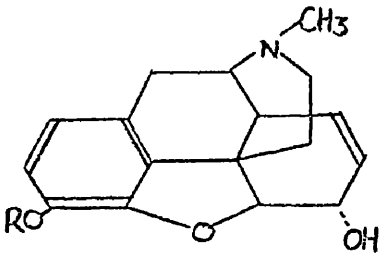
INTRODUCTION

The extraction of opium from the unripe seed capsules of the poppy plant, Papaver somniferum, was well known by the ancient Greeks and to them is accredited the compounding of tincture of opium, or laudanum, which is still the official preparation. By the middle of the sixteenth century the uses of opium which are valid today were fairly well understood in Europe but until well into the nineteenth century the only opium preparations used medicinally were crude extracts.

The isolation of the related alkaloids, morphine (I, R = H) (Serturner 1805), codeine (I, R = CH_3) (Robiquet 1811), and thebaine (II)(Pelletier 1832) along with papaverine (III) (Merck 1848) resulted in the use of pure alkaloids rather than crude preparations spreading throughout the medicinal world. Further accounts of the history of opium and its alkaloids are given by Macht (1915)[1] and Hanzlik (1929).[2]



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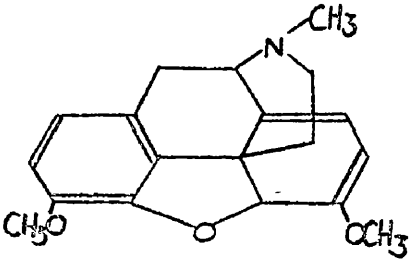

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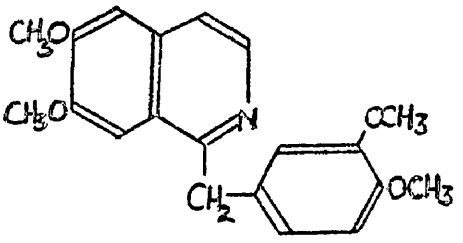

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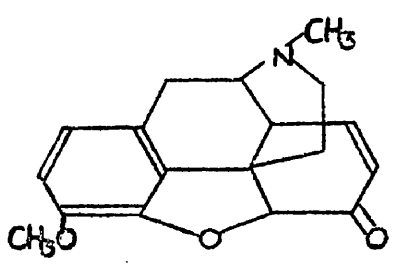
The initial researches of von Gerichten,[3,4,5,6] Knorr,[7,8] and Pschorr[9,10] which established the positions of the oxygen substituents and the existence of a bridged-phenanthrene type of structure for morphine were followed in the next twenty years by attempts to place the nitrogen bridge. All the positions proposed however failed to provide a basis for the many transformations which morphine, thebaine, and codeinone (IV) undergo with acid, until Gulland and Robinson,[11,12] supported by Schöpf,[13] in 1925 proposed the structure (I, R = H) for morphine in which the carbon end of the nitrogen bridge is attached to the fully substituted angular position 13. The rearrangement of the chain leads to transformation products e.g. metathebainone (V), thebenine (VI), and morphothebaine (VII) which arise from the addition of a proton to the postulated[14] common intermediate (VIII).

The total synthesis of morphine was first carried out by Gates and Tschudi[15,16] and confirmed Gulland and Robinson's structure.



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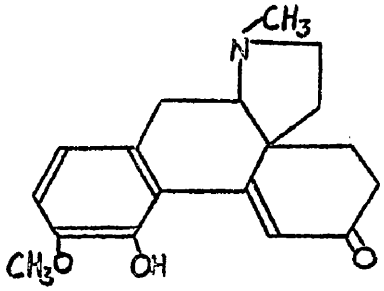

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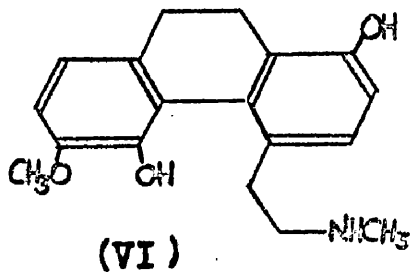

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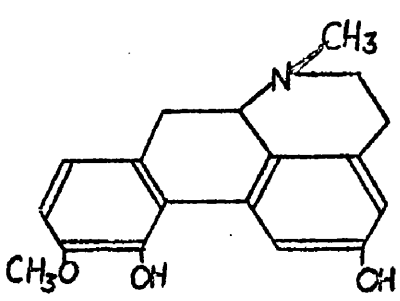

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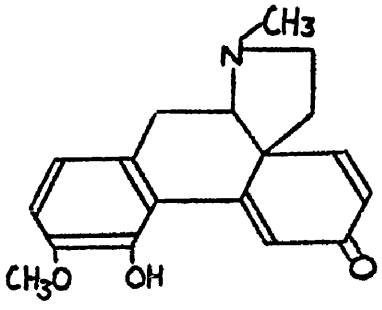

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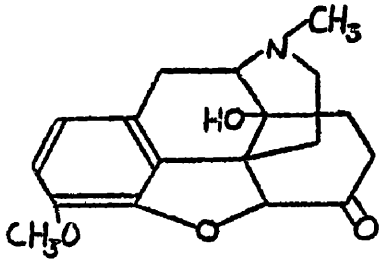


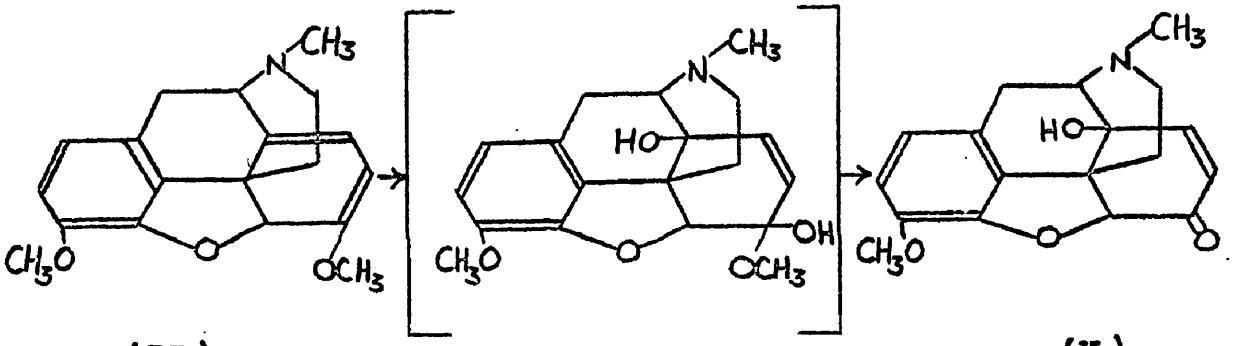
(IX)

Morphine and codeine have wide clinical use as analgesics but thebaine has little activity. Thebaine can be converted to codeine[17] but it is also desirable to prepare new codeine derivatives from thebaine which will enhance the analgesic potency of codeine (one sixth that of morphine). 14-Hydroxydihydrocodeinone (IX) is marketed as a drug under the trade name "eukodal"[18,19,20] (eucodal) and is easily prepared from thebaine.[21,22,23,24] 14-Hydroxy derivatives of codeine therefore showed great promise as analgesics and the object of this work was to prepare 14-hydroxy and 14-acyloxy codeine derivatives for pharmacological testing. The preparation of these compounds introduced many problems of stereochemistry and reaction mechanism.

14-<u>Hydroxycodeinone</u>.

(Note: The convention[15] of denoting 14β-substituents by a full line into ring B will be used. The nomenclature is that used by Bentley[14] e.g. 14-hydroxydihydrocodeinone instead of dihydro-14-hydroxycodeinone).

14-Hydroxycodeinone (X) is prepared by the oxidation of thebaine with peracetic acid[21] or performic acid[25] (in 60-77% and 80-90% yield respectively) the reaction involving 1,4 addition of hydroxyl groups to the conjugated diene system of thebaine followed by elimination of methanol from the C_6 intermediate hemiacetal.



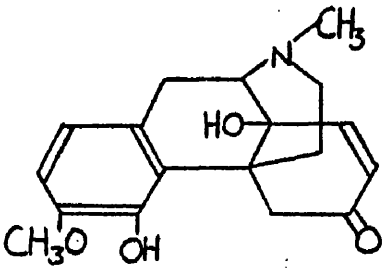
(II) (X)

Freund[25a] showed that 14-hydroxy- and 14-bromocodeinone[17,25a] have the morphine skeleton intact by conversion of the latter to 14-hydroxycodeinone oxime with hydroxylamine and by its reduction with ferrous hydroxide to codeinone. 14-Hydroxycodeinone was first considered to be an α-hydroxy ketone but this formulation was rejected by Gulland and Robinson[12] since the base was stable to alkaline silver and cupric solutions. A β-hydroxy ketone structure was also rejected because of the difficulties observed of dehydrating 14-hydroxycodeinone and derivatives, but a γ-hydroxy ketone structure is in agreement with all the experimental facts and although 14-hydroxycodeinone does not show the properties of

a methylene ketone, the dihydro ketone (IX) does indicating the presence of the system -CO-C=C-C-OH in the former.

Since the 14-position in 14-hydroxycodeinone is blocked, the morphine type of intermediate (VIII) cannnot be formed and this fact accounts for the great stability of 14-hydroxycodeinone in acid solution compared with codeinone.

14-Hydroxycodeinone on catalytic hydrogenation affords 14-hydroxydihydrocodeinone[21,22,23,24] but on reduction with zinc dust and acetic acid[21,26] yields "hydroxycodeine" the reaction presumably involving a change in ring structure.[26,27] Opening of the cyclic ether link occurs when 14-hydroxycodeinone is reduced under acid conditions; reduction with stannous chloride and hydrochloric acid giving 14-hydroxythebainone (XI)[22,22a,48] which can be catalytically reduced to 14-hydroxydihydrothebainone (XII) also prepared by Clemmensen reduction,[21] prolonged catalytic hydrogenation,[48] or sodium amalgam in alcohol reduction[21] of 14-hydroxycodeinone.



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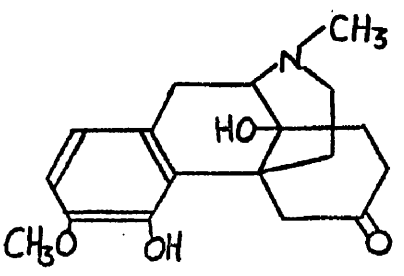
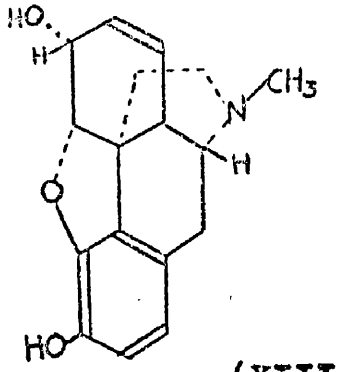


(XII)

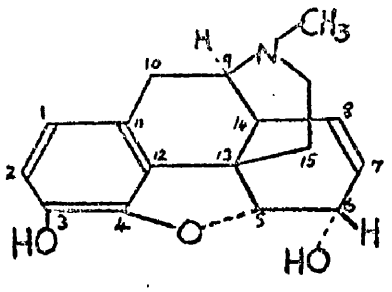
Hydrogenation of both 14-hydroxycodeinone and 14-hydroxydihydrocodeinone using platinum oxide as catalyst gives a mixture of epimers 14-hydroxydihydrocodeine B and 14-hydroxydihydrocodeine C both different from 14-hydroxydihydrocodeine A the catalytic hydrogenation product of "hydroxycodeine".[28]

Stereochemistry of Morphine.

The stereochemistry of the five asymmetric centres in morphine was deduced by Stork[28] on mechanistic grounds but he made no claims as to the absolute stereochemistry; Bentley and Cardwell[29] from molecular rotation studies and Jeger et al.[30] from degradations have subsequently shown that the absolute stereochemistry of (-)-morphine is represented by (XIIIb) and not by its enantiomorph (XIIIa). The validity of Stork's deductions are however unaffected and can be summarised as follows:



(XIIIa)

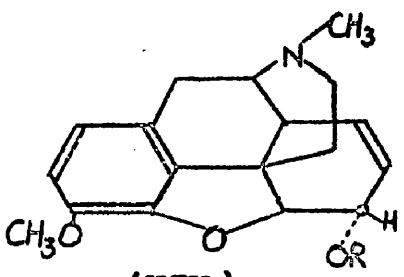


(XIIIb)

(i) Relation of C_5 oxygen to C_6 hydrogen.

The assumption is made that the C_6 hydrogen in codeine extends above the plane of the ring (XIV, R = H); the C_6 epimeric alcohol, isocodeine is represented by (XV, R = H). Of the two methyl ethers, one is recovered from sodium methoxide without

epimerisation while the other, codeine methyl ether (XIV, R = CH_3) is isomerised to the phenolic enol methyl ether (XVI). This β-elimination reaction requires the C_5 oxygen to be <u>trans</u> to the C_8 hydrogen. The rates of cleavage of derived glycols[31] by lead tetra-acetate support this conclusion.



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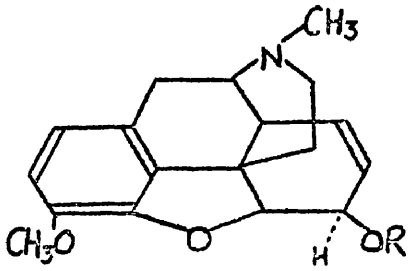

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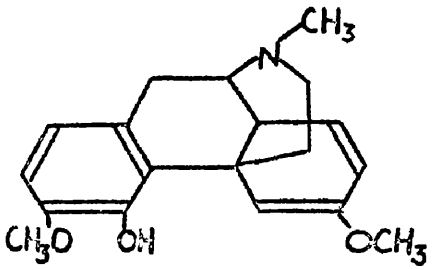
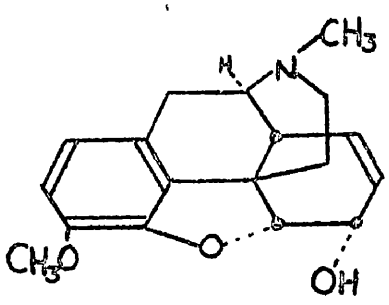


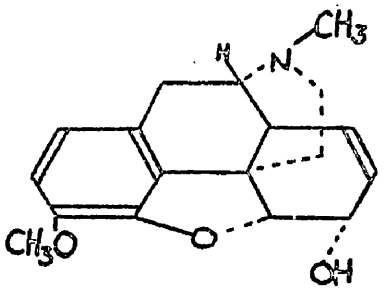
(XVI)

(ii) Relation of C_9-C_{13} side chain to the C_8-hydrogen.

There are two possible orientations for the C_{13} side chain with respect to C_8, viz., (XVII) and (XVIII)



(XVII)



(XVIII)

In the former, the five membered oxide ring and ring C have a <u>cis</u> junction and of necessity C_{13} is <u>trans</u> to the bridge oxygen whereas in (XVIII) the ring junction is <u>trans</u> and the relationship of C_{13} to the bridge oxygen is <u>cis</u>. The formula (XVII) must

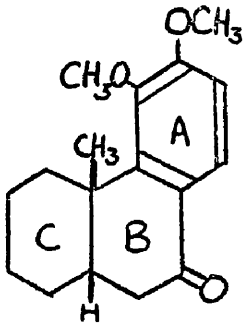
represent the relationship existing in codeine since if a trans 6-5 fused ring system were present in dihydrocodeinone it would be epimerised by base to the more stable cis system.

This does not happen[28] and since dihydrocodeine is the sole product of catalytic hydrogenation of dihydrocodeinone[32] the C_5-C_{13} cis relationship must also exist in codeine and dihydrocodeine.

(iii) The configuration at C_{14}.

The catalytic hydrogenation of the diene system of thebaine requires that the C_5 and C_{14} hydrogen atoms be cis, and since the product dihydrocodeine methyl ether has the same configuration as codeine methyl ether (C_5 and C_6 hydrogens cis), the hydrogen atoms at C_5, C_6, and C_{14} are cis.

Jeger et al.[30] in a controlled degradation of thebaine through ketone (XIX) to (-)-cis-2-methyl-2-carboxycyclohexyl acetic acid (XX) proved that the junction between rings B and C in 8,14-dihydrothebaine (and hence in morphine) is cis. He also concluded that rings C and B in morphine correspond to rings A and B in the 5β steroids and the ethanamine bridge (including carbon atoms 15 and 16) has the same spatial position as the β-methyl group at C_{10} of the steroids (XXI) and polyterpenes.



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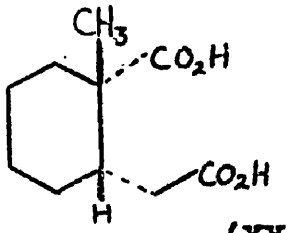

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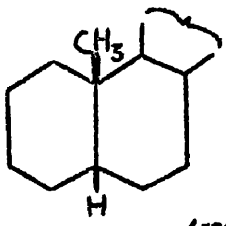
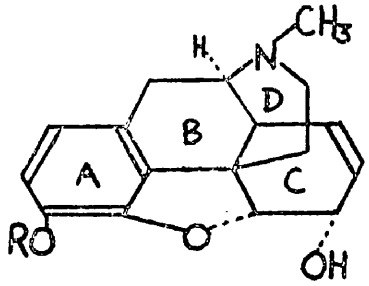


(XXI)

Conformation.

These stereochemical relationships and the crystallographic studies by Mrs. Hodgkin[33] showed that morphine (XXII, R = H) and codeine (XXII, R = CH_3) are roughly T-shaped with two planes nearly at right angles to each other; one plane includes the aromatic ring A, the ether-ring, and ring B. B and C form a cis-octalin system, while rings C and D are fused in the form of a trans octahydroisoquinoline system to give the second plane.



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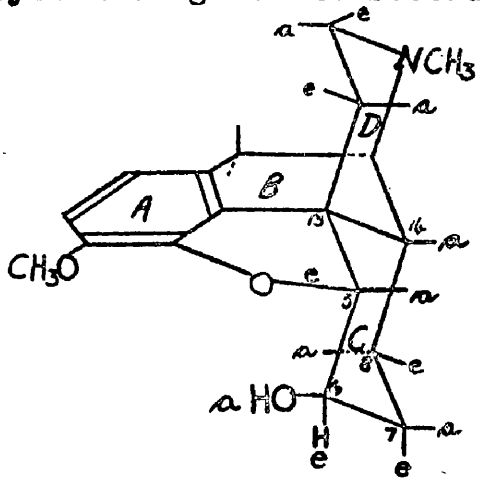


(XXIII)

In 14-hydroxy- and 14-bromocodeinone, the attacking reagent must approach from the less hindered side[14,34] and therefore the 14-substituent must be cis to the ethanamine chain.

The conformation of dihydrocodeine (XXIII), codeine,

and their isomers has been deduced in the following ways: from relative ease of oxidation of epimeric alcohols[35] since axial alcohols are oxidised preferentially to equatorial alcohols;[36] from reduction of ketones with different reagents which often give alcohols of definite configuration;[36] and from solvolysis reactions of alicyclic chlorocompounds. These deductions are the subject of a review[37] by Ginsburg on conformational analysis of the morphine alkaloids.

SUMMARY

A series of 14-substituted codeine derivatives were prepared for pharmacological study by sodium borohydride reduction of the corresponding 14-hydroxy and 14-acyloxycodeinones. The epimeric 14-substituted isocodeines were not formed by this reaction but were prepared using 14-hydroxycodeine tosylate as an intermediate. The latter compound on treatment with 70% acetic acid gave the 14-hydroxyallopseudocodeine series. Lithium aluminium hydride reduction of 14-hydroxycodeine tosylate gave 14-hydroxydeoxycodeine and the very active analgesics, the 14-acyloxydeoxycodeines.

Attempts to prepare known codeine derivatives from "hydroxycodeine", the non-phenolic compound from the reaction of zinc dust and acetic acid on 14-hydroxycodeinone are described and a new structure is postulated. A new method is reported for the synthesis of 14-hydroxy-N-alkylnorcodeines. This involves the formation of 14-hydroxy-N-acylnorcodeine derivatives from the corresponding 14-acyloxy-N-cyano compound by acyl migration, and their reduction with lithium aluminium hydride.

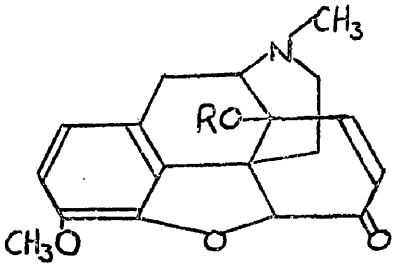
THEORETICAL

The reduction of 14-hydroxycodeinone (XXIV, R = H) with sodium borohydride was recently described by Sargent, Schwartzman, and Small.[27] They obtained an unsaturated diol hydrogenation of which gave 14-hydroxydihydrocodeine B previously obtained[26] together with 14-hydroxydihydrocodeine C by catalytic hydrogenation of 14-hydroxydihydrocodeinone (XXV, R = H). Since sodium borohydride reduction of codeinone gives a nearly quantitative yield of codeine,[38] Sargent *et al.* inferred that the product obtained by similar reduction of 14-hydroxycodeinone is 14-hydroxycodeine (XXVI, R = R' = H). If this inference is correct, it follows that 14-hydroxydihydrocodeine B is 14-hydroxydihydrocodeine (XXVII, R = R' = H) and that 14-hydroxydihydrocodeine C is 14-hydroxydihydroisocodeine (XXVIII, R = R' = H).

Before the appearance of the paper by Sargent *et al.*, 14-hydroxycodeine was prepared by both sodium borohydride and lithium aluminium hydride reduction of 14-hydroxycodeinone and it was shown that on catalytic hydrogenation, 14-hydroxycodeine is converted into 14-hydroxydihydrocodeine B.[39] On oxidation with activated manganese dioxide[40] 14-hydroxycodeine is converted back to 14-hydroxycodeinone showing that C_6 alone is involved in the metal hydride reductions. It was also found that reduction of 14-hydroxydihydrocodeinone with sodium borohydride gives both 14-hydroxydihydrocodeine B and 14-hydroxydihydrocodeine C and

Oppenauer[38] oxidation of these dihydro diols gave 14-hydroxy-dihydrocodeinone, the B epimer in 53% yield and the C epimer in 19% yield.[41,41a]

Since axial alcohols are oxidised more readily than equatorial alcohols, and the dihydrocodeine conformation at C_6 is axial (α) this behaviour confirms that the epimer B is 14-hydroxydihydrocodeine and the epimer C is 14-hydroxydihydro-isocodeine as suspected by Lutz and Small from the reactions of each with phosphorus pentachloride.[26] It follows that the product obtained by metal hydride reduction of 14-hydroxycodeinone is correctly described as 14-hydroxycodeine.



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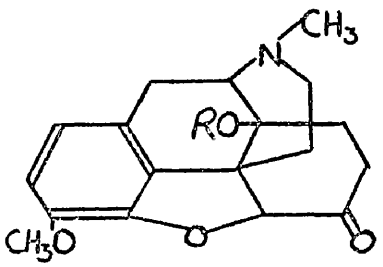

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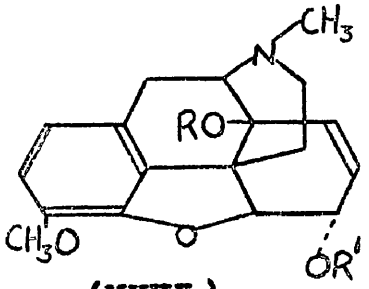

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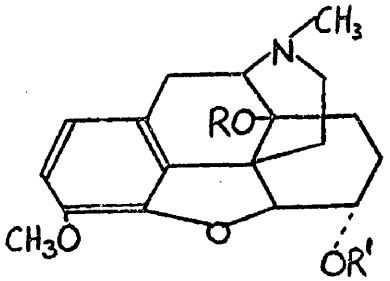

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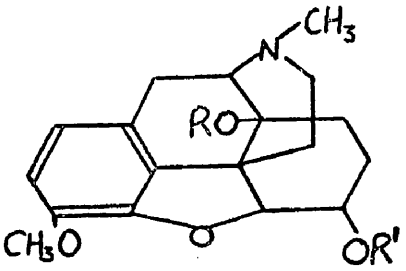

(XXVIII)

A careful examination of the mother liquors from 14-hydroxycodeine failed to disclose the presence of even traces of 14-hydroxyisocodeine despite the fact that metal hydride reduction of unhindered ketones should give a greater proportion of the equatorial alcohol.[36] Likewise Meerwein-Ponndorf reduction of 14-hydroxycodeinone gave 14-hydroxycodeine as sole product.

Even though the Δ^7 and saturated ketones may be hindered, the difference in spatial position seems too slight to account for the great difference in reduction and in particular the total absence of the Δ^7 equatorial alcohol from reduction of the αβ-unsaturated ketone. Distortion of the conformation of ring C by the double bond and the ether bridge makes the 6-OH group in 14-hydroxycodeine appear equatorial (or pseudo-equatorial) and this conformation may therefore be preferred for mechanistic rather than steric reasons.

Acylation of 14-hydroxycodeinone with lower anhydrides proceeds easily (yields ca. 85%) but becomes more difficult with n-valeric anhydride (yield ca 50%) probably due to the steric effect of the coiled chain.[42] Using the sodium borohydride reduction method, 14-acetoxycodeinone (XXIV, R = Ac), 14-propionyloxycodeinone (XXIV, R = EtCO), 14-n-butyryloxycodeinone (XXIV, R = PrCO), 14-n-valeryloxycodeinone (XXIV, R = BuCO) and 14-benzoyloxycodeinone (XXIV, R = PhCO) were all reduced to the corresponding 14-acyloxycodeine (XXVI, R = acyl, R' = H).

Sodium borohydride reduction of 14-acetoxydihydrocodeinone gives as major product 14-acetoxydihydroisocodeine (XXVIII, R = Ac, R' = H) and as minor product 14-acetoxydihydrocodeine (XXVII, R = Ac, R' = H), also prepared by catalytic hydrogenation of 14-acetoxycodeine (XXVI, R = Ac, R' = H). Acetylation of the latter and 14-hydroxycodeine gave 14-acetoxycodeine acetate (XXVI, R = R' = Ac). Similarly acetylation of the dihydro diols and the 14-acetoxydihydrocodeines gave the known diacetates 14-acetoxydihydroisocodeine acetate (XXVIII, R = R' = Ac) and 14-acetoxydihydrocodeine acetate (XXVII, R = R' = Ac) the latter also prepared by catalytic hydrogenation of 14-acetoxycodeine acetate (XXVI, R = R' = Ac).

When treated with methanol, 14-acetoxycodeine acetate is converted in part into 14-hydroxycodeine acetate (XXVI, R = H, R' = Ac).

The hydrochlorides of all the codeine derivatives were prepared and tested pharmacologically for analgesic activity, maximum values being obtained with 14-n-butyryloxycodeine compounds.[43]

14-Hydroxydeoxycodeine.

Since opening of the cyclic ether occurs when 14-hydroxycodeinone is reduced under acid conditions, the preparation of 14-hydroxydeoxy derivatives of codeine presents many problems. A route to this series was sought using a p-toluene sulphonate

ester at C_6.

Tosylation[n] of 14-hydroxycodeine gives 14-hydroxycodeine tosylate (XXVI, R = H, R' = Ts) acetylation of which gives 14-acetoxycodeine tosylate (XXVI, R = Ac, R' = Ts). The last compound is also obtained by tosylation of 14-acetoxycodeine (XXVI, R = Ac, R' = H). Hydrogenation of 14-hydroxycodeine tosylate afforded 14-hydroxydihydrocodeine tosylate (XXVII, R = H, R' = Ts) which was also obtained by tosylation of 14-hydroxydihydrocodeine. Acetylation of 14-hydroxydihydrocodeine tosylate gave 14-acetoxydihydrocodeine tosylate (XXVII, R = Ac, R' = Ts) which was also obtained by tosylation of 14-acetoxydihydrocodeine and by hydrogenation of 14-acetoxycodeine tosylate. 14-Acetoxydihydrocodeine tosylate was converted into 14-hydroxydihydrocodeine tosylate by the action of lithium aluminium hydride at 0°. In contrast similar treatment of either 14-acetoxycodeine tosylate or 14-hydroxycodeine tosylate gave 14-hydroxydeoxycodeine (XXIX, R = OH). Acetylation of 14-hydroxydeoxycodeine, which is stable to hot dilute mineral acid and therefore has a Δ7-8 double bond,[44] gave 14-acetoxydeoxycodeine (XXIX, R = OAc), alkaline hydrolysis of which regenerated the original alcohol. Hydrogenation of 14-hydroxydeoxycodeine yielded 14-hydroxydihydrodeoxycodeine (XXX, R = H) acetylation of which gave 14-acetoxydihydrodeoxycodeine (XXX, R = Ac) also obtained by hydrogenation of

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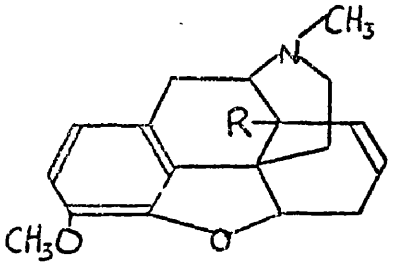
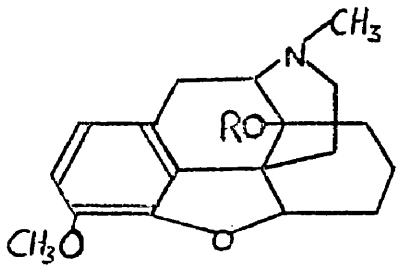
[n] for brevity the terms tosylation, tosylate, and Ts will be used for p-toluene sulphonylation, p-toluene sulphonate, and the group $MeC_6H_6SO_2$.

14-acetoxydeoxycodeine. In all these respects, 14-hydroxydeoxycodeine is an analogue of deoxycodeine (XXIX, R = H) itself prepared by lithium aluminium hydride reduction of codeine tosylate.[44,45]



(XXIX)

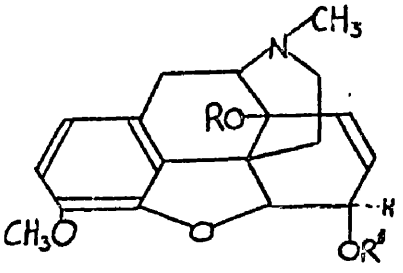


(XXX)

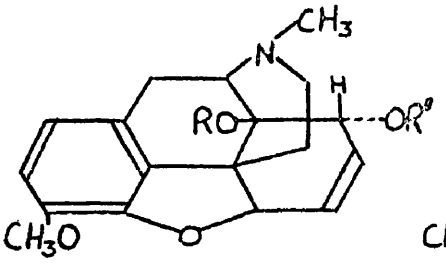
Preparation of 14-Hydroxyisocodeine Derivatives.

Since no trace of 14-hydroxyisocodeine was found in the product from metal hydride reduction of 14-hydroxycodeinone and all attempts to epimerise 14-hydroxycodeine failed, the preparation of 14-hydroxyisocodeine from the 14-substituted codeine tosylates by substitution with inversion appeared a more suitable route. Treatment of 14-acetoxycodeine tosylate with fused sodium acetate and acetic anhydride[46] returned starting material. 14-Hydroxycodeine tosylate on treatment with 10% acetic acid gives as major product, a diol, $C_{18}H_{21}O_4N$ isomeric with 14-hydroxycodeine, which on hydrogenation afforded 14-hydroxydihydroisocodeine (XXVIII, R = R' = H). The new diol is therefore 14-hydroxyisocodeine (XXXI, R = R' = H) its preparation involving an S_N2 reaction mechanism i.e. the expected displacement with inversion. 14-Hydroxyisocodeine

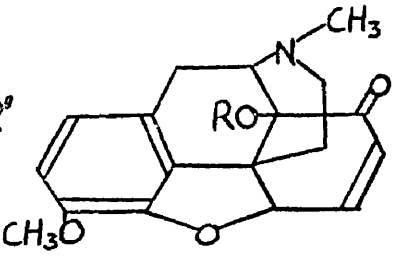
readily forms a diacetate (XXXI, R = R' = Ac) from which the diol is regenerated by alkaline hydrolysis; treatment of this diacetate with methanol partially converts it into 14-hydroxyisocodeine acetate (XXXI, R = H, R' = Ac). Whereas 14-hydroxycodeine (XXVI, R = R' = H) is rapidly oxidised by activated manganese dioxide to 14-hydroxycodeinone in quantitative yield, similar treatment of 14-hydroxyisocodeine (XXXI, R = R' = H) gives only a 10% yield of this ketone after a prolonged reaction time.



(XXXI)



(XXXII)

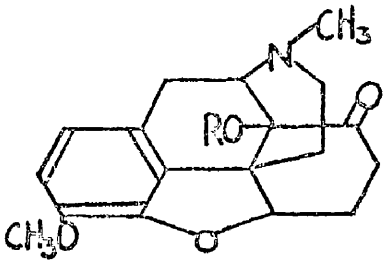


(XXXIII)

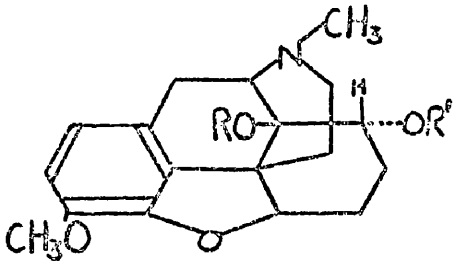
14-Hydroxyallopseudocodeine Derivatives.

Treatment of 14-hydroxycodeine tosylate with 70% acetic acid gives, as principal product, the monoacetate, $C_{20}H_{23}O_6N$ of a diol, $C_{18}H_{21}O_4N$. Further acetylation of this monoacetate gives a diacetate, isomeric with, but different from either 14-acetoxycodeine acetate or 14-acetoxyisocodeine acetate. The monoacetate is considered to be 14-hydroxyallopseudocodeine

acetate (XXXII, R = H, R' = Ac) and its formation from 14-hydroxycodeine tosylate is considered to involve an S_N2' reaction mechanism i.e. substitution with rearrangement and no inversion.[47] The monoacetate on treatment with mineral acid gives a phenol showing a $\Delta 6$ double bond in conjugation with the ether linkage. Treatment of the related diacetate, 14-acetoxyallopseudocodeine acetate (XXXII, R = R' = Ac), with methanol gives back the monoacetate 14-hydroxyallopseudocodeine acetate. 14-Hydroxyallopseudocodeine (XXXII, R = R' = H), obtained by alkaline hydrolysis of both the di- and the monoacetate is oxidised by activated manganese dioxide to 14-hydroxypseudocodeinone (XXXIII, R = H). Partial hydrogenation of 14-hydroxypseudocodeinone gave



(XXXIV)



(XXXV)

14-hydroxydihydropseudocodeinone (XXXIV, R = H) together with a phenol, presumably formed by hydrogenolysis. Further hydrogenation of 14-hydroxydihydropseudocodeinone gave 14-hydroxydihydroallopseudocodeine (XXXV, R = R' = H) which is also obtained by hydrogenation of 14-hydroxyallopseudocodeine (XXXII, R = R' = H). 14-Hydroxypseudocodeinone was

directly converted into the dihydro diol (XXXV, R = R' = H) by reduction with sodium borohydride, reduction of the double bond in this reaction being most unusual. This diol on Oppenauer oxidation gives back 14-hydroxydihydropseudocodeinone (XXXIV, R = H) in good yield; Rapoport et al.[35] showed that under the same conditions dihydroallopseudocodeine was oxidised whereas its epimer was unaffected. This confirms that the 8-hydroxyl group is axial (α) in the allopseudo compounds. Acetylation of 14-hydroxydihydroallopseudocodeine gave a mixture of two isomeric monoacetates, each of which is hydrolysed to the parent diol by alkali. One of these monoacetates is 14-hydroxydihydroallopseudocodeine acetate (XXXV, R = H, R' = Ac) since it is also formed by catalytic hydrogenation of 14-hydroxyallopseudocodeine acetate (XXXII, R = H, R' = Ac). The isomeric monoacetate is considered to be 14-acetoxydihydroallopseudocodeine (XXXV, R = Ac, R' = H) although epimerisation could have occurred to give 14-hydroxydihydropseudocodeine acetate in turn being epimerised by alkaline hydrolysis to 14-hydroxydihydroallopseudocodeine. This monoacetate was recovered unchanged after attempted acetylation. Catalytic hydrogenation of 14-acetoxyallopseudocodeine acetate (XXXII, R = R' = Ac) yielded only starting material along with phenolic compounds.

"Hydroxycodeine"

The reduction of 14-hydroxycodeinone (XXIV, R = H) with zinc dust and acetic acid or formic acid[21,22,48] and zinc dust and copper sulphate solution[48] has been investigated by a number of workers who were concerned with the non-phenolic compound isolated in ca.20% yield. This compound was designated "hydroxycodeine" since it appeared to exhibit no ketonic properties[21] and its catalytic hydrogenation product was called "dihydrohydroxycodeine A".[26] The latter however differs from 14-hydroxydihydrocodeine B(XXVII, R = R' = H) and 14-hydroxydihydrocodeine C (XXVIII, R = R' = H) both prepared by hydrogenation of 14-hydroxydihydrocodeinone(XXV, R = H) and Lutz and Small[26] therefore suggested a structural change taking place in the reduction of 14-hydroxycodeinone to "hydroxycodeine" this being supported by pharmacological studies.[26,27]

The constants [m.p. 285-290° (decomp., evac. tube) $[\alpha]_D$ - 141° (c,1.0 in 10% acetic acid)] of "hydroxycodeine", found in the present work, differ slightly from those reported by Lutz and Small[26] [m.p. 304-305° (decomp., evac. tube), $[\alpha]_D$ - 143°] and by Freund and Speyer[21] (m.p. 293°, $[\alpha]_D$ - 119°). The infrared spectrum shows bands at 3540, 3320 and 1729 $cm.^{-1}$ indicating a hydroxyl group and a carbonyl group. Attempted oxidation with manganese dioxide and attempted hydrolysis led to the recovery of the original substance showing the absence of an allylic

alcohol and an unhindered acetate respectively.

The variation in constants and the comparatively low intensity of the carbonyl band in the infrared spectrum suggested a mixture, but extensive attempts to separate the components failed.

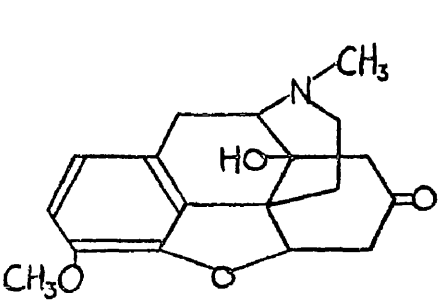
Acetylation of "hydroxycodeine" gave an acetate in 50% yield along with starting material. The analysis of this acetate, m.p. 168-172° (which can be hydrolysed to "hydroxycodeine") did not show conclusively whether the original substance contained two hydroxyl groups or one. However sodium borohydride reduction of the acetate followed by acetylation yielded a diacetate (A) m.p. 203-204°. Similar reduction of "hydroxycodeine" gave in 45% yield a diol, m.p. 222-223° acetylation of which also gave the diacetate (A). The mother liquors from the latter sodium borohydride reduction failed to produce crystalline material despite attempts to "seed" out "dihydrohydroxycodeine A". This latter compound on acetylation yielded intractable material. Oppenauer[35] oxidation of the diol, m.p. 222-223° gave "hydroxycodeine" in 50% yield but similar oxidation of "dihydrohydroxycodeine A" gave mainly starting material.

"Hydroxycodeine" therefore appears to have a tertiary hydroxyl and a saturated keto group. Clemmensen reduction of "hydroxycodeine" however gave a phenol, m.p. 271-273° compared with the compound, m.p. 141°, obtained by Clemmensen reduction of 14-hydroxydihydrocodeinone in both cases the ketone group having been

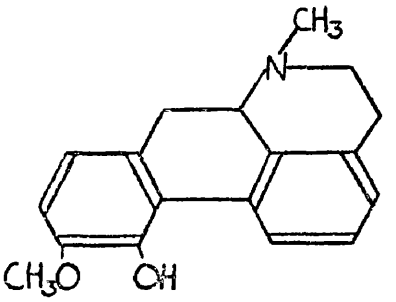
reduced. This confirms a structural change in the reduction of 14-hydroxycodeinone to "hydroxycodeine" since 14-hydroxycodeine--7-one (XXXVI) (the only saturated ketone still unknown in the series) would also be expected to give the carbonyl free compound m.p. 141° on Clemmensen reduction.

Since zinc dust and acetic acid reduction of 14-hydroxydihydrocodeinone returned starting material the mechanism of the similar reduction of 14-hydroxycodeinone presumably involves carbanion formation at the $\Delta 7$ double bond. The carbanion could stabilise by forming an apocodeine derivative although the presence of the 14-hydroxyl group excludes the possibility of the intermediate (VIII) suggested by Bentley[14] for the formation of apocodeine (XXXVII)[49,50,51] from codeine, and models show the mechanism of formation of an apocodeine derivative from 14-hydroxycodeinone must involve more than just a simple rearrangement of the ethanamine chain. However a structural change must have taken place and a structure (XXXVIII) is postulated a model of which shows the hydroxyl group to be much more hindered than in 14-hydroxycodeinone which would account for the low yield of "hydroxycodeine" acetate.

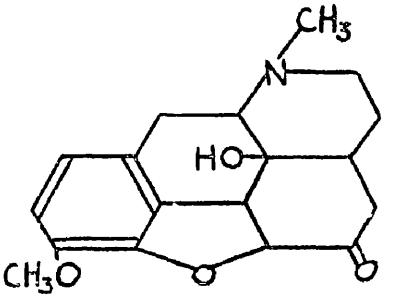
Rearrangements appear to take place fairly readily with 14-hydroxycodeinone and on treatment with ethanolic potash a compound, m.p. $> 300°$, ν max. 1710 $cm.^{-1}$ is obtained very similar in many respects to "hydroxycodeine".



(XXXVI)



(XXXVII)

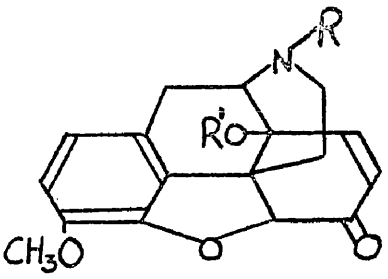


(XXXVIII)

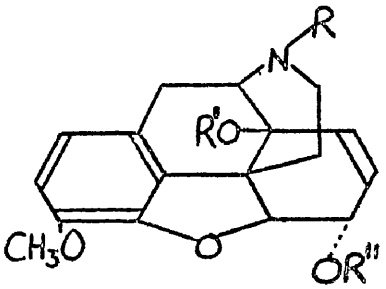
14-Hydroxynorcodeine Derivatives.

The reaction of 14-acetoxycodeinone (XXXIX, R = Me, R' = Ac) with cyanogen bromide[83] affords 14-acetoxy-N-cyanonorcodeinone (XXXIX, R = CN, R' = Ac) contrary to the claim[21] that 14-hydroxy--N-cyanonorcodeinone was so formed. Attempts to form the latter from the reaction of cyanogen bromide with 14-hydroxycodeinone gave a quaternary salt but using this reaction 14-acetoxy-N--cyanonorcodeine acetate (XL, R = CN, R' = R'' = Ac), 14-benzoyloxy--N-cyanonorcodeine acetate (XL, R = CN, R' = PhCO, R'' = Ac), 14-acetoxy-N-cyanodihydronorcodeinone (XLI, R = CN, R' = Ac), 14-propionyloxy-N-cyanonorcodeinone (XXXIX, R = CN, R' = EtCO), and 14--n-butyryloxy-N-cyanonorcodeinone (XXXIX, R = CN, R' = PrCO) were all prepared from the corresponding N-methyl compounds.

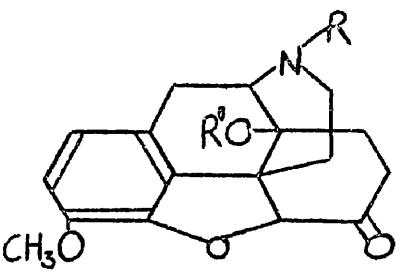
14-Acetoxy-N-cyanonorcodeine (XL, R = CN, R' = Ac, R'' = H) was prepared from 14-acetoxy-N-cyanonorcodeinone by sodium borohydride reduction. It was also formed in low yield by the



(XXXIX)



(XL)



(XLI)

action of this reagent or pyridine in methanol on 14-acetoxy-N-cyanonorcodeine acetate.

Lithium aluminium hydride which converts the N-cyano derivatives of a secondary amine to the related amine,[54] when used for the reduction of 14-acetoxy-N-cyanonorcodeinone and 14-acetoxy-N-cyanonorcodeine acetate yielded 14-hydroxynorcodeine (XL, R = R' = R'' = H) which was smoothly oxidised by activated manganese dioxide to 14-hydroxynorcodeinone (XXXIX, R = R' = H) m.p. 185-187°. The compound, m.p. 218° (decomp.) obtained by mineral acid hydrolysis of 14-acetoxy-N-cyanonorcodeinone and described as 14-hydroxynorcodeinone[55] appears to be heterogeneous its infrared spectrum showing weak bands in the O-acetyl region. Acetylation of the compound, m.p. 218° (decomp.) gives 14-acetoxy-N-acetyl-norcodeinone (XXXIX, R = R' = Ac) the acetylation product of 14-hydroxynor codeinone, m.p. 185-187°. Mineral acid hydrolysis of 14-acetoxy-N-cyanodihydronorcodeinone gave in poor yield 14-hydroxydihydronorcodeinone (XLI, R = R' = H), m.p.175-176°

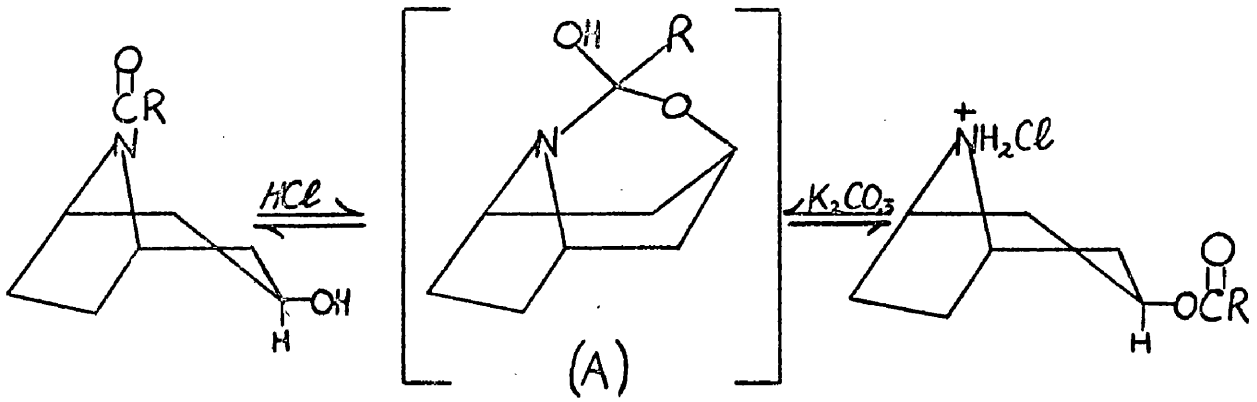
previously described as an oil.[55] All the secondary amines described crystallise with difficulty and in very poor yield from the reaction products although their infrared spectra show these products to be substantially homogeneous. Because of the difficulty in preparing these secondary amines, a more convenient route was sought for the preparation of N-acyl derivatives of 14-hydroxynorcodeine.

14-Acetoxy-N-cyanonorcodeine acetate on heating with aqueous acetic acid gave a compound, m.p. 249-250° also obtained by the action of acetic anhydride on 14-hydroxynorcodeine. This compound was unaffected by manganese dioxide oxidation and since its infrared spectrum shows bands in the hydroxyl, O-acetyl, and N-acetyl regions it must be 14-hydroxy-N-acetylnorcodeine acetate (XL, R' = H, R = R'' = Ac). Both this compound and 14-hydroxynorcodeine on more vigorous treatment with acetic anhydride yielded 14-acetoxy--N-acetylnorcodeine acetate (XL, R = R' = R'' = Ac) also obtained by refluxing 14-acetoxy-N-cyanonorcodeine acetate in glacial acetic acid. Attempts to hydrogenate the latter compound in acetic acid over platinum resulted in the formation of 14-hydroxy-N-acetylnorcodeine acetate also prepared by the action of aqueous propionic acid on the N-cyano compound (XL, R = CN, R' = R'' = Ac).

Similarly 14-acetoxy-N-cyanonorcodeinone when treated with aqueous propionic acid gave 14-hydroxy-N-acetylnorcodeinone (XXXIX, R = Ac, R' = H) vigorous acetylation of which gave 14-acetoxy-N-acetylnorcodeinone. The latter was also the product obtained from

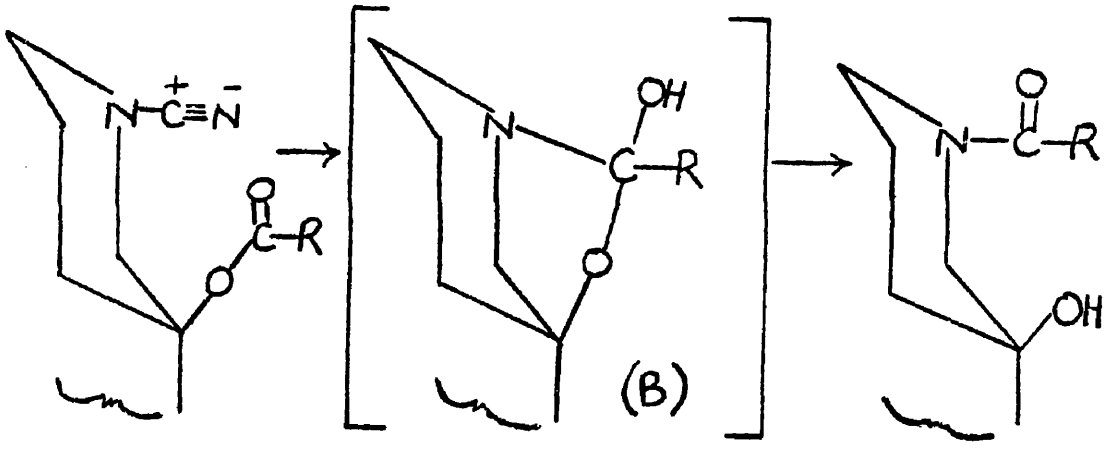
refluxing glacial acetic acid (or the successive reactions of aqueous acetic acid and acetic anhydride) on 14-acetoxy-N-cyanonorcodeinone. 14-Hydroxy-N-acetyldihydronorcodeinone (XLI, R = Ac, R' = H) was prepared by aqueous acetic or propionic acid on 14-acetoxy-N-cyanodihydronorcodeinone, and glacial acetic acid on the latter gave 14-acetoxy-N-acetyldihydronorcodeinone (XLI, R = R' = Ac), the acetylation product of both 14-hydroxy-N-acetyldihydronorcodeinone and 14-hydroxydihydronorcodeinone.

The mechanism of the formation of N-acetyl derivatives from 14-acetoxy-N-cyano compounds must involve migration of the O-acetyl group. Acyl groups are known to migrate from nitrogen to oxygen under acid catalysis[56] and studies of the mechanisms of the reactions have indicated that they probably proceed through cyclic intermediates.[57,58,59,60] Nickon and Fieser[56] postulate the intermediate (A) in the migrations in the tropine series.



Since the formation of N-acetylcodeine derivatives from the 14-acetoxy-N-cyano compounds can take place under anhydrous acid conditions and since in most of these hydrolysis reactions,

mixtures of both 14-acetoxy-N-cyano and N-acetyl but no NH compounds exist in the reaction products it seems likely that the reaction takes place synchronously and probably through an intermediate (B) and not by hydrolysis of the N-cyano function to $\geq$NCOOH to give $\geq$NH with subsequent acyl migration.



The reverse process of migration of the acetyl group from oxygen to nitrogen proceeds under base catalysis[56] in the tropine alkaloids. Treatment of 14-hydroxy-N-acetylnorcodeine acetate with base gave intractable material the infrared spectrum of which showed that this process may be taking place to some extent. However treatment of 14-acetoxy-N-cyanodihydronorcodeinone (XLI, R = CN, R' = Ac) with 1% potassium hydroxide in methanol, gave 14-hydroxy-N-acetyldihydronorcodeinone (XLI, R = Ac, R' = H). That migration took place under base conditions was confirmed by the action of 1% potassium hydroxide in methanol on 14-acetoxy-N-cyanonorcodeine acetate and 14-acetoxy-N-cyanonorcodeine to give

14-hydroxy-N-acetylnorcodeine (XL, R = Ac, R' = R'' = H) manganese dioxide oxidation of which gave 14-hydroxy-N-acetyl norcodeinone. With αβ unsaturated ketones however the action of basic reagents gives intractable material the infrared spectrum showing a band in the saturated ketone region.

This series of reactions shows for the first time experimentally the close proximity of the nitrogen atom to the 14-carbon atom in 14-hydroxycodeinone and provides a general route to N-acyl derivatives of 14-hydroxynorcodeine.

14-Propionyloxy-N-cyanonorcodeinone when refluxed with aqueous acetic or propionic acid gave 14-hydroxy-N-propionylnorcodeinone (XXXIX, R = EtCO, R' = H). Sodium borohydride reduction of the latter followed by heating with propionic anhydride yielded 14-propionyloxy-N-propionylnorcodeine propionate (XL, R = R' = R'' = EtCO) also prepared by the action of propionic anhydride on 14-hydroxynorcodeine. Sodium borohydride reduction of 14-propionyloxy-N-cyanonorcodeinone followed by refluxing 1% potassium hydroxide in methanol gave a gum whose infrared spectrum shows bands in the N-acyl and hydroxyl regions. On heating this gum with propionic anhydride, 14-propionyloxy-N-propionylnorcodeine propionate was obtained in good yield.

Similarly 14-n-butyryloxy-N-cyanonorcodeinone when successively reduced with sodium borohydride and treated with 1% potassium hydroxide in methanol gave a gum showing bands in the N-acyl and

hydroxyl regions of the infrared spectrum. Oxidation of the gum with active manganese dioxide yielded 14-hydroxy-N-n-butyryl-norcodeinone (XXXIX, R = PrCO, R' = H) as a reasonably pure amorphous powder also obtained by refluxing aqueous n-butyric acid on 14-n-butyryloxy-N-cyanonorcodeinone.

The general route to 14-substituted-N-acyl derivatives of codeine also makes available a convenient method for the preparation of a series of N-alkyl derivatives of 14-hydroxynorcodeine by lithium aluminium hydride reduction of the appropriate N-acyl derivatives.[61]

Reduction of either 14-hydroxy-N-acetyl norcodeine acetate (XL, R = R'' = Ac, R' = H) or its acetate (XL, R = R' = R'' = Ac) with lithium aluminium hydride afforded 14-hydroxy-N-ethylnorcodeine (XL, R = Et, R' = R'' = H). The latter on mild acetylation yielded 14-acetoxy-N-ethylnorcodeine (XL, R = Et, R' = Ac, R'' = H) while more vigorous acetylation gave the diacetate (XL, R = Et, R' = R'' = Ac); both acetates have been hydrolysed to 14-hydroxy-N-ethylnorcodeine by alkali. Manganese dioxide oxidation of the latter afforded 14-hydroxy-N-ethylnorcodeinone (XXXIX, R = Et, R' = H) the reverse change being effected by sodium borohydride reduction. Similar reduction of 14-acetoxy-N-ethylnorcodeinone (XXXIX, R = Et, R' = Ac) gave 14-acetoxy-N-ethylnorcodeine. Treatment of 14-acetoxy-N-ethylnorcodeine acetate with cyanogen bromide gave 14-acetoxy-N-cyanonorcodeine acetate.

Lithium aluminium hydride reduction of 14-propionyloxy--N-propionylnorcodeine propionate yielded 14-hydroxy-N-propylnorcodeine (XL, R = Pr, R' = R'' = H) which on oxidation with activated manganese dioxide gave 14-hydroxy-N-propylnorcodeinone (XXXIX, R = Pr, R' = H). The latter on acetylation gave 14-acetoxy-N-propylnorcodeinone (XXXIX, R = Pr, R' = Ac).

Approximate estimates of analgesic potency were obtained[43] by injecting the compounds subcutaneously into groups of five rats and determining their responses to a painful stimulus thirty minutes later. The values obtained confirmed that esterification of the 14-hydroxyl group of 14-hydroxycodeine and derivatives increased analgesic activity. Maximum effects were obtained with 14-n-butyryloxycodeine and 14-n-butyryloxyisocodeine acetate which were about ten times more active than morphine. 14-n-Butyryloxycodeine was almost twice as potent as morphine. Further increase in the size of the substituent group as in 14-n-valeryloxycodeine did not lead to increased activity. N-acyl derivatives showed comparatively little activity and the N-methyl compounds were four times more potent than the corresponding N-ethyl compounds.

EXPERIMENTAL

Rotations were measured for chloroform solutions except where otherwise stated. Light petroleum where specified had b.p. 60-80°. Infrared spectra were determined in Nujol for mulls and identities were confirmed by infrared comparison. Acetylations were carried out using the procedure described for the preparation of 14-acetoxycodeine acetate.

14-Hydroxycodeine. - (a) 14-Hydroxycodeinone[21] (10 g.) was placed in the thimble of a Soxhlet apparatus and a suspension of lithium aluminium hydride (10 g.) in ether (350 c.c.) was placed in the boiling flask. The ether was refluxed for 96 hr. The mixture was cooled to 0° and treated, with stirring, with ice. After washing with water the dried (Na_2SO_4) ethereal solution was evaporated to a colourless gum (9.15 g.) which crystallised from benzene-light petroleum to yield 14-hydroxycodeine (8.0 g.) as prisms, m.p. 155-157°, $[\alpha]_D$ - 129.5° (c, 1.75) (lit.[27] m.p. 156-157°), $\nu_{max.}$ 3390 $cm.^{-1}$ (OH) (Found: C, 68.6; H, 6.5. Calc. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.7%).

(b) A boiling solution of 14-hydroxycodeinone (1.0 g.) in dioxan (25 c.c.) was rapidly cooled to 15°. The suspension was treated, with stirring, with a solution of sodium borohydride (1.2 g.) in water (10 c.c.) added in one portion. The reaction

mixture was stirred for 2 hr. at room temperature and diluted with aqueous sodium hydroxide solution (100 c.c.; 0.2N) and the product isolated by means of chloroform. Crystallisation of the product from benzene-light petroleum gave 14-hydroxycodeine (850 mg.) as prisms, m.p. and mixed m.p. 156-157°, $[\alpha]_D$- 132° (c, 2.1). The hydrochloride separated as a microcrystalline powder, m.p. 263-264° (decomp.), when a solution of the base in chloroform-ether was treated with dry hydrogen chloride (Found: Cl, 9.7. $C_{18}H_{21}O_4N$. HCl requires Cl, 10.1%).

(c) 14-Hydroxycodeinone (4 g.) was added to a solution of aluminium isopropoxide (5 g.) in dry isopropanol (50 c.c.) and the stirred solution was distilled slowly (3 hr.) until the distillate was free from acetone. The excess isopropanol was removed by distillation and the residue was diluted with water (30 c.c.), basified with ammonia (d, 0.88) and the product isolated using chloroform. Crystallisation of the product from benzene-light petroleum gave 14-hydroxycodeine (2.75 g., 69%) as prisms, m.p. and mixed m.p. 154-157°.

14-Acetoxycodeine Acetate. - 14-Hydroxycodeine (200 mg.) was heated on the steam bath with acetic anhydride (2.5 c.c.) for 1½ hr. The cooled solution was treated with water, the mixture cooled to 0°, and basified with ammonia (d, 0.88). The precipitated solid was collected, dried in vacuo over phosphoric oxide and crystallised from benzene-light petroleum to give 14-acetoxycodeine

acetate (100 mg.) as rosettes of blades, m.p. 198-200°, $[\alpha]_D$ -126° (c,1.5) (lit.[27] m.p. 199° [evac. tube]; $\nu_{max.}$ 1730 cm.$^{-1}$ (ester C = O) (Found: C,66.35; H,6.0. Calc. for $C_{22}H_{25}O_6N$: C,66.15; H,6.3%). The hydrochloride separated from methanol-ether as blades, m.p. 164-167° (decomp.) (Found: Cl,8.2. $C_{22}H_{25}O_6N$ HCl requires Cl,8.15%).

14-Hydroxycodeine Acetate. - A solution of 14-acetoxycodeine acetate (5 g.) in methanol (100 c.c.) was refluxed for 4 hr. The solution was concentrated to one-quarter bulk and cooled, 14-acetoxycodeine acetate (1.5 g.) separating as prisms, m.p. 190-200°. On further concentration, the mother liquor yielded prisms, m.p. 140-150° (3 g.) which recrystallised from chloroform-light petroleum to yield 14-hydroxycodeine acetate (1.5 g.) as prismatic needles, m.p. 155-156°, $[\alpha]_D$ - 220° (c,6.0), $\nu_{max.}$ 3333 (OH) and 1742 cm.$^{-1}$ (ester C = O) (Found: C,67.2; H,6.3. $C_{20}H_{23}O_6N$ requires C,67.2; H,6.5%). Acetylation of 14-hydroxycodeine acetate gave 14-acetoxycodeine acetate, m.p. and mixed m.p. 198-200°. Hydrolysis of 14-hydroxycodeine acetate with 5% methanolic potassium hydroxide gave 14-hydroxycodeine, m.p. and mixed m.p. 155-157°.

14-Propionyloxycodeinone. - 14-Hydroxycodeinone (2.0 g.) was heated with propionic anhydride (10 c.c.) on the steam bath for 1 hr. with occasional shaking. Working up in the usual way

followed by crystallisation of the product from benzene-light petroleum gave 14-propionyloxycodeinone (1.7 g.) as slightly yellowish needles, m.p. 182-183°, $[\alpha]_D$ - 91° (c, 1.3), $\nu_{max.}$ 1733 (ester C = O) and 1684 $cm.^{-1}$ (αβ C = O) (Found: C, 68.6; H, 6.35. $C_{21}H_{23}O_5N$ requires C, 68.3; H, 6.3%).

14-n-Butyryloxycodeinone. - 14-Hydroxycodeinone (2.7 g.) was heated on the steam bath with n-butyric anhydride (10 c.c.) with occasional shaking for 2½ hr. The product was isolated in the usual way and crystallised from benzene-light petroleum. The crystals were washed with methanol and ether to remove colour and recrystallised from chloroform-methanol to yield 14-n-butyryloxycodeinone (2.8 g.) as needles, m.p. 152.5-153.5°, $[\alpha]_D$ - 89° (c, 2.0), $\nu_{max.}$ 1736 (ester C = O) and 1689 $cm.^{-1}$ (αβ C = O) (Found: C, 69.3; H, 6.8. $C_{22}H_{25}O_5N$ requires C, 68.9; H, 6.6%).

14-n-Valeryloxycodeinone. - (a) 14-Hydroxycodeinone (3.0 g.) was heated with n-valeryl chloride (5 c.c.) and pyridine (10 c.c.) for 3 hr. on the steam bath. The cooled solution was diluted with water (400 c.c.), extracted with chloroform and the product isolated in the usual way. A solution of the product in benzene was filtered through an alumina column (3 x 1 cm.). Evaporation of the benzene and crystallisation of the residue from chloroform-light petroleum gave 14-n--valeryloxycodeinone (1.2 g.) as needles, m.p. 133-134°, $[\alpha]_D$

- 77° (c,1.0), $\nu_{max.}$ 1736 (ester C = O) and 1692 cm.$^{-1}$ (αβ C = O) (Found: C,69.9; H,6.8. $C_{23}H_{27}O_5N$ requires C,69.5; H,6.85%).

(b) 14-Hydroxycodeinone (2.95 g.) was heated on the steam bath with n-valeric anhydride (15 c.c.) for 2½ hr. 14-n-Valeroxycodeinone (1.5 g.) separated from chloroform-light petroleum as fine needles, m.p. 133-134° alone or mixed with preparation (a).

Preparation of 14-Acyloxycodeines. The 14-acyloxycodeines described below were obtained in 80-90% yield by reduction of the corresponding 14-acyloxycodeinones using the conditions described for the preparation of 14-hydroxycodeine (Method b.).

14-Acetoxycodeine. - 14-Acetoxycodeinone[21] gave 14-acetoxycodeine as prismatic needles, m.p. 203-205° from benzene-light petroleum, $[\alpha]_D$ - 64°, - 61° (c,1.2, 1.0), $\nu_{max.}$ 3610 (OH) and 1745 cm.$^{-1}$ (ester C = O) (Found: C,67.4; H,6.3. $C_{20}H_{23}O_5N$ requires C,67.2; H,6.5%). The hydrochloride separated from methanol-ether as needles, m.p. 222-224° (decomp.) (Found: Cl,8.7. $C_{20}H_{23}O_5N.HCl$ requires Cl,9.0%). Acetylation of 14-acetoxycodeine gave 14-acetoxycodeine acetate, m.p. 198-200° alone or mixed with a specimen prepared by acetylation of 14-hydroxycodeine.

14-Propionyloxycodeine separated from chloroform-light petroleum as prismatic needles, m.p. 164-165.5°, $[\alpha]_D$ - 54°, - 54° (c,1.0, 1.7), $\nu_{max.}$ 3571 (OH) and 1736 cm.$^{-1}$ (ester C = O) (Found: C,67.85; H,6.8. $C_{21}H_{25}O_5N$ requires C,67.9; H,6.8%). The hydrochloride has m.p. 165-170° (decomp.) (Found: Cl,8.5. $C_{21}H_{25}O_5N.HCl$ requires Cl,8.7%).

Acetylation of 14-propionyloxycodeine gave 14-propionyloxycodeine acetate which crystallised from benzene-light petroleum as prismatic needles, m.p. 153-154°, $[\alpha]_D$ - 127, -129° (c,1.7, 1.3), $\nu_{max.}$ 1742 cm.$^{-1}$ (ester C = O) (Found: C,66.7; H,6.4. $C_{25}H_{27}O_6N$ requires C,66.8; H,6.6%). The hydrochloride has m.p. 215-220° (decomp.) (Found: Cl,8.0. $C_{25}H_{27}O_6N.HCl$ requires Cl,7.9%).

14-n-Butyryloxycodeine separated from chloroform-light petroleum as fine needles, m.p. 131-132°, $[\alpha]_D$ - 49° (c,1.0), $\nu_{max.}$ 3610 (OH) and 1733 cm.$^{-1}$ (ester C = O) (Found: C,68.6; H,6.7. $C_{22}H_{27}O_5N$ requires C,68.55; H,7.1%). The hydrochloride has m.p. 165° (decomp.) after softening at 150° (Found: Cl,8.3. $C_{22}H_{27}O_5N.HCl$ requires Cl,8.4%).

14-n-Valeryloxycodeine crystallised from chloroform-light petroleum as prismatic needles, m.p. 110-111°, $[\alpha]_D$ - 47° (c,1.4), $\nu_{max.}$ 3472 (OH) and 1704 cm.$^{-1}$ (ester C = O) (Found: C,69.2; H,6.8. $C_{23}H_{29}O_5N$ requires C,69.15; H,7.3%. The hydrochloride separates from ethanol-ether as stout needles, m.p. 138-148° (decomp.) (Found: Cl,7.8. $C_{23}H_{29}O_5N.HCl$ requires Cl,8.1%).

14-Benzoyloxycodeine. - 14-Benzoyloxycodeinone[21] was converted into 14-benzoyloxycodeine which separated from chloroform-light petroleum as prismatic needles, m.p. 221-222°, $[\alpha]_D$ - 120°, - 124° (c,1.2; 1.0), $\nu_{max.}$ 3546 (OH) 1709 cm.$^{-1}$ (ester C = O) (Found: C,71.5; H,6.2; N,3.0. $C_{28}H_{25}O_5N$ requires C,71.6; H,6.0; N,3.3%). The hydrochloride separated from ethanol-ether as blades, m.p.177-180°

(Found: Cl,7.7. $C_{25}H_{25}O_5N.HCl$ requires Cl,7.8%). Acetylation of 14-benzoyloxycodeine gave 14-benzoyloxycodeine acetate which separated from ethanol as prismatic needles, m.p. 194-195°, $[\alpha]_D$ - 174°, - 168° (c,2.0; 6.0), $\nu_{max.}$ 1748 (acetoxy C = O) and 1712 cm.$^{-1}$ (benzoyloxy C = O)(Found: C,70.5; H,5.6; N,3.0. $C_{27}H_{27}O_6N$ requires C,70.3; H,5.9; N,3.0%). The hydrochloride crystallised from ethanol-ether as needles, m.p. 227-229° (decomp.) (Found: Cl,7.3. $C_{27}H_{27}O_6N$ requires Cl,7.0%).

14-Hydroxydihydrocodeine. - A solution of 14-hydroxycodeine (850 mg.) in glacial acetic acid (25 c.c.) and water (25 c.c.) was shaken with hydrogen and platinum (from 150 mg. platinum oxide) until hydrogen absorption ceased. The filtered solution was evaporated under reduced pressure to small bulk, the concentrate was diluted with water and basified with ammonia (d,0.88) and the gum which separated isolated using ether. Crystallisation from benzene-light petroleum gave 14-hydroxydihydrocodeine (500 mg.) as rosettes of felted needles, m.p. 140-141°, $[\alpha]_D$ - 169° (c,0.6), $[\alpha]_D$ - 138° (c,1.8 in 10% HOAc) [lit.[26] m.p. 145-145.5°, $[\alpha]_D$ - 136° (10% HOAc)], $\nu_{max.}$ 3425 cm.$^{-1}$ (OH) (Found: C,68.2; H,7.1; N,4.7. Calc. for $C_{18}H_{23}O_4N$: C,68.1; H,7.3; N,4.4%). 14-Acetoxydihydrocodeine acetate formed by acetylation of the diol separated from benzene-light petroleum as small needles, m.p. 180.5-181.5°, $[\alpha]_D$ -211° (c,1.3), $[\alpha]_D$ - 127° (c,0.8) in 10% HOAc) [lit.[26] m.p.181-182°,

$[\alpha]_D$ - 127° (10% HOAc)], $\nu_{max.}$ 1739 cm.$^{-1}$ (ester C = O) (Found: C,66.3; H,6.8; N,4.1, Calc. for $C_{22}H_{27}O_6N$: C,65.8; H,6.8; N,3.5%).

14-Acetoxydihydrocodeine. - Hydrogenation of 14-acetoxycodeine (750 mg.) gave 14-acetoxydihydrocodeine (600 mg.) which separated from benzene-light petroleum as needles, m.p. 164-166°, $[\alpha]_D$ - 202° (c,1.6), $\nu_{max.}$ 3448 (OH) and 1733 cm.$^{-1}$ (ester C = O) (Found: C,66.5; H,6.6; N,4.3. $C_{20}H_{25}O_5N$. requires C,66.8; H,7.0; N,3.9%). The hydrochloride had m.p. 175-182° (decomp.) (Found: Cl,8.8. $C_{20}H_{25}O_5N.HCl$ requires Cl,9.0%). Acetylation gave 14-acetoxydihydrocodeine acetate which separated from benzene-light petroleum as small needles, m.p. 182-183° alone or mixed with the specimen described above, $[\alpha]_D$ - 208° (c,2.0).

Hydrogenation of 14-Acetoxycodeine Acetate. - A solution of the acetate (1.135 g.) was catalytically hydrogenated using the method described above. Isolation of the product using chloroform followed by crystallisation from benzene-chloroform and chromatography of a benzene solution on an alumina column (2 x 0.5 cm.) and final crystallisation of the eluted solid from benzene-light petroleum gave 14-acetoxydihydrocodeine acetate (1.1 g.) as prisms, m.p. 181.5-182.5° alone or mixed with a specimen prepared as described above, $[\alpha]_D$ - 206° (c,1.0), $[\alpha]_D$ - 128° (c,0.9 in 10% HOAc).

Reduction of 14-Hydroxydihydrocodeinone with Sodium Borohydride.- 14-Hydroxydihydrocodeinone (5.0 g.) was reduced with sodium borohydride (3 g.) in the usual way and the product was isolated using

chloroform, as felted needles, m.p. 147-150°. Fractional crystallisation of this solid from benzene-light petroleum gave two compounds; the less soluble is 14-hydroxydihydroisocodeine, which separated as fine needles, m.p. 167-168°, $[\alpha]_D$ - 142° (c,1.3) $[\alpha]_D$ - 125° (c,1.3 in 10% HOAc) [lit.[26] m.p. 166-167°, $[\alpha]_D$ - 152° (10% HOAc)], $\nu_{max.}$ 3509 and 3425 $cm.^{-1}$ (OH) (Found: C,68.15; H,7.4. Calc. for $C_{18}H_{23}O_4N$: C,68.1; H,7.3%). Acetylation of this diol gave 14-acetoxydihydroisocodeine acetate which separated from benzene-light petroleum as needles, m.p. 199-201°, $[\alpha]_D$ - 191° (c,1.4), $[\alpha]_D$ - 110° (c,1.6 in 10% HOAc) [lit.[26] m.p. 203°, $[\alpha]_D$ - 107° (10% HOAc)], $\nu_{max.}$ 1736 $cm.^{-1}$ (ester C = O) (Found: C,65.6; H,6.9. Calc. for $C_{22}H_{27}O_6N$: C,65.8; H,6.8%). The hydrochloride separated from ether-ethanol as needles, m.p. 197-201° (decomp.) (Found: Cl,7.8. $C_{22}H_{27}O_6N.HCl$ requires Cl,8.1%). The more soluble compound is 14-hydroxydihydrocodeine, which forms fine needles, m.p. 141-142° alone or mixed with the product obtained by catalytic hydrogenation of 14-hydroxycodeine; $[\alpha]_D$ - 170° (c,1.2), $[\alpha]_D$ - 142° (c,1.5 in 10% HOAc) (Found: C,68.2 H,7.5. Calc. for $C_{18}H_{23}O_4N$: C,68.1; H,7.3%). Acetylation of this diol gave 14-acetoxydihydrocodeine acetate which crystallised from benzene-light petroleum as prisms, m.p. and mixed m.p. 180.5-181.5°, $[\alpha]_D$ - 211° (c,1.3), $[\alpha]_D$ - 128°, (c,0.7) in 10% HOAc).

Reduction of 14-Acetoxydihydrocodeinone with Sodium Borohydride.- 14-Acetoxydihydrocodeinone[21] (2.0 g.) was reduced with sodium borohydride using the usual method. The crude product was isolated by means of chloroform and crystallised from benzene-light petroleum to give rosettes of micro-needles m.p. ca.130°. Six recrystallisations of this product from the same solvent gave 14-acetoxydihydroisocodeine as needles, m.p. 180-182° (300 mg.), $[\alpha]_D$ - 177° (c,1.3), $\nu_{max.}$ 3650 (OH) and 1724 $cm.^{-1}$ (ester C = O) (Found: C,67.25; H,6.7; N,4.0 $C_{20}H_{25}O_5N$ requires C,66.8; H,7.0; N,3.9%. Acetylation of 14-acetoxydihydroisocodeine gave 14-acetoxydihydroisocodeine acetate, m.p. and mixed m.p.199-201°.

The earlier mother liquors from the recrystallisation of the solid m.p. 130° were set aside and allowed to evaporate spontaneously. A mixture of needles (predominating) and hard prisms separated. The prisms m.p. 135-160° were mechanically separated and crystallised from benzene-light petroleum to give prismatic needles, m.p. 165-166°, alone or mixed with 14-acetoxydihydrocodeine prepared by catalytic hydrogenation of 14-acetoxycodeine; $[\alpha]_D$ - 200° (c,2.1). Acetylation of 14-acetoxydihydrocodeine gave 14-acetoxydihydrocodeine acetate, m.p. 180.5-181.5° alone or mixed with a specimen prepared by hydrogenation of 14-acetoxycodeine acetate.

14-Hydroxycodeinone. - 14-Hydroxycodeine (0.5 g.) in chloroform (25 c.c.) was stirred at room temperature with active

manganese dioxide (5 g.) for 20 minutes. The filtered solution was evaporated and the residue crystallised from chloroform--ethanol to give 14-hydroxycodeinone (400 mg.) as prisms m.p. and mixed m.p. 275-277°.

14-Hydroxydihydrocodeinone. - (a) 14-Hydroxydihydrocodeine (0.5 g.) was oxidised with potassium t-butoxide and benzophenone using Rapoport's conditions.[55] The cooled solution was extracted with dilute hydrochloric acid and the extract was washed with ether (2 x 30 c.c.), basified with ammonia (d, 0.88) and shaken with chloroform (5 x 30 c.c.). The chloroform solution was washed with water (20 c.c.), dried (Na_2SO_4), and the solvent evaporated. The product (390 mg.) was crystallised from ethanol to give 14-hydroxydihydrocodeinone (265 mg., 53%), m.p. 218-219°, $[\alpha]_D$ - 217° (c, 1.3).

(b) Oxidation of 14-hydroxydihydroisocodeine (150 mg.) using the method described under (a) gave 14-hydroxydihydrocodeinone (27.6 mg, 19%) as long blades, m.p. 217-218°.

14-Hydroxycodeine Tosylate. - 14-Hydroxycodeine (5 g.) in pyridine (10 c.c.) was cooled to 0° and p-toluene sulphonyl chloride (3.5 g.) in pyridine (3 c.c.) was added at such a rate that the temperature remained below 10°. The solution was kept overnight at 5°, and then diluted with ice water (150 c.c.). The product (6.4 g.) was isolated by means of chloroform and crystallised from chloroform-methanol to give 14-hydroxycodeine

tosylate as prismatic needles, m.p. 165°, $[\alpha]_D$ - 211° (c,3.0), $\nu_{max.}$ 3333 $cm.^{-1}$ (OH) (Found: C,64.3; H,6.1. $C_{25}H_{27}O_6NS$ requires C,63.9; H,5.8%).

14-Acetoxycodeine Tosylate. - (a) 14-Acetoxycodeine (5 g.) in pyridine (10 c.c.) was treated with p-toluenesulphonyl chloride (3.5 g.) in pyridine (3 c.c.) at 0-10°. The solution was kept overnight at 5° and the product isolated in the usual manner. Crystallisation from benzene-light petroleum gave 14-acetoxycodeine tosylate (6.0 g.) as hard prisms, m.p. 91-92°, $[\alpha]_D$ - 130° (c,2.5), $\nu_{max.}$ 1739 $cm.^{-1}$ (ester C = O) (Found: C,67.3; H,5.8; $C_{27}H_{29}O_7NS$ requires C,63.4; H,5.7. $C_{27}H_{29}O_7NS.C_6H_6$ requires C,67.2; H,6.0%).

(b) 14-Hydroxycodeine tosylate (0.1 g.) was heated on the steam bath for 1 hr. in acetic anhydride (2 c.c.). The excess acetic anhydride was decomposed with water and the solution basified with ammonia. The product was isolated by means of chloroform and crystallised from benzene-light petroleum to give 14-acetoxycodeine tosylate as prisms, m.p. and mixed m.p. 90-91°, $[\alpha]_D$ - 128° (c,1.0).

14-Acetoxydihydrocodeine Tosylate. - (a) 14-Acetoxydihydrocodeine (5 g.) in pyridine (10 c.c.) was tosylated as described above. The crude product, (6.6 g.), crystallised from chloroform-methanol to give 14-acetoxydihydrocodeine tosylate as

needles, m.p. 134°, $[\alpha]_D$ - 214.5° (c,4.5), $\nu_{max.}$ 1733 cm.$^{-1}$ (ester C = O) (Found: C,63.0; H,6.2. $C_{27}H_{31}O_7NS$ requires C,63.1; H,6.1%).

(b) 14-Acetoxycodeine tosylate (2 g.) in aqueous acetic acid (50 c.c., 50%) was shaken with hydrogen and platinum until gas absorption ceased. The filtered solution was basified with ammonia (d,0.88). The product was isolated by means of chloroform and crystallised from chloroform-light petroleum to give 14-acetoxydihydrocodeine tosylate as needles, m.p. and mixed m.p. 134°.

14-Hydroxydihydrocodeine Tosylate. - (a) 14-Acetoxydihydrocodeine tosylate (0.5 g.) in dry ether (25 c.c.) was treated with lithium aluminium hydride (0.4 g.) in dry ether (10 c.c.) at 0° with vigorous stirring which was continued for 2½ hr. The product was isolated in the usual way and crystallised from chloroform-methanol to give 14-hydroxydihydrocodeine tosylate as prisms, m.p. 138°, $[\alpha]_D$ - 199° (c,3.0), $\nu_{max.}$ 3356 cm.$^{-1}$ (OH) (Found: C, 63.3; H,6.4. $C_{25}H_{29}O_6NS$ requires C,63.7; H,6.2%).

(b) 14-Hydroxydihydrocodeine (1.25 g.) in pyridine (5 c.c.) was tosylated with p-toluenesulphonyl chloride (1 g.) in pyridine (3 c.c.) at 0°. The product crystallised from chloroform-methanol to give 14-hydroxydihydrocodeine tosylate as prisms, m.p. 138° identical with the compound obtained by method (a).

(c) 14-Hydroxycodeine tosylate (1.8 g.) in aqueous acetic acid (60 c.c.; 50%) was hydrogenated over platinum. When absorption of hydrogen was complete, the solution was filtered and the product, isolated in the usual way, was crystallised from chloroform--methanol to give 14-hydroxydihydrocodeine tosylate, m.p. and mixed m.p. 138°.

Acetylation of 14-hydroxydihydrocodeine tosylate in the usual way gave 14-acetoxydihydrocodeine tosylate, m.p. and mixed m.p. 134°.

14-Hydroxydeoxycodeine. - 14-Acetoxycodeine tosylate (1.9 g.) in dry ether (40 c.c.) was treated with a suspension of lithium aluminium hydride (1.0 g.) in dry ether (15 c.c.) at 0°C. Stirring was continued at 0° for 2¾ hr. The excess hydride was decomposed by the addition of a mixture of ice and chloroform and the mixture filtered through kieselguhr. The chloroform layer was separated and the product isolated in the usual way was crystallised from chloroform-methanol to give 14-hydroxydeoxycodeine as prisms, m.p. 125°, $[\alpha]_D$ - 80° (c, 2.0), $\nu_{max.}^{CCl_4}$ 3333 $cm.^{-1}$ (OH) (Found: C, 72.6, 72.2; H, 7.1, 7.5. $C_{18}H_{21}O_3N$ requires C, 72.2; H, 7.1%).

Similar reduction of 14-hydroxycodeine tosylate in dry tetrahydrofuran gave 14-hydroxydeoxycodeine in 60% yield. 14-Hydroxycodeine tosylate (40%) was recovered.

14-Hydroxydihydrodeoxycodeine. - 14-Hydroxydeoxycodeine (0.4 g.) in aqueous acetic acid (50 c.c.; 50%) was hydrogenated over platinum at room temperature. When gas absorption ceased, the solution was filtered and the product isolated in the usual way. Crystallisation from chloroform-methanol gave 14-hydroxy dihydrodeoxycodeine (0.35 g.) as prisms, m.p. 116-117°, $[\alpha]_D$ - 106° (c,1.5), $\nu_{max.}$ 3333 $cm.^{-1}$ (OH) (Found: C,71.7; H,7.7. $C_{18}H_{23}O_3N$ requires C,71.7; H,7.7%).

14-Acetoxydeoxycodeine. - A solution of 14-hydroxydeoxy-codeine (0.4 g.) in acetic anhydride (4 c.c.) was heated on the steam bath for 2 hr. The product, isolated in the usual way, was crystallised from chloroform-light petroleum to give 14-acetoxydeoxycodeine (0.4 g.) as needles, m.p. 182-183°, $[\alpha]_D$ - 17° (c,3.5), $\nu_{max.}$ 1739 $cm.^{-1}$ (ester C = O) (Found: C,70.35; H,6.75. $C_{20}H_{23}O_4N$ requires C,70.4; H,6.8%).

Hydrolysis of 14-Acetoxydeoxycodeine. - The acetate, m.p. 182-183° (0.15 g.) was refluxed for 2 hr. in a solution of potassium hydroxide (1 g.) in water (5 c.c.) and ethanol (15 c.c.). Dilution of the solution with water (200 c.c.) and extraction with chloroform gave a gum which crystallised from chloroform-methanol to give 14-hydroxydeoxycodeine (0.12 g.) as prisms, m.p. and mixed m.p. 125°.

14-n-Butyryloxydeoxycodeine. - 14-Hydroxydeoxycodeine (200 mg.) was heated on the steam bath for 2.5 hr. with n-butyric anhydride. The cooled solution was worked up in the usual way to give a red gum which crystallised from chloroform-light petroleum to give 14-n-butyryloxydeoxycodeine (140 mg.) as prism, m.p. 117-118°, $[\alpha]_D$ - 18° (c,0.3), $\nu_{max.}$ 1730 $cm.^{-1}$ (ester C = O) (Found: C,71.1; H,7.3. $C_{22}H_{27}O_4N$ requires C,71.5; H,7.4%).

14-Acetoxydihydrodeoxycodeine. - (a) 14-Acetoxydeoxycodeine (0.2 g.) in aqueous acetic acid (30 c.c., 50%) was hydrogenated using platinum as catalyst. After 4 hr., when 1 mol. of hydrogen had been absorbed, the solution was filtered and worked up in the usual way to give a crystalline mass which on recrystallisation from chloroform-methanol gave 14-acetoxydihydrodeoxycodeine (0.2 g.) as needles, m.p. 124-126.5°, $[\alpha]_D$ - 136° (c,4.0), $\nu_{max.}$ 1718 $cm.^{-1}$ (ester C = O) (Found: C,70.15; H,7.5. $C_{20}H_{25}O_4N$ requires C,69.95; H,7.3%).

(b) 14-Hydroxydihydrodeoxycodeine (0.5 g.) was heated on the steam bath for 2.5 hr. with acetic anhydride (5 c.c.). Working up in the usual way gave the product which crystallised from chloroform-methanol to give 14-acetoxydihydrodeoxycodeine (0.5 g.) as needles, m.p. and mixed m.p. 124-126.5°.

14-Hydroxyisocodeine. - 14-Hydroxycodeine tosylate (1.6 g.) in acetic acid (8 c.c.) and water (72 c.c.) was refluxed for 4 hr. The solution was cooled, basified with ammonia (d,0.88)

and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4) and evaporated to yield a gum which crystallised from chloroform-methanol to give 14-hydroxyisocodeine (0.3 g.) as prisms, m.p. 149-150°, $[\alpha]_D$ - 176° (c,0.8), $\nu_{max.}$ 3425 and 3247 $cm.^{-1}$ (OH). (Found: C,68.7; H,6.9. $C_{18}H_{21}O_4N$ requires C,68.55; H,6.7%).

14-Acetoxyisocodeine Acetate. - (a) 14-Hydroxyisocodeine (100 mg.) was heated on the steam bath for 1 hr. with acetic anhydride (3 c.c.). The cooled solution was warmed to 40-45° with water (10 c.c.) and then cooled to 0° and basified with ammonia (d,0.88). The precipitated solid was collected, dried and crystallised from chloroform-methanol to give 14-acetoxyisocodeine acetate as prismatic needles, m.p. 187°, $[\alpha]_D$ - 193° (c,9.0), $\nu_{max.}$ 1730 and 1718 $cm.^{-1}$ (ester C = O) (Found: C,66.3; H,6.6. $C_{22}H_{25}O_6N$ requires C,66.15; H,6.3%).

(b) The first chloroform-methanol mother liquor from the crystallisation of crude 14-hydroxyisocodeine was evaporated and the residue heated with acetic anhydride on the steam bath for 1 hr. Working up in the usual way followed by crystallisation from chloroform-light petroleum gave a mixture of acetates (1.05 g.). This was separated by crystallisation from the same solvent mixture into a less soluble fraction (fraction A), m.p. 230-240° (0.35 g.), and more soluble fraction recrystallisation of which gave 14-acetoxyisocodeine acetate (0.25 g.) as prisms, m.p. and mixed m.p. 187°.

14-Hydroxyisocodeine Acetate. - 14-Acetoxyisocodeine acetate (2 g.) in methanol (100 c.c.) was refluxed for 4 hr. on the steam bath. The methanol solution was concentrated to 5-10 c.c. and the crystals separating on cooling were collected, m.p. 150-170°. Fractional crystallisation of this solid from chloroform-methanol yielded 14-hydroxyisocodeine acetate (0.4 g.) as prismatic needles, m.p. 163-164°, $[\alpha]_D$ - 252° (c,0.9), $\nu_{max.}$ 3226 (OH) and 1727 cm.$^{-1}$ (ester C = O) (Found: C,67.4; H,6.2. $C_{20}H_{23}O_5N$ requires C,67.2; H,6.5%). Hydrolysis of 14-hydroxyisocodeine acetate with alcoholic potassium hydroxide gave 14-hydroxyisocodeine, m.p. and mixed m.p. 149-150°.

14-n-Butyryloxyisocodeine Acetate. - 14-Hydroxyisocodeine acetate (200 mg.) was heated on the steam bath with n-butyric anhydride (5 c.c.) for 2.5 hr. After working up in the usual way a gum was obtained which crystallised from chloroform-light petroleum to give 14-n-butyryloxyisocodeine acetate (140 mg.) as prisms, m.p. 141-142°, $[\alpha]_D$ - 177° (c,0.6), $\nu_{max.}$ 1725 cm.$^{-1}$ (ester C = O) (Found: C,67.5; H,7.2. $C_{24}H_{29}O_6N$ requires C,67.4; H,6.85%).

14-Hydroxycodeinone. - 14-Hydroxyisocodeine (40 mg.) in chloroform (2 c.c.) was stirred at room temperature with active manganese dioxide (200 mg.) for 3 hr. The filtered solution was evaporated and the residue crystallised from chloroform-methanol to give 14-hydroxycodeinone (4 mg.) as prismatic needles, m.p. and mixed m.p. 265-268°. 14-Hydroxyisocodeine was

recovered from the mother liquor.

14-Hydroxydihydroisocodeine. - A solution of 14-hydroxyisocodeine (100 mg.) in aqueous acetic acid (40 c.c.; 50%) was shaken with platinum (from platinum oxide, 100 mg.) and hydrogen at room temperature and atmospheric pressure until 1 mol. had been absorbed (2 hr.). The filtered solution was basified with ammonia (d, 0.88). The product was isolated using chloroform, and crystallised to give 14-hydroxydihydroisocodeine which separated from chloroform-light petroleum as needles, m.p. and mixed m.p. 165-166°.

14-Hydroxydihydroisocodeine Acetate. - 14-Hydroxyisocodeine acetate (0.5 g.) in 50% aqueous acetic acid (50 c.c.) was hydrogenated over platinum until absorption ceased. The filtered solution was made basic with ammonia (d, 0.88) and the product isolated with chloroform and crystallised from chloroform-methanol to give 14-hydroxydihydroisocodeine acetate (0.4 g.) as prisms, m.p. 208-209°, $[\alpha]_D$ - 169° (c, 0.6), $\nu_{max.}$ 3367 (OH), 1745 $cm.^{-1}$ (ester C = O) (Found: C, 66.7; H, 7.2. $C_{20}H_{25}O_5N$ requires C, 66.8; H, 7.0%).

14-Hydroxyallopseudocodeine Acetate. - 14-Hydroxycodeine tosylate (0.5 g.) in acetic acid (21 c.c.) and water (9 c.c.) was refluxed for 4 hr. Isolation of the product in the usual way gave 14-hydroxyallopseudocodeine acetate, (0.15 g.) which separated from chloroform-methanol as needles, m.p. 194-195°,

$[\alpha]_D$ - 322.5° (c,1.75), $\nu_{max.}$ 3257 (OH) and 1721 cm.$^{-1}$ (ester C = O) (Found: C,66.9; H,6.5. $C_{20}H_{23}O_5N$ requires C,67.2; H,6.5%). A small amount of 14-hydroxyisocodeine was obtained from the mother liquors.

14-Acetoxyallopseudocodeine Acetate. - Fraction A, m.p. 230-240°, obtained during the preparation of 14-acetoxyisocodeine acetate (method b) was crystallised from chloroform-light petroleum to give 14-acetoxyallopseudocodeine acetate as needles, m.p. 240-243°, $[\alpha]_D$ - 333° (c,2.5), $\nu_{max.}$ 1739 and 1724 cm.$^{-1}$ (ester C = O) (Found: C,65.85; H,6.2. $C_{22}H_{25}O_6N$ requires C,66.15; H,6.3%). This compound, was also obtained by acetylation of 14-hydroxyallpseudocodeine acetate.

A solution of 14-acetoxyallopseudocodeine acetate (1 g.) in methanol (100 c.c.) was refluxed for 4 hr. The solution was concentrated to 10 c.c. and the solid which separated on standing, was recrystallised from chloroform-methanol to give 14-hydroxyallopseudocodeine acetate (0.75 g.) as needles, m.p. and mixed m.p. 194-195°.

14-Hydroxyallopseudocodeine. - 14-Acetoxyallopseudocodeine acetate (1.0 g.) in ethanol (30 c.c.) was refluxed for 1 hr. with a solution of potassium hydroxide (2 g.) in water (10 c.c.). The solution was diluted with water and the product isolated using chloroform, crystallised from chloroform-light petroleum to give 14-hydroxyallopseudocodeine as prisms, m.p. 135-137°, $[\alpha]_D$ - 286° (c,1.5), $\nu_{max.}$ 3425 and 3175 cm.$^{-1}$ (OH) (Found: C,68.8; H,6.6.

$C_{18}H_{21}O_4N$ requires C,68.55; H,6.7%). Hydrolysis of 14-hydroxyallopseudocodeine acetate under the same conditions gave 14-hydroxyallopseudocodeine, m.p. and mixed m.p. 135-137°.

14-Hydroxypseudocodeinone. - 14-Hydroxyallopseudocodeine (0.55 g.) in chloroform (15 c.c.) was stirred for 4.5 hr. with active manganese dioxide (2.0 g.). The filtered solution was evaporated to dryness and the gum crystallised from chloroform--methanol to give 14-hydroxypseudocodeinone (0.1 g.) as prismatic needles, m.p. 186-187°, $[\alpha]_D$ - 66° (c,1.1), $\nu_{max.}^{CCl_4}$ 3311 (OH) and 1695 $cm.^{-1}$ ($\alpha\beta$ C = O) (Found: C,69.0; H,5.8. $C_{18}H_{19}O_4N$ requires C,69.0; H,6.1%).

14-Acetoxypseudocodeinone. - 14-Hydroxypseudocodeinone (0.2 g.) was heated for 1 hr. on the steam bath with acetic anhydride (6 c.c.). Isolation of the base in the usual way followed by crystallisation from chloroform-light petroleum gave 14-acetoxypseudocodeinone (0.2 g.) as prismatic needles, m.p. 155-156°, $[\alpha]_D$ - 63° (c,0.4), $\nu_{max.}$ 1755 (ester C = O), 1695 $cm.^{-1}$ ($\alpha\beta$ C = O) (Found: C,67.35; H,6.2. $C_{20}H_{21}O_5N$ requires C,67.6; H,6.0%).

14-Hydroxydihydropseudocodeinone. - A solution of 14-hydroxypseudocodeinone (0.6 g.) in glacial acetic acid (47 c.c.) and hydrochloric acid (3 c.c.; d,1.15) was shaken with catalyst from Adams platinum oxide (0.25 g.) and hydrogen at room temperature

and atmospheric pressure until 1 mol. had been absorbed (1½ hr.). The filtered solution was basified with ammonia (d,0.88). The product was crystallised from chloroform-methanol to give 14-hydroxydihydropseudocodeinone (0.15 g.) as prismatic needles, m.p. 156-157°, $[\alpha]_D$ + 15° (c,1.0), $\nu_{max.}$ 3425 (OH) and 1706 cm.$^{-1}$ (C = O) (Found: C,68.7; H,6.5. $C_{18}H_{21}O_4N$ requires C,68.55; H,6.7%).

The mother liquor yielded a phenol, m.p. 204-205° (0.2 g.) which gives a positive reaction with diazotised sulphanilic acid.

14-Hydroxydihydroallopseudocodeine. - (a) 14-Hydroxypseudocodeinone (0.24 g.) in dioxan (10 c.c.) was stirred for 2 hr. with a solution of sodium borohydride (0.2 g.) in water (5 c.c.). After dilution of the mixture with water (250 c.c.) and sodium hydroxide solution (10 c.c., 2N), the base was separated using chloroform. Crystallisation of the product from chloroform-light petroleum gave 14-hydroxydihydroallopseudocodeine (0.18 g.) as needles, m.p.175-176°, $[\alpha]_D$ - 135° (c,0.8), $\nu_{max.}$ 3484 and 3247 cm.$^{-1}$ (OH) (Found: C,68.1; H,7.3. $C_{18}H_{23}O_4N$ requires C,68.1; H,7.3%). (b) 14-Hydroxydihydropseudocodeinone (62 mg.) was hydrogenated at room temperature and atmospheric pressure using the catalyst from Adams platinum oxide (50 mg.). After absorption was complete (18 hr.), the solution was filtered, basified, and the precipitate isolated using chloroform. The product was

crystallised from chloroform-light petroleum ether to give 14-hydroxydihydroallopseudocodeine (52 mg.) m.p. and mixed m.p. 175-176°.

(c) 14-Hydroxyallopseudocodeine (0.75 g.) in glacial acetic acid (47 c.c.) and hydrochloric acid (3 c.c.; d,1.15) was shaken with catalyst from Adams platinum oxide and hydrogen at room temperature and atmospheric pressure until absorption was complete (1½ hr.). The filtered solution was basified and the precipitate extracted with chloroform. The red gum left on evaporation of the chloroform was crystallised six times from chloroform-methanol to give 14-hydroxydihydroallopseudocodeine (0.2 g.) as prisms, m.p. and mixed m.p. 175-176°.

14-Acetoxydihydroallopseudocodeine. - 14-Hydroxydihydroallopseudocodeine (0.1 g.) was heated on the steam bath for 1 hr. with acetic anhydride (3 c.c.). The solution was cooled and chloroform (50 c.c.) added. The chloroform solution was shaken with ammonia (d,0.88) and then washed several times with water and dried (Na_2SO_4). On evaporation a gum was obtained which crystallised from chloroform-light petroleum to give 14-acetoxydihydroallopseudocodeine (30 mg.) as needles, m.p. 206-207°, $[\alpha]_D$ - 207° (c,0.2), $\nu_{max.}$ 3460 (OH), 1715 $cm.^{-1}$ (ester C = O) (Found: C,66.9; H,7.2. $C_{20}H_{25}O_5N$ requires C,66.8; H,7.0%).

14-Hydroxydihydroallopseudocodeine Acetate. - (a) 14-Hydroxyallopseudocodeine acetate (0.5 g.) in glacial acetic acid

(40 c.c.) and hydrochloric acid (3 c.c.; d,1.15) was hydrogenated over platinum from Adams platinum oxide (0.2 g.). The filtered solution was shaken with chloroform (100 c.c.) and ammonia (20 c.c.; d,0.88) added in portions with shaking. The chloroform layer was washed with water, dried (Na_2SO_4) and the chloroform evaporated *in vacuo* to give a red gum which crystallised from chloroform-methanol yielding 14-hydroxydihydroallopseudocodeine acetate (0.15 g.) as prisms, m.p. 154-156°, $[\alpha]_D$ - 101° (c,0.2), $\nu_{max.}$ 3226 (OH) and 1730 $cm.^{-1}$ (ester C = O) (Found: C,67.1; H,7.2. $C_{20}H_{25}O_5N$ requires C,66.8; H,7.0%).

(b) The mother liquors from the initial crystallisation of 14-acetoxydihydroallopseudocodeine were evaporated and the residue crystallised from chloroform-methanol to give 14-hydroxydihydroallopseudocodeine acetate (30 mg.) as needles, m.p. and mixed m.p. 154-156°. Hydrolysis of both 14-acetoxydihydroallopseudocodeine and 14-hydroxydihydroallopseudocodeine acetate using 5% ethanolic potassium hydroxide gave 14-hydroxydihydro allopseudocodeine, m.p. and mixed m.p. 175-176°.

14-Hydroxydihydropseudocodeinone from 14-hydroxydihydro allopseudocodeine. - The diol (200 mg.) was oxidised with potassium t-butoxide and benzophenone using Rapoport's conditions[35] Isolation in the usual way followed by crystallisation from chloroform-methanol gave 14-hydroxydihydropseudocodeinone (140 mg.; 70%) as needles, m.p. and mixed m.p. 155-156°.

Reduction of 14-Hydroxycodeinone by Zinc Dust and Acetic Acid.[26] - Glacial acetic acid (150 c.c.) was mechanically stirred and 14-hydroxycodeinone (30 g.) added. When solution was complete, zinc dust (25 g.) was added slowly with stirring, and the temperature did not rise above 50°. The temperature was maintained at 50-55° for 30 min. and the solution stirred for a further 90 min. at room temperature. The zinc was filtered off and washed with hot glacial acetic acid (100 c.c.). The solution was neutralised cautiously with ammonia (d,0.88) with ice bath cooling, and the solid extracted with chloroform. After washing with water, the chloroform solution was successively extracted with 150 c.c. N/10, 250 c.c. N/10, and 75 c.c. N. sulphuric acid, and these acid fractions were in turn basified with ammonia (d,0.88) and worked up through chloroform. The gum (7.0 g.) obtained from the last fraction was crystallised from chloroform-ethanol to yield "hydroxycodeine" as prisms, m.p. 285-290° (decomp., evac. tube), $[\alpha]_D$ - 141° (c,1.0 in 10% acetic acid), $\nu_{max.}$ 3540, 3320 (OH), and 1729 $cm.^{-1}$ (C = O) (Found: C,68.5; H,6.6. Calc. for $C_{18}H_{21}O_4N$: C,68.55; H,6.7%).

As determined by the standard ebullioscopic method, the molecular weight of "hydroxycodeine" was variously found to be 330, 370 (benzene) and 327 (ethanol). $C_{18}H_{21}O_4N$ requires molecular weight 315. "Hydroxycodeine" was recovered unchanged and is therefore monomolecular.

Attempted Reduction of 14-Hydroxydihydrocodeinone with Zinc Dust and Acetic Acid. - 14-Hydroxydihydrocodeinone (30 g.) in glacial acetic acid (150 c.c.) was treated with zinc dust (25 g.) under the same conditions as described above. After working up in the same manner, the fractions obtained were crystallised from chloroform-methanol to yield 14-hydroxydihydrocodeinone (24 g.) m.p. and mixed m.p. 218°.

"Dihydrohydroxycodeine A"[26] - "Hydroxycodeine" (1 g.) in 10% aqueous acetic acid (50 c.c.) was hydrogenated over platinum at room temperature. When absorption was complete the solution was filtered, made basic with ammonia (d,0.88) and the base obtained by extraction with chloroform was crystallised from chloroform-ethanol to give "dihydrohydroxycodeine A" as prisms, m.p. 303-304° (decomp.), $[\alpha]_D$ - 66° (c,0.6), $\nu_{max.}$ 3390 $cm.^{-1}$ (OH).

Sodium Borohydride Reduction of "Hydroxycodeine". -"Hydroxycodeine" (0.5 g.) in dioxan (20 c.c.) was treated with sodium borohydride (0.5 g.) in water (10 c.c.) and the solution stirred for 2 hr. at room temperature. The solution was diluted with water (500 c.c.) and the base extracted with chloroform. On removal of the chloroform, the gum obtained was crystallised from chloroform-methanol to give a compound (0.2 g.) as prisms, m.p. 222-223°, $[\alpha]_D$ - 120° (c,0.4), $\nu_{max.}$ 3390 $cm.^{-1}$ (OH) (Found: C,66.4; H,7.0; N,4.0; O,22.75. $C_{18}H_{23}O_4N.\frac{1}{2}H_2O$ requires C,66.25; H,7.4; N,4.3; O,22.1%).

Acetate of "Hydroxycodeine". - "Hydroxycodeine" (0.5 g.) in acetic anhydride (6 c.c.) was heated for 3 hr. on the steam bath. The cooled solution was diluted with water (40 c.c.), made basic with ammonia (d,0.88) and worked up through chloroform. The gum obtained was crystallised from chloroform-methanol to give a compound (0.2 g.) as needles, m.p. 168-172°, $[\alpha]_D$ - 169° (c,0.5), $\nu_{max.}$ 1740 cm.$^{-1}$ (C = O) (Found: C,65.3; H,6.6; N,3.4. $C_{20}H_{23}O_6N.\frac{1}{2}H_2O$ requires C,65.6; H,6.6; N,3.8%). "Hydroxycodeine" (0.2 g.) m.p. and mixed m.p. 285° was obtained from the mother liquors.

Acetylation of the Diol m.p. 222-223°. - The diol m.p. 222-223° (0.1 g.) was acetylated with acetic anhydride (5 c.c.). The gum obtained on working up through chloroform was crystallised from chloroform-methanol to give a monoacetate (A) (60 mg.) as needles, m.p. 203-204°, $[\alpha]_D$ - 132° (c,0.2), $\nu_{max.}$ 1740 cm.$^{-1}$ (ester C = O). (Found: C,65.4; H,6.6. $C_{22}H_{27}O_6N$ requires C,65.8; H,6.8%).

Sodium Borohydride Reduction of "Hydroxycodeine" Acetate. - The acetate of "hydroxycodeine" (0.2 g.) was dissolved in dioxan (5 c.c.) and with stirring, a solution of sodium borohydride (0.2 g.) in water (2 c.c.) added. After stirring for 2 hr., water (200 c.c.) was added and the solution extracted with chloroform. The froth obtained on removal of the chloroform was acetylated to give the compound (A) (50 mg.) m.p. and mixed m.p. 203-204°.

"Hydroxycodeine" from the Diol m.p. 222-223°. - The diol (0.12 g.) was oxidised with potassium t-butoxide and benzophenone under Rapoport's conditions.[35] Isolation of the base in the usual way followed by crystallisation from chloroform-ethanol gave "hydroxycodeine" (60 mg.) as prisms, m.p. and mixed m.p. 285°.

"Dihydrohydroxycodeine A" (0.15 g.) under the same conditions returned starting material in 80% yield.

Clemmensen Reduction of "Hydroxycodeine". - "Hydroxycodeine" (1 g.) in glacial acetic acid (50 c.c.) was heated on the steam bath and zinc amalgam (12 g.) added. After addition of a mixture of concentrated hydrochloric acid (17 c.c.) and glacial acetic acid (25 c.c.) the mixture was heated for a further 1 hr. on the steam bath. The filtered solution was made basic with ammonia (d,0.88) and the base extracted with chloroform. Removal of the solvent gave a gum which crystallised from chloroform-ethanol to give a carbonyl free compound as needles, m.p. 271-273° (decomp.), $[\alpha]_D$ - 68° (c,1.0),) $\nu_{max.}$ 3355 $cm.^{-1}$ (OH) (Found: C,70.15, 70.65; H,6.5, 6.8. $C_{20}H_{23}O_4N$ requires C,70.4; H,6.8%. $C_{18}H_{23}O_3N$ requires C,71.7; H,7.7%).

Clemmensen Reduction of 14-Hydroxydihydrocodeinone. - 14-Hydroxydihydrocodeinone (5 g.) was reduced under the conditions described above. When the reaction was complete the ketonic material was removed by treating the product with Girard's (T) reagent.[52] The non-ketonic fraction (4 g.) was crystallised from acetone-water to give a carbonyl free phenolic

compound as platelets, m.p. 141°, $[\alpha]_D$ - 41° (c,0.25), $\nu_{max.}$ 3333 cm.$^{-1}$ (OH) (Found: C,71.25; H,8.2. $C_{18}H_{23}O_3N$ requires C,71.25; H,8.25%).

Ethanolic Potash on 14-Hydroxycodeinone. - 14-Hydroxycodeinone (5 g.) was refluxed for 2.5 hr. with a solution of potassium hydroxide (30 g.) in water (50 c.c.) and ethanol (100 c.c.). The cooled solution was diluted with water (500 c.c.) and the dark red gum obtained by extraction with chloroform yielded on trituration with ethanol a compound (0.5 g.) as needles, m.p.>300°, $[\alpha]_D$ -313° (c,1.0), $\nu_{max.}$ 3495 (OH), 1750 cm.$^{-1}$ (C = O) (Found: C,66.5, 66.1; H,5.9, 6.25. $C_{18}H_{21}O_4N.\frac{1}{2}H_2O$ requires C,66.65; H,6.8%).

Acetate of Compound m.p.>300°. - The compound m.p.>300° (150 mg.) in acetic anhydride (5 c.c.) was heated on the steam bath for 3 hr. Working up in the usual way gave a gum which crystallised from chloroform-ethanol to give a compound as needles m.p. 221-223°, $[\alpha]_D$ - 274° (c,3.0), $\nu_{max.}$ 1730 cm.$^{-1}$ (C = O). (Found: C,65.3, 65.6; H,5.95, 5.9. $C_{20}H_{23}O_5N.\frac{1}{2}H_2O$ requires C,65.6; H,6.6%).

14-Acetoxy-N-cyanonorcodeine Acetate. - 14-Acetoxycodeine acetate (6 g.) was heated in a test-tube with cyanogen bromide[83] (10 g.) for 3 min. at 100°. The mixture fused and was left to cool for 1 hr. Ethanol (20 c.c.) was added and the mixture filtered. The solid product was washed with ethanol (40 c.c.)

and crystallised from chloroform-methanol to give 14-acetoxy-N--cyanonorcodeine acetate (5 g.) as prism, m.p. 190°, $[\alpha]_D$ - 123° (c,0.8), $\nu_{max.}$ 2222 (C≡N), 1730 cm.$^{-1}$ (ester C = O) (Found: C,64.6; H,5.2; N,6.6. $C_{22}H_{22}O_6N_2$ requires C,64.4; H,5.4; N,6.8%).

14-Acetoxy-N-cyanonorcodeinone. - (a) 14-Acetoxycodeinone (4 g.) was heated in a test-tube with cyanogen bromide (8 g.) for 6 min. at 100°. The mixture did not fuse completely, but addition of ethanol followed by filtration gave a solid which on crystallisation from chloroform-ethanol gave 14-acetoxy-N-cyano norcodeinone (3.5 g.) as rosettes of needles, m.p. 260-262°, $[\alpha]_D$ -60° (c,1.9), $\nu_{max.}$ 2222 cm.$^{-1}$ (C≡N), 1739 (ester C = O) and 1686 cm.$^{-1}$ (αβ C = O) (Found: C,65.9; H,4.9. $C_{20}H_{18}O_5N_2$ requires C,65.6; H,4.95%).

(b) 14-Acetoxycodeinone (5 g.) in chloroform (400 c.c.) was refluxed for 2 hr. with a solution of cyanogen bromide (20 g.) in chloroform (200 c.c.). Evaporation of the solvent gave a gum which crystallised from chloroform-methanol to give 14-acetoxy--N-cyanonorcodeinone (4 g.) as prismatic needles, m.p. and mixed m.p. 260-262°.

14-Acetoxy-N-cyanonorcodeine. - (a) To a solution of 14-acetoxy-N-cyanonorcodeinone (1 g.) in dioxan (75 c.c.) was added sodium borohydride (0.5 g.) in water (10 c.c.). The mixture was stirred for 2 hr., diluted with water (500 c.c.) and extracted with chloroform. The gum left on removal of the chloroform was

crystallised from chloroform-light petroleum to give 14-acetoxy--N-cyanonorcodeine (0.8 g.) as prisms, m.p. 220-222°, $[\alpha]_D$ - 69° (c,0.9), $\nu_{max.}$ 3333 (OH), 2212 (C≡N), 1730 cm.$^{-1}$ (ester C = O) (Found: C,65.2, 65.7; H,5.0, 5.7. $C_{20}H_{20}O_5N_2$ requires C,65.2; H,5.5%).

(b) 14-Acetoxy N-cyanonorcodeine acetate (2 g.) was reduced with sodium borohydride as described above. The product on crystallisation from chloroform-methanol returned starting material (1.8 g.). From the mother liquors, 14-acetoxy N-cyanonorcodeine (0.1 g.) was obtained as prisms, m.p. and mixed m.p. 220-222°.

(c) 14-Acetoxy-N-cyanonorcodeine acetate (0.2 g.) in methanol (75 c.c.) was refluxed for 5 hr. with pyridine (4 c.c.). Removal of the solvent followed by crystallisation from chloroform-methanol gave 14-acetoxy N-cyanonorcodeine (0.15 g.) as prisms, m.p. and mixed m.p. 220-222°.

14-Acetoxy-N-cyanonorcodeine on acetylation gave 14-acetoxy N-cyanonorcodeine acetate and on oxidation with manganese dioxide gave 14-acetoxy-N-cyanonorcodeinone.

14-Acetoxy-N-cyanodihydronorcodeinone. - 14-Acetoxydihydronorcodeinone (10 g.) in chloroform (500 c.c.) was refluxed with a solution of cyanogen bromide (30 g.) in chloroform (200 c.c.). Evaporation of the chloroform followed by addition of methanol gave 14-acetoxy N-cyanodihydronorcodeinone as prisms, m.p. and mixed m.p. 260° (decomp.) (An authentic specimen was provided by Dr. F. R. Smith of T. and H. Smith Ltd.).

Preparation of 14-Acyloxy-N-cyanonorcodeine Derivatives.- The following 14-acyloxy N-cyanocodeine derivatives were obtained in 80-90% yield from the corresponding 14-acyloxycodeine derivatives as described for the preparation of 14-acetoxy N-cyanonorcodeinone (method b.)

14-Propionyloxy-N-cyanonorcodeinone (from chloroform-light petroleum) as prisms, m.p. 220-221°, $[\alpha]_D$ - 46.5° (c,0.8), $\nu_{max.}$ 2200 (C≡N), 1680 (αβ C = O), 1725 cm.$^{-1}$ (ester C = O) (Found: C,66.4; H,5.3. $C_{21}H_{20}O_5N_2$ requires C,66.3; H,5.3%).

14-n-Butyryloxy-N-cyanonorcodeinone (from chloroform-light petroleum) as prisms, m.p. 179-180°, $[\alpha]_D$ - 40° (c,0.8), $\nu_{max.}$ 2200 (C≡N) 1680 (αβ C = O), 1725 cm.$^{-1}$ (ester C = O) (Found: C,67.3; H,5.75. $C_{22}H_{22}O_5N_2$ requires C,67.0; H,5.6%).

14-Benzoyloxy-N-cyanonorcodeine acetate (from chloroform-ethanol) as needles, m.p. 220°, $[\alpha]_D$ -117° (c,0.7), $\nu_{max.}$ 2250 (C≡N), 1715, 1740 cm.$^{-1}$ (ester C=O) (Found: C,68.6; H,5.0; N,6.6. $C_{27}H_{24}O_6N_2$ requires C,68.6; H,5.1; N,6.2%).

14-Hydroxynorcodeine. - (a) 14-Acetoxy N-cyanonorcodeinone (478 mg.) was placed in the thimble of a Soxhlet apparatus containing a suspension of lithium aluminium hydride (500 mg.) in ether (200 c.c.) in the boiling flask. After 66 hr. reflux, solution was complete, and the cooled solution was treated with water and chloroform to decompose excess lithium aluminium hydride, filtered through kieselguhr and the organic layer evaporated to

dryness to yield a gum which crystallised from chloroform-light petroleum-ethanol to give 14-hydroxynorcodeine as prisms, m.p. 203° $[\alpha]_D$ - 101° (c,2.0), $\nu_{max.}$ 3226 cm.$^{-1}$ (OH) (Found: C,66.6; H,6.8. $C_{17}H_{19}O_4N.\frac{1}{2}C_2H_5OH$ requires C,66.6; H,6.8%).

Recrystallisation from chloroform-methanol gave prismatic needles, m.p. 203° (Found: C,65.9; H,6.8. $C_{17}H_{19}O_4N.\frac{1}{2}CH_3OH$ requires C,66.2; H,6.7%).

(b) 14-Acetoxy N-cyanonorcodeine acetate (4.5 g.) in suspension in anhydrous ether (1 l.) was cooled to room temperature and a suspension of lithium aluminium hydride (4 g.) in anhydrous ether (200 c.c.) added in portions. The mixture was then refluxed for 2 hr., cooled and worked up as described in preparation (a). The gum left on removal of the solvent was crystallised from chloroform-methanol to give 14-hydroxynorcodeine (1 g.) as needles m.p. and mixed m.p. 203°.

14-Hydroxynorcodeinone. - 14-Hydroxynorcodeine (200 mg.) in chloroform (10 c.c.) was stirred for 1 hr. with active manganese dioxide (1 g.). The filtered solution was evaporated to dryness and the gum obtained crystallised from chloroform-methanol to give 14-hydroxynorcodeinone (150 mg.), m.p. 185-187°, $[\alpha]_D$ - 40° (c,0.2), $\nu_{max.}$ 3390 (OH), 1678 cm.$^{-1}$ ($\alpha\beta$ C = O) (Found: C,68.7; H,5.5. $C_{17}H_{17}O_4N$ requires C,68.2; H,5.7%).

14-Hydroxydihydronorcodeinone. - 14-Acetoxy N-cyanodihydronorcodeinone (5 g.) in 25% sulphuric acid (50 c.c.) was refluxed for 4 hr. The cooled solution was diluted with water (500 c.c.) and after addition of ammonia (d,0.88), the base was isolated using chloroform. Removal of the solvent under vacuum at room temperature followed by addition of methanol and concentration of the solution to low bulk under vacuum gave 14-hydroxydihydronorcodeinone (1 g.) as rosettes of needles, m.p. 174-175°, $[\alpha]_D$ - 205° (c,0.4), $\nu_{max.}$ 3280 (OH), 1713 $cm.^{-1}$ (C = O). A satisfactory analysis could not be obtained for this compound due to difficulties involved in obtaining a pure specimen.

14-Hydroxydihydronorcodeinone hydriodide (250 mg.) prepared as described by Speyer and Sarre[55] was dissolved in water (200 c.c.), ammonia (d,0.88) added and the base extracted with chloroform. The gum obtained was crystallised from chloroform-methanol to give 14-hydroxydihydronorcodeinone (35 mg.) as needles, m.p. and mixed m.p. 174-175°.

14-Hydroxy-N-acetylnorcodeine Acetate. - (a) 14-Hydroxynorcodeine (100 mg.) was heated on the steam bath for 1 hr. with acetic anhydride (5 c.c.) then cooled, taken up in chloroform, and shaken with water and ammonia (d,0.88). The chloroform solution was washed with water and evaporated to dryness. The gum obtained was crystallised from chloroform-methanol to give 14-hydroxy-N-acetylnorcodeine acetate (80 mg.) as needles, m.p. 249-250° (decomp.), $[\alpha]_D$ - 206° (c,0.5), $\nu_{max.}$ 3311 (OH), 1713 (ester C = O), 1613 $cm.^{-1}$ (N-acetyl C = O) (Found: C,65.35; H,6.4.

$C_{21}H_{23}O_6N$ requires C,65.4; H,6.0%).

(b) 14-Acetoxy-N-cyanonorcodeine acetate (5 g.) in glacial acetic acid (245 c.c.) and water (105 c.c.) was refluxed for 4 hr. The cooled solution was basified and the solid extracted with chloroform to yield on evaporation a gum which crystallised from chloroform-methanol to give 14-hydroxy N-acetylnorcodeine acetate (2.5 g.) as needles, m.p. and mixed m.p. 249-250° (decomp.) A further crop (2.0 g.) was obtained by recycling the mother liquor with aqueous acetic acid.

(c) 14-Acetoxy-N-cyanonorcodeine acetate (350 mg.) in (I) glacial acetic acid (75 c.c.) and (II) 50% aqueous acetic acid (75 c.c.) was hydrogenated using platinum oxide (150 mg.) as catalyst. In each case starting material (90%) was returned but the mother liquors yielded from chloroform-light petroleum 14-hydroxy-N-acetylnorcodeine acetate (10%) as needles, m.p. and mixed m.p. 249-250° (decomp.)

(d) 14-Acetoxy-N-cyanonorcodeine acetate (750 mg.) in propionic acid (35 c.c.) and water (15 c.c.) was refluxed for 14 hr. After working up in the usual way, the gum obtained was crystallised from chloroform-methanol to give 14-hydroxy N-acetylnorcodeine acetate as needles, m.p. and mixed m.p. 249-250° (decomp.)

14-Acetoxy-N-acetylnorcodeine Acetate. - (a) 14-Hydroxy-N-acetylnorcodeine acetate (300 mg.) in acetic anhydride (15 c.c.) was refluxed for 2 hr. The cooled solution was worked up through

chloroform in the usual way and the gum obtained crystallised from chloroform-methanol to give 14-acetoxy N-acetylnorcodeine acetate (300 mg.) as needles, m.p.185-186°, $[\alpha]_D$ - 167° (c,0.4), $\nu_{max.}$ 1727 (ester C =O), 1634 cm.$^{-1}$ (N-acetate C = O) (Found: C,63.8; H,6.2. $C_{23}H_{25}O_7N.\frac{1}{2}CH_3OH$ requires C,63.6; H,6.1%).

(b) 14-Hydroxynorcodeine (35 mg.) in acetic anhydride (5 c.c.) was refluxed for 2 hr. The gum obtained after working up through chloroform crystallised from chloroform-methanol to give 14-acetoxy N-acetylnorcodeine acetate, m.p. and mixed m.p. 185-186°.

(c) 14-Acetoxy N-cyanonorcodeine acetate (250 mg.) in glacial acetic acid (35 c.c.) and acetic anhydride (1 c.c.) was refluxed for 5 hr. After removal of the solvent under vacuum the residue was crystallised from chloroform-methanol to give 14-acetoxy-N-acetylnorcodeine acetate (200 mg.) as needles, m.p. and mixed m.p. 185-186°.

14-Acetoxy-N-acetylnorcodeinone. - (a) 14-Hydroxynorcodeinone (80 mg.) in acetic anhydride (10 c.c.) was refluxed for 2 hr. After cooling and basifying, the solid was extracted with chloroform to give a gum which crystallised from chloroform-light petroleum-ethanol to give 14-acetoxy-N-acetylnorcodeinone (80 mg.) as needles, m.p. 174-176°, $[\alpha]_D$ - 104° (c,0.6), $\nu_{max.}$ 1737 (ester C = O), 1681 ($\alpha\beta$, C = O), 1639 cm.$^{-1}$ (N-acetate C = O) (Found: C,65.4; H,5.5. $C_{21}H_{21}O_6N$ requires C,65.8; H,5.5%).

(b) 14-Acetoxy N-cyanonorcodeinone (1 g.) in glacial acetic acid (70 c.c.) and water (30 c.c.) was refluxed for 4 hr. The product

obtained by basification and extraction with chloroform was refluxed with acetic anhydride (20 c.c.) for 2 hr. The cooled solution was made basic with ammonia (d,0.88) and worked up through chloroform-light petroleum-ethanol to give 14-acetoxy N-acetylnorcodeinone (0.8 g.) as needles, m.p. and mixed m.p. 174-176°.

(c) 14-Acetoxy N-cyanonorcodeinone (300 mg.) in glacial acetic acid (35 c.c.) and acetic anhydride (0.5 c.c.) was refluxed for 5 hr. After removing the solvent, the residual gum was crystallised from ether-ethanol to give 14-acetoxy-N-acetylnorcodeinone (250 mg.) as needles, m.p. and mixed m.p. 176°.

(d) 14-Acetoxy-N-cyanonorcodeinone (1.2 g.) in 25% sulphuric acid (15 c.c.) was refluxed for 3 hr. After boiling with charcoal, the solution was filtered, made basic, and extracted with chloroform. The gum obtained was refluxed with acetic anhydride (20 c.c.) for 2 hr. then cooled and worked up through chloroform. The gum obtained on evaporation of the solvent crystallised from chloroform-light petroleum-ethanol to give 14-acetoxy-N-acetylnorcodeinone as needles, m.p. and mixed m.p. 174-176°.

14-Hydroxy-N-acetylnorcodeinone. - 14-Acetoxy-N-cyanonorcodeinone (5 g.) in propionic acid (140 c.c.) and water (60 c.c.) was refluxed for 20 hr. The cooled solution was made basic with ammonia (d, 0.88) and then extracted with chloroform. After removal of the solvent the gum obtained was crystallised from chloroform-methanol to give 14-hydroxy-n-acetylnorcodeinone (1.5 g.) as prisms, m.p. 222-223°, $[\alpha]_D$ - 221° (c, 0.25), $\nu_{max.}$ 3333 (OH), 1695 (αβ C = O), 1600 $cm.^{-1}$ (N-acetyl) (Found: C, 66.8; H, 5.6. $C_{19}H_{19}O_6N$ requires C, 66.85; H, 5.6%). Acetylation of 14-hydroxy-N-acetylnorcodeinone gave 14-acetoxy-N-acetylnorcodeinone, m.p. and mixed m.p. 174-176°.

14-Acetoxy-N-acetylnorcodeine. - 14-Acetoxy-N-acetylnorcodeinone (200 mg.) in dioxan (10 c.c.) was stirred for 2 hr. with a solution of sodium borohydride (200 mg.) in water (2 c.c.). The solution was worked up in the usual way through chloroform to give a gum which crystallised from chloroform-light petroleum to give 14-acetoxy-N-acetylnorcodeine (150 mg.) as prisms, m.p. 195°, $[\alpha]_D$ - 73° (c, 0.15), $\nu_{max.}$ 1730 (ester C = O), 1630 $cm.^{-1}$ (N-acetyl) (Found: C, 66.0; H, 6.0; $C_{21}H_{23}O_6N$ requires C, 65.45; H, 6.0%).

14-Hydroxy-N-acetylnorcodeine. - (a) 14-Acetoxy-N-cyanonorcodeine acetate (1 g.) was refluxed for 6 hr. with a solution of potassium hydroxide (1 g.) in methanol (99 c.c.) and water (1 c.c.). After addition of water (600 c.c.) the solution was

extracted with chloroform (4 x 50 c.c.). The chloroform solution was washed with water (2 x 100 c.c.), dried (Na_2SO_4), and the chloroform removed under vacuum. The solid obtained was triturated with anhydrous ether to give 14-hydroxy-N-acetylnorcodeine (700 mg.) as an amorphous powder, m.p. 115-120°, $[\alpha]_D$ - 113.5° (c,0.3) $\nu_{max.}$ 3333 (OH), 1618 $cm.^{-1}$ (N-acetyl) (Found: C,62.3; H,6.7. $C_{19}H_{21}O_5N.H_2O$ requires C,63.1; H,6.4%).

(b)14-Acetoxy-N-cyanonorcodeine (0.5 g.) was refluxed for 6 hr. with a solution of potassium hydroxide (0.5 g.) in methanol (49 c.c.) and water (1 c.c.). Working up as in preparation (a) gave a solid which was triturated with anhydrous ether to give 14-hydroxy-N-acetylnorcodeine, as an amorphous powder, m.p. and mixed m.p. 115-120°.

(c) 14-Hydroxy-N-acetylnorcodeinone (135 mg.) in dioxan (10 c.c.) was stirred for 2 hr. with a solution of sodium borohydride (100 mg.) in water (3 c.c.). After addition of water (500 c.c.) the solution was extracted with chloroform to give, on removal of the solvent, a gum which was triturated with anhydrous ether to give 14-hydroxy-N-acetylnorcodeine as an amorphous powder, m.p. and mixed m.p. 115-120°.

14-Hydroxy-N-acetylnorcodeinone. - 14-Hydroxy-N-acetylnorcodeine (200 mg.) in chloroform (10 c.c.) was stirred at room

temperature for 1 hr. with active manganese dioxide (1 g.). The filtered solution was evaporated and the residue crystallised from chloroform-methanol to give 14-hydroxy-N-acetylnorcodeinone (100 mg.) as prisms, m.p. and mixed m.p. 222-223°.

14-Hydroxy-N-acetyldihydronorcodeinone. - (a) 14-Acetoxy--N-cyanodihydronorcodeinone (4 g.) in 70% acetic acid (300 c.c.) was refluxed for 4 hr. The solution was cooled and made basic with ammonia (d,0.88) and shaken with chloroform (100 c.c.). The chloroform layer was washed with water, dried (Na_2SO_4) and the solvent removed under vacuum to give a gum which crystallised from chloroform-methanol to give 14-hydroxy-N-acetyldihydronorcodeinone (3 g.) as prisms, m.p. 254-255°, $[\alpha]_D$=260° (c,1.2), $\nu_{max.}$ 3225 (OH), 1725 (C = O), 1612 $cm.^{-1}$ (N-acetate C = O) (Found: C,64.7; H,6.1. $C_{19}H_{21}O_5N.\frac{1}{2}H_2O$ requires C,64.8; H,6.3%). (b) 14-Acetoxy-N-cyanodihydronorcodeinone (750 mg.) in 70% propionic acid (50 c.c.) was refluxed for 8 hr. After working up in the usual way through chloroform, the gum obtained was crystallised from chloroform-light petroleum to give 14-hydroxy-N-acetyldihydronorcodeinone (500 mg.) as prisms, m.p. and mixed m.p. 254-255°.

(c) 14-Acetoxy-N-cyanodihydronorcodeinone (750 mg.) was refluxed for 4 hr. with a solution of potassium hydroxide (0.7 g.) in methanol (70 c.c.) and water (1 c.c.). The cooled solution was diluted with water (700 c.c.) and the base, extracted with

chloroform, was crystallised from chloroform-light petroleum to give 14-hydroxy-N-acetyldihydronorcodeinone (500 mg.) as prisms, m.p. and mixed m.p. 254-255°.

14-Acetoxy-N-acetyldihydronorcodeinone. - (a) 14-Hydroxy-N-acetyldihydronorcodeinone (0.5 g.) was refluxed in acetic anhydride (25 c.c.) for 1 hr. After working up in the usual way, the gum obtained was crystallised from chloroform-light petroleum to give 14-acetoxy-N-acetyldihydronorcodeinone (0.4 g.) as prisms, m.p. 254-258°, $[\alpha]_D$ - 311° (c,1.0), $\nu_{max.}$ 1725 (C = O), 1626 cm.$^{-1}$ (N-acetate C = O) (Found: C,65.3; H,6.4. $C_{21}H_{23}O_6N$ requires C,65.4; H,6.0%)

(b) 14-Acetoxy-N-cyanodihydronorcodeinone (250 mg.) in glacial acetic acid (35 c.c.) and acetic anhydride (1 c.c.) was refluxed for 4 hr. Removal of the solvent under vacuum gave a gum which crystallised from chloroform-light petroleum to give 14-acetoxy-N-acetyldihydronorcodeinone (200 mg.) as prisms, m.p. and mixed m.p. 254-258°.

(c) 14-Acetoxy-N-cyanodihydronorcodeinone (200 mg.) in methanol (50 c.c.) was refluxed for 5 hr. with diethylamine (2 c.c.). The solid obtained ($\nu_{max.}$ 3225,1725, 1612 cm.$^{-1}$) on removal of the solvent was refluxed with acetic anhydride (10 c.c.) for 1 hr. The gum obtained by the usual work up was crystallised from chloroform-light petroleum to give 14-acetoxy-N-acetyldihydronorcodeinone (150 mg.) as prisms, m.p. and mixed m.p. 254-258°.

14-Propionyloxy-N-propionyldihydronorcodeinone. - 14-Hydroxydihydronorcodeinone (200 mg.) in propionic anhydride (10 c.c.) was heated on the steam bath for 3 hr. The cooled solution was taken up in chloroform, washed with ammonia (d,0.88) and water and the chloroform layer dried (Na_2SO_4). Removal of the solvent gave a gum which crystallised from chloroform-light petroleum to give 14-propionyloxy-N-propionyldihydronorcodeinone (150 mg.) as prisms, m.p. 180-181°, $[\alpha]_D$ - 296° (c,1.0), $\nu_{max.}$ 1725 (ester C = O), 1640 $cm.^{-1}$ (N-propionyl C = O). (Found: C,66.75; H,6.9. $C_{23}H_{27}O_6N$ requires C,66.8; H,6.6%).

14-Hydroxy-N-propionylnorcodeinone. - (a) 14-Propionyloxy--N-cyanonorcodeinone (5 g.) in 70% propionic acid (100 c.c.) was refluxed for 20 hr. The solution was worked up in the usual way to give a gum which crystallised from chloroform-methanol to give 14-hydroxy-N-propionylnorcodeinone (1.5 g.) as prisms, m.p. 229-230°, $[\alpha]_D$ - 172.5° (c,0.6), $\nu_{max.}$ 3195(OH), 1666 (αβ C = O), 1612 $cm.^{-1}$ (N-propionyl C = O) (Found: C,67.9; H,5.6. $C_{20}H_{21}O_5N$ requires C,67.6; H,6.0%).

(b) 14-Propionyloxy-N-cyanonorcodeinone (5 g.) in 70% acetic acid (200 c.c.) was refluxed for 5 hr and the solvent was then removed under vacuum. The residual gum crystallised from chloroform-methanol to give 14-hydroxy-N-propionylnorcodeinone (1 g.) as prisms, m.p. and mixed m.p. 229-230°.

Propionate of 14-Hydroxynorcodeine. - (a) 14-Hydroxynorcodeine (5 g.) was heated on the steam bath for 3 hr. with propionic anhydride (20 c.c.). The cooled solution was made basic with ammonia (d,0.88) and extracted with chloroform. The gum obtained on removal of the solvent was taken up in benzene and filtered through alumina. After eluting with benzene (500 c.c.), and removal of the solvent, the gum obtained was crystallised from chloroform-light petroleum to give 14-propionyloxy-N-propionylnorcodeine propionate (1.5 g.) as prisms, m.p. 157-158°, $[\alpha]_D$ - 145° (c,2.0), $\nu_{max.}$ 1724 (ester C = O), 1640 $cm.^{-1}$ (N-propionyl) (Found: C,66.35; H,6.7. $C_{26}H_{31}O_7N$ requires C,66.5; H,6.7%).

(b) 14-Hydroxy-N-propionylnorcodeinone (200 mg.) in dioxan (20 c.c.) was stirred with sodium borohydride (200 mg.) in water (5 c.c.) for 2 hr. After working up in the usual way, the gum obtained was heated for 3 hr. on the steam bath with propionic anhydride (5 c.c.). Removal of the propionic anhydride under vacuum gave a gum which crystallised from chloroform-light petroleum to give 14-propionyloxy-N-propionylnorcodeine propionate as prisms, m.p. and mixed m.p. 157-158°.

(c) 14-Propionyloxy-N-cyanonor codeinone (400 mg.) in dioxan (20 c.c.) was stirred at room temperature for 2 hr. with sodium borohydride (300 mg.) in water (5 c.c.). After working up through chloroform, the gum obtained was refluxed for 12 hr. with

potassium hydroxide (250 mg.) in methanol (25 c.c.) and water (0.5 c.c.). The solution was diluted with water (500 c.c.) and worked up in the usual way through chloroform, to give on removal of the solvent, solid material (230 mg.), $\nu_{max.}$ 3333 (OH), 1612 $cm.^{-1}$ (N-propionyl). This solid was heated on the steam bath for 3 hr. with propionic anhydride (5 c.c.) to give on removal of the solvent under vacuum a gum which crystallised from chloroform-light petroleum to give 14-propionyloxy-N-propionylnorcodeine propionate (130 mg.) as prisms, m.p. and mixed m.p. 157-158°.

14-Hydroxy-N-n-butyrylnorcodeinone. - (a) 14-n-Butyryloxy--N-cyanonorcodeinone (0.6 g.) in n-butyric acid (35 c.c.) and water (15 c.c.) was refluxed for 18 hr. The cooled solution was made basic with ammonia (d, 0.88) and the gum obtained on extraction with chloroform was triturated with anhydrous ether to give 14-hydroxy-N-n-butyrylnorcodeinone (0.6 g.) as an amorphous powder, m.p. 185-190°, $[\alpha]_D$ - 162° (c, 0.2), $\nu_{max.}$ 3333(OH), 1685($\alpha\beta$ C = O), 1613 $cm.^{-1}$ (N-n-butyryl). A satisfactory analysis could not be obtained for this compound.

(b) 14-n-Butyryloxy-N-cyanonorcodeinone (3 g.) in dioxan (100 c.c.) was stirred for 2 hr. with sodium borohydride (1.5 g.) in water (20 c.c.). After working up through chloroform, the gum obtained was refluxed for 18 hr. with potassium hydroxide (1 g.) in methanol (100 c.c.) and water (1 c.c.). The cooled solution was diluted with water (750 c.c.) and extracted with chloroform

(6 x 50 c.c.). The bulked chloroform layers yielded on removal of the solvent a gum (1.8 g.), $\nu_{max.}$ 3333 (OH), 1613 cm^{-1} (N-n-butyryl), which was taken up in chloroform (20 c.c.) and stirred for 1 hr. with active manganese dioxide (4.5 g.). The filtered solution was evaporated and the residue on trituration with anhydrous ether gave 14-hydroxy-N-n-butyrylnorcodeinone (1.5 g.) as an amorphous powder, m.p. and mixed m.p. 185-190°.

14-Hydroxy-N-ethylnorcodeine. - (a) 14-Hydroxy N-acetyl norcodeine acetate (100 mg.) in suspension in anhydrous ether (200 c.c.) was cooled and lithium aluminium hydride (250 mg.) in anhydrous ether (20 c.c.) added. The mixture was refluxed for 2 hr., cooled, and the excess lithium aluminium hydride destroyed by the addition of chloroform and ice. The filtered solution was shaken with water and the chloroform-ether layer separated. After removal of the solvent, the gum was crystallised from chloroform-light petroleum to give 14-hydroxy-N-ethylnorcodeine (90 mg.) as prisms, m.p. 128°, $[\alpha]_D$ - 105° (c,0.3), $\nu_{max.}$ 3448, 3226 $cm.^{-1}$ (OH) (Found: C,69.75; H,7.3. $C_{19}H_{23}O_4N$ requires C,69.3; H,7.0%).

(b) Both 14-acetoxy-N-acetylnorcodeine acetate and 14-acetoxy N-acetylnorcodeine when treated with lithium aluminium hydride in the analogous manner to preparation (a) yielded 14-hydroxy-N-ethylnorcodeine (crystallised from chloroform-light petroleum) as prisms, m.p. and mixed m.p. 128°.

14-Hydroxy-N-ethylnorcodeinone. - 14-Hydroxy-N-ethylnorcodeine (60 mg.) in chloroform (5 c.c.) was stirred for 1 hr. with activated manganese dioxide. The filtered solution was evaporated to dryness and the gum crystallised from chloroform-light petroleum-ethanol to give 14-hydroxy N-ethylnorcodeinone (50 mg.) as prisms, m.p. 230° (decomp.), $[\alpha]_D$ - 220° (c,1.0), $\nu_{max.}$ 3257(OH), 1669 cm.$^{-1}$ ($\alpha\beta$ C = O) (Found: C,68.7; H,6.7. $C_{19}H_{21}O_4N.\frac{1}{2}C_2H_5OH$ requires C,68.55; H,6.9%).

14-Hydroxy-N-ethylnorcodeine. - 14-Hydroxy-N-ethylnorcodeinone (100 mg.) in dioxan (25 c.c.) was treated with a suspension of sodium borohydride (100 mg.) in water (3 c.c.) with stirring. After 2 hr., stirring was stopped, water (500 c.c.) added, and the solid extracted with chloroform. The gum left on removal of the solvent crystallised from chloroform-light petroleum to give 14-hydroxy N-ethylnorcodeine (100 mg.) as prisms, m.p. and mixed m.p. 128°.

14-Acetoxy-N-ethylnorcodeinone. - 14-Hydroxy-N-ethylnorcodeinone (100 mg.) in acetic anhydride (5 c.c.) was heated on the steam bath for 2 hr. The cooled solution was taken up in chloroform and shaken with water and ammonia (d,0.88) till the aqueous layer was basic. The chloroform layer was washed, dried (Na_2SO_4) and evaporated to give a gum which crystallised from chloroform-light petroleum-ethanol to give 14-acetoxy-N-ethylnorcodeinone (100 mg.) as prisms, m.p. 183-185°, $[\alpha]_D$ - 115° (c,0.2),

$\nu_{max.}$ 1730 (ester C = O), 1684 cm.$^{-1}$ ($\alpha\beta$ C = O) (Found: C,68.0; H,6.3. $C_{21}H_{25}O_5N$ requires C,68.3; H,6.3%).

14-Acetoxy-N-ethylnorcodeine. - (a) 14-Hydroxy-N-ethylnorcodeine (100 mg.) in acetic anhydride (2 c.c.) was heated on the steam bath for 1 hr. The gum obtained by the usual work up through chloroform was crystallised from chloroform-methanol to give 14-acetoxy-N-ethylnorcodeine (80 mg.) as needles, m.p. 224-225°, $[\alpha]_D$ - 83° (c,0.3), $\nu_{max.}$ 3571 (OH), 1733 cm.$^{-1}$ (ester C = O) (Found: C,67.7; H,6.8. $C_{21}H_{25}O_5N$ requires C,67.9; H,6.8%). (b) A solution of 14-acetoxy-N-ethylnorcodeinone (350 mg.) in dioxan (20 c.c.) was stirred with sodium borohydride (200 mg.) in water (5 c.c.) for 2 hr. The solution was diluted with water (500 c.c.) and the base extracted with chloroform. After removal of the solvent, the residual gum was crystallised from chloroform-methanol to give 14-acetoxy-N-ethylnorcodeine as needles, m.p. and mixed m.p. 224-225°.

14-Acetoxy-N-ethylnorcodeine Acetate. - 14-Hydroxy-N-ethyl norcodeine (100 mg.) in acetic anhydride (10 c.c.) was refluxed for 1 hr. The gum obtained by the usual work up through chloroform was crystallised from chloroform-light petroleum--ethanol to give 14-acetoxy-N-ethylnorcodeine acetate (80 mg.) as prisms, m.p.170-171°, $[\alpha]_D$ - 143° (c,0.4), $\nu_{max.}$ 1742, 1724 cm.$^{-1}$ (ester C = O) (Found: C,67.15; H,6.9. $C_{23}H_{27}O_6N$ requires C,66.8 H,6.6%).

14-Acetoxy-N-cyanonorcodeine Acetate. - 14-Acetoxy-N-ethyl norcodeine acetate (100 mg.) was heated in a test-tube with cyanogen bromide (1 g.) for 3 min., at 100°. The mixture fused and on cooling crystals separated out. The crystals were filtered, washed with ethanol and on recrystallisation from chloroform-methanol gave 14-acetoxy-N-cyanonorcodeine acetate as prisms, m.p. and mixed m.p. 190°.

14-Hydroxy-N-propylnorcodeine. - 14-Propionyloxy-N--propionylnorcodeine propionate (400 mg.) in dry tetrahydrofuran (10 c.c.) and anhydrous ether (90 c.c.) was refluxed for 4 hr. after the addition of lithium aluminium hydride (300 mg.). The excess lithium aluminium hydride was destroyed by the addition of chloroform (100 c.c.) and ice, and the mixture filtered through kieselguhr. The chloroform-ether layer was separated and the product, isolated in the usual way, was crystallised from chloroform-light petroleum to give 14-hydroxy-N-propylnorcodeine (300 mg.) as prisms, m.p.111-112°, $[\alpha]_D$ - 121° (c,1.5), $\nu_{max.}$ 3390 cm.$^{-1}$ (OH) (Found: C,69.9; H,7.6. $C_{20}H_{25}O_4N$ requires C,69.95; H,7.3%).

14-Hydroxy-N-propylnorcodeinone. - 14-Hydroxy-N-propyl norcodeine (100 mg.) in chloroform (5 c.c.) was stirred for 1 hr. with active manganese dioxide (500 mg.). The filtered solution was evaporated and the residue crystallised from chloroform-light petroleum to give 14-hydroxy-N-propylnorcodeinone (100 mg.)

as needles, m.p. 126-127°, $[\alpha]_D$ - 208° (c,0.6), $\nu_{max.}$ 3333 (OH) and 1680 cm.$^{-1}$ ($\alpha\beta$ C = O)(Found: C,70.4; H,7.0. $C_{20}H_{23}O_4N$ requires C,70.4; H,6.8%).

14-Acetoxy-N-propylnorcodeinone. - 14-Hydroxy-N-propylnorcodeinone (200 mg.) was heated on the steam bath for 4 hr. with acetic anhydride. Removal of the acetic anhydride under vacuum gave a gum which was crystallised from chloroform-light petroleum-ethanol to give 14-acetoxy-N-propylnorcodeinone (150 mg.) as needles, m.p. 178°, $[\alpha]_D$ - 102° (c,1.1), $\nu_{max.}$ 1686 ($\alpha\beta$ C =O) and 1730 cm.$^{-1}$ (ester C = O) (Found: C,68.8; H,6.8. $C_{22}H_{25}O_5N$ requires C,68.9; H,6.6%).

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