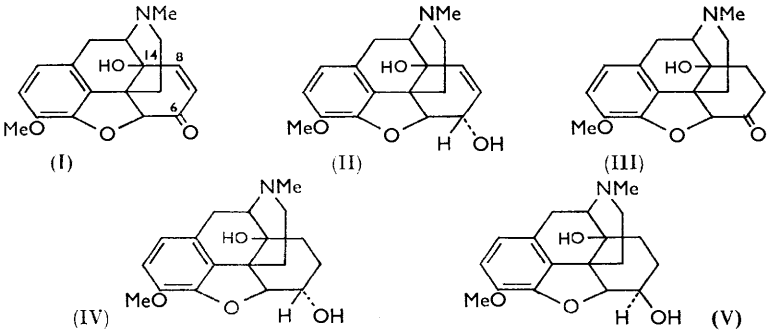
157. *Some Reactions of 14-Hydroxycodeine.**

By A. C. Currie, John Gillon, G. T. Newbold, and F. S. Spring.

Reduction of 14-hydroxycodeinone and of some 14-acyloxycodeinones with sodium borohydride gives the corresponding 14-substituted codeines without their 6-epimers, but similar reduction of dihydro-14-hydroxycodeinone and of its acetate gives a mixture of the related dihydrocodeine and dihydroisocodeine derivatives. Lithium aluminium hydride reduces 14-hydroxycodeine 6-toluene-*p*-sulphonate to deoxy-14-hydroxycodeine. This ester in 10% acetic acid gives mainly 14-hydroxyisocodeine, but with 70% acetic acid gives mainly the acetate of the isomeric 14-hydroxyallopseudocodeine.

Sargent, Schwartzman, and Small [1] recently described the reduction of 14-hydroxycodeinone (I) with sodium borohydride. They obtained an unsaturated diol, hydrogenation of which gave dihydro-14-hydroxycodeine B previously obtained [2] together with dihydro-14-hydroxycodeine C by catalytic hydrogenation of dihydro-14-hydroxycodeinone (III). Since borohydride reduction of codeinone gives a nearly quantitative yield of codeine,[3] Sargent *et al.* inferred that the product obtained by similar reduction of 14-hydroxycodeinone is 14-hydroxycodeine (II). If this is correct, it follows that dihydro-14-hydroxycodeine B is 14-hydroxydihydrocodeine (IV) and that dihydro-14-hydroxycodeine C is the 6-epimeric dihydro-14-hydroxyisocodeine (V).



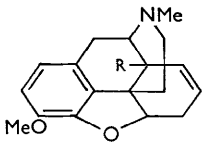
Before the appearance of the paper by Sargent *et al.*, we had prepared 14-hydroxycodeine (II) by reduction of 14-hydroxycodeinone (I) with sodium borohydride or lithium aluminium hydride, and we had shown that catalytic reduction converts 14-hydroxycodeine into 14-hydroxydihydrocodeine B. We had also found that reduction of dihydro-14-hydroxycodeinone (III) with sodium borohydride gives both dihydro-14-hydroxycodeine B and dihydro-14-hydroxycodeine C. In addition we observed that Oppenauer [4] oxidation of dihydro-14-hydroxycodeine B or C gives dihydro-14-hydroxycodeinone (III) in 53% and 19% yield respectively. This proves that the 6-hydroxyl groups in 14-hydroxydihydrocodeine B and C are axial (α) and equatorial (β), respectively. It follows that the product obtained by metal hydride reduction of 14-hydroxycodeinone is correctly described as 14-hydroxycodeine (II). The mother-liquors from 14-hydroxycodeine did not contain even traces of 14-hydroxyisocodeine. Likewise Meerwein–Ponndorf reduction of 14-hydroxycodeinone gave 14-hydroxycodeine as sole product. When treated with methanol, 14-acetoxycodeine 6-acetate is converted in part into 14-hydroxycodeine 6-acetate.

* Some of the experiments described in this paper are the subject of patent applications.

[1] Sargent, Schwartzman, and Small, *J. Org. Chem.*, 1958, **23** 1247.
[2] Lutz and Small, *ibid.*, 1939, **4**, 220.
[3] Gates, *J. Amer. Chem. Soc.*, 1953, **75**, 4340.
[4] Rapoport Naumann, Bissell, and Bonner, *J. Org. Chem.*, 1950, **15**, 1103.

Reduction of 14-acetoxy-, 14-benzoyloxy-, 14-propionyloxy-, 14-butyryloxy-, and 14-valeryloxy-codeinone by sodium borohydride gave the 14-acyloxycodeines. However, similar reduction of 14-acetoxydihydrocodeinone gave mainly 14-acetoxydihydroisocodeine, together with 14-acetoxydihydrocodeine. Acetylation of these epimeric diol monoacetates gave the known diacetates.

14-Hydroxycodeine gave a 6-toluene-*p*-sulphonate, acetylation of which gave 14-acetoxycodeine 6-toluene-*p*-sulphonate, which was also obtained by toluene-*p*-sulphonylation of 14-acetoxycodeine. Hydrogenation of 14-hydroxycodeine 6-toluene-*p*-sulphonate afforded the dihydro-ester which was also formed by esterification of dihydro-14-hydroxycodeine. Acetylation of dihydro-14-hydroxycodeine 6-toluene-*p*-sulphonate gave the 14-acetate 6-toluene-*p*-sulphonate which was also obtained by esterification of 14-acetoxydihydrocodeine and by hydrogenation of the codeine diester. 14-Acetoxydihydrocodeine



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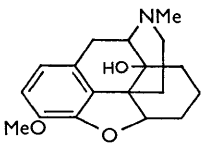
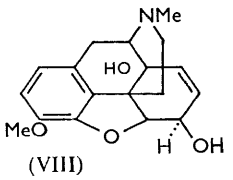


(VII)

6-toluene-*p*-sulphonate was converted into dihydro-14-hydroxycodeine 6-toluene-*p*-sulphonate by lithium aluminium hydride at 0°. In contrast, similar treatment of the 6-toluene-*p*-sulphonate of either 14-acetoxy- or 14-hydroxy-codeine gave deoxy-14-hydroxycodeine (VI; R = OH). This compound is stable to hot dilute mineral acid and gave a 14-acetate, alkaline hydrolysis of which regenerated the original alcohol. Hydrogenation of deoxy-14-hydroxycodeine yielded deoxydihydro-14-hydroxycodeine (VII), whose 14-acetate was also obtained by hydrogenation of 14-acetoxydeoxycodeine. In all these respects, deoxy-14-hydroxycodeine is an analogue of deoxycodeine E (VI; R = H), itself prepared by reduction of codeine toluene-*p*-sulphonate with lithium aluminium hydride.[5, 6]

Treatment of 14-hydroxycodeine 6-toluene-*p*-sulphonate with 10% acetic acid gives, as major product, a diol, $C_{18}H_{21}O_4N$, isomeric with 14-hydroxycodeine and on hydrogenation



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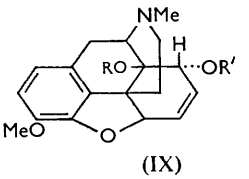

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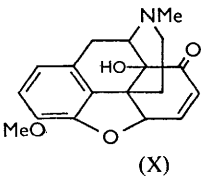


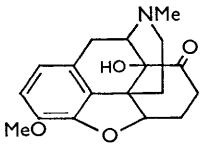
(X)

affording 14-hydroxydihydroisocodeine (V). The new diol is therefore 14-hydroxyisocodeine (VIII); it readily forms a diacetate from which the diol is regnerated by alkaline hydrolysis; methanol converts this diacetate partly into 14-hydroxyisocodeine acetate. Whereas 14-hydroxycodeine (II) is rapidly oxidised by manganese dioxide to 14-hydroxycodeinone (I) in quantitative yield, similar treatment of 14-hydroxyisocodeine (VIII) gives only a 10% yield of this ketone after a prolonged reaction time.

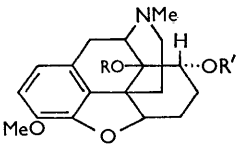
Treatment of 14-hydroxycodeine 6-toluene-*p*-sulphonate with 70% acetic acid gives, as principal product, the monoacetate of a diol, $C_{18}H_{21}O_4N$. Further acetylation of this monoacetate gives a diacetate, isomeric with 14-acetoxycodeine acetate and 14-acetoxyisocodeine acetate. The monoacetate is considered to be 14-hydroxyallopseudocodeine 8-acetate (IX; R = H, R' = Ac) and its formation (involving a structural change) from 14-hydroxycodeine 6-toluene-*p*-sulphonate is considered to be an S_N2' displacement without inversion.[7] The related diacetate (IX; R = R' = OAc) with methanol regenerates the

[5] Rapoport and Bonner, *J. Amer. Chem. Soc.*, 1951, **73**, 2872.
[6] Karrer and Widmark, *Helv. Chim. Acta*, 1951, **34**, 34.
[7] Stork and Clarke, *J. Amer. Chem. Soc.*, 1956, **78**, 4619.

monoacetate (IX; R = H, R′ = Ac). 14-Hydroxyallopseudocodeine (IX; R = R′ = H), obtained by alkaline hydrolysis of both the mono- and the di-acetate, is oxidised by manganese dioxide to 14-hydroxypseudocodeinone (X). Partial hydrogenation of this ketone (X) gave dihydro-14-hydroxypseudocodeinone (XI) together with a phenol, presumably formed by hydrogenolysis. Further hydrogenation of dihydro-14-hydroxypseudocodeinone afforded the allopseudo-diol (XII; R = R′ = H) which is also obtained by hydrogenation of the unsaturated diol (IX; R = R′ = H). 14-Hydroxypseudocodeinone (X) was directly reduced by sodium borohydride to the dihydro-diol (XII; R = R′ = H), which on Oppenauer oxidation afforded dihydro-14-hydroxypseudocodeinone (XI) in good yield; Rapoport *et al.*[4] showed that under the same conditions dihydroallopseudocodeine was oxidised whereas its epimer was unaffected. This confirms the view



(XI)



(XII)

that the 8-hydroxyl group is axial (α) in the allopseudo-compounds. Acetylation of dihydro-14-hydroxyallopseudocodeine (XII; R = R′ = H) gave two isomeric monoacetates, each of which is hydrolysed to the parent diol by alkali. One of these monoacetates is the 8-acetate (XII; R = H, R′ = Ac) since it is also formed by catalytic hydrogenation of the unsaturated 8-acetate (IX; R = H, R′ = Ac). The isomeric monoacetate is considered to be the 14-acetate (XII; R = Ac, R′ = H): it was recovered unchanged after attempted acetylation.

A report on the pharmacology of some of the codeine derivatives described in this paper will appear elsewhere.

Experimental

Rotations were measured for chloroform solutions except where otherwise stated. Acetylations were carried out as described for the preparation of 14-acetoxycodeine 6-acetate. Light petroleum had b. p. 60—80°. Infrared spectra were determined for Nujol mulls, and identities were confirmed by infrared comparison.

14-Hydroxycodeine (II).—(*a*) 14-Hydroxycodeinone [8] (10 g.) was leached from the thimble of a Soxhlet apparatus by a boiling suspension of lithium aluminium hydride (10 g.) in ether (350 c.c.). After refluxing for 96 hr., the mixture was cooled to 0° and treated, with stirring, with ice. After being washed with water, the dried (Na_2SO_4) ethereal solution was evaporated to a 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.,[1] 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 whole was stirred for 2 hr. at room temperature and diluted with aqueous 2N-sodium hydroxide (100 c.c.), and the product was isolated by means of chloroform. Crystallisation 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*, m. p. 263—264° (decomp.), separated 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 propan-2-ol (50 c.c.), and the stirred solution was distilled slowly (3 hr.) until the distillate was free from acetone. The excess of propan-2-ol was removed by distillation, the residue was diluted with water (30 c.c.) and basified with ammonia (*d* 0·88), and the product isolated in chloroform. Crystallisation from benzene–light petroleum gave 14-hydroxycodeine (2·75 g., 69%) as prisms, m. p. and mixed m. p. 154—157°.

[8] Freund and Speyer, *J. prakt. Chem.*, 1916, **94**, 135.

14-*Acetoxycodeine* 6-*Acetate*.—14-Hydroxycodeine (200 mg.) was heated on the steam-bath with acetic anhydride (2·5 c.c.) for 1½ hr. The diacetate crystallised from benzene–light petroleum as blades (100 mg.), m. p. 198—200°, $[\alpha]_D$ −126° (*c* 1·5) [lit.,[1] m. p. 199° (vacuum)], $\nu_{max.}$ 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* 6-*Acetate*.—A solution of the diacetate (5 g.) in methanol (100 c.c.) was refluxed for 4 hr., 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* 6-*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. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·5%). Acetylation of this gave the diacetate, m. p. and mixed m. p. 198—200°, and hydrolysis with 5% methanolic potassium hydroxide gave 14-hydroxycodeine, m. p. and mixed m. p. 155—157°.

Esters of 14-*Hydroxycodeinone*.—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-unsaturated C=O) (Found: C, 68·6; H, 6·35. $C_{21}H_{23}O_5N$ requires C, 68·3; H, 6·3%).

Butyric anhydride similarly (heating for 2½ hr.) gave 14-*butyryloxycodeinone* (2·8 g.), needles (from chloroform–methanol), m. p. 152·5—153·5°, $[\alpha]_D$ −89° (*c* 2·0) $\nu_{max.}$ 1736 (ester C=O) and 1689 cm.$^{-1}$ (C:C·C=O) (Found: C, 69·3; H, 6·8. $C_{22}H_{25}O_5N$ requires C, 68·9; H, 6·6%).

14-Hydroxycodeinone (3·0 g.) was heated with 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.) and extracted with chloroform, and the product isolated in the usual way. A solution of the product in benzene was filtered through alumina (3 × 1 cm.). Evaporation and crystallisation of the residue from chloroform–light petroleum gave *valeryloxycodeinone* (1·2 g.) as needles, m. p. 133—134°, $[\alpha]_D$ −77° (*c* 1·0), $\nu_{max.}$ 1726 (ester C=O) and 1692 cm.$^{-1}$ (C:C·C=O) (Found: C, 69·9; H, 6·8. $C_{23}H_{27}O_5N$ requires C, 69·5; H, 6·85%). Heating 14-hydroxycodeinone (2·95 g.) on the steam-bath with valeric anhydride (15 c.c.) for 2½ hr. gave the same ester (1·5 g.), m. p. and mixed m. p. 133—134°.

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

14-*Acetoxycodeine* (from 14-acetoxycodeinone [8]), 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% [*hydrochloride* (from methanol–ether), needles, m. p. 222—224° (decomp.) (Found: Cl, 8·7. $C_{20}H_{23}O_5N$,HCl requires Cl, 9·0%)]. Acetylation gave the diacetate, m. p. and mixed m. p. 198—200°.

14-*Propionyloxycodeine* (from chloroform–light petroleum), 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%) [*hydrochloride*, m. p. 165—170° (decomp.) (Found: Cl, 8·5. $C_{21}H_{25}O_5N$,HCl requires Cl, 8·7%)]. Acetylation gave 14-*propionyloxycodeine* 6-*acetate*, prismatic needles (from benzene–light petroleum), 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. $C_{23}H_{27}O_6N$ requires C, 66·8; H, 6·6%) [*hydrochloride*, m. p. 215—220° (decomp.) (Found: Cl, 8·0. $C_{23}H_{27}O_6N$,HCl requires Cl, 7·9%)].

14-*Butyryloxycodeine* (from chloroform–light petroleum), 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%) [*hydrochloride*, m. p. 165° (decomp.) after softening at 150° (Found: Cl, 8·3. $C_{22}H_{27}O_5N$,HCl requires Cl, 8·4%)].

14-*Valeryloxycodeine* (from chloroform–light petroleum), 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%) [*hydrochloride* (from ethanol–ether), needles, m. p. 138—148° (decomp.) (Found: Cl, 7·8. $C_{23}H_{29}O_5N$,HCl requires Cl, 8·1%)].

14-*Benzoyloxycodeine* (from 14-benzoyloxycodeinone [8]) 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. $C_{25}H_{25}O_5N$ requires C, 71·6; H, 6·0; N, 3·3%) [*hydrochloride* (from ethanol–ether), blades, m. p. 177—180° (Found: Cl, 7·7. $C_{25}H_{25}O_5N$,HCl requires Cl, 7·8%)]. Acetylation gave 14-*benzoyloxycodeine* 6-*acetate*, prismatic needles (from ethanol), 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%) [*hydrochloride*, needles (from ethanol–ether), m. p. 227—229° (decomp.) (Found: Cl, 7·3. $C_{27}H_{27}O_6N$,HCl requires Cl, 7·0%)].

Dihydro-14-hydroxycodeine.—14-Hydroxycodeine (850 mg.) in acetic acid (25 c.c.) and water (25 c.c.) was shaken with hydrogen and platinum (from 150 mg. of platinum oxide) until 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 in ether. Crystallisation from benzene–light petroleum gave dihydro-14-hydroxycodeine (500 mg.) as felted needles, m. p. 140—141°, $[\alpha]_D$ −169° (*c* 0·6), $[\alpha]_D$ −138° (*c* 1·8 in 10% acetic acid) [lit.,[2] m. p. 145—145·5°, $[\alpha]_D$ −136° (in 10% acetic acid)], $\nu_{max.}$ 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%). The diacetate formed by acetylation separated from benzene–light petroleum as needles, m. p. 180·5—181·5°, $[\alpha]_D$ −211° (*c* 1·3), $[\alpha]_D$ −127° (*c* 0·8 in 10% acetic acid) {lit.,[2] m. p. 181—182°, $[\alpha]_D$ −127° (in 10% acetic acid)}, $\nu_{max.}$ 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%). It gave the diacetate, needles (from benzene–light petroleum), m. p. 182—183° alone or mixed with the specimen described above, $[\alpha]_D$ −208° (*c* 2·0).

Hydrogenation of 14-*Acetoxycodeine* 6-*Acetate.*—The acetate (1·135 g.) was hydrogenated as described above. Isolation in chloroform followed by crystallisation from benzene–chloroform, chromatography of a benzene solution on alumina (2 × 0·5 cm.), and crystallisation of the eluted solid from benzene–light petroleum gave 14-acetoxydihydrocodeine 6-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% acetic acid).

Reduction of Dihydro-14-hydroxycodeinone with Sodium Borohydride.—The ketone (5·0 g.) was reduced with sodium borohydride (3 g.) in the usual way and the product was isolated by using chloroform, as needles, m. p. 147—150°. Fractional crystallisation of this solid from benzene–light petroleum gave two compounds; the less soluble is dihydro-14-hydroxyisocodeine, which separated as needles, m. p. 167—168°, $[\alpha]_D$ −142° (*c* 1·3), $[\alpha]_D$ −125° (*c* 1·3 in 10% acetic acid) {lit.,[2] m. p. 166—167°, $[\alpha]_D$ −152° (in 10% acetic acid)}, $\nu_{max.}$ 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 the diacetate 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% acetic acid) {lit.,[2] m. p. 203°, $[\alpha]_D$ −107° (in 10% acetic acid)}, $\nu_{max.}$ 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 dihydro-14-hydroxycodeine, which forms needles, m. p. 141—142° alone or mixed with the product obtained by catalytic hydrogenation of 14-hydroxycodeine, and has $[\alpha]_D$ −170° (*c* 1·2), $[\alpha]_D$ −142° (*c* 1·5 in 10% acetic acid) (Found: C, 68·2; H, 7·5. Calc. for $C_{18}H_{23}O_4N$: C, 68·1; H, 7·3%); it gave 14-acetoxydihydrocodeine 6-acetate, prisms (from benzene–light petroleum), m. p. and mixed m. p. 180·5—181·5°, $[\alpha]_D$ −211° (*c* 1·3), $[\alpha]_D$ −128° (*c* 0·7 in 10% acetic acid).

Reduction of 14-*Acetoxydihydrocodeinone with Sodium Borohydride.*—14-Acetoxydihydrocodeinone [8] (2·0 g.) was reduced with sodium borohydride by the usual method. The crude product was isolated by means of chloroform and crystallised from benzene–light petroleum to give 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%); it gave the diacetate, m. p. and mixed m. p. 199—201°.

The earlier mother-liquors from the recrystallisation of the solid of m. p. 130° were 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, $[\alpha]_D$ −200° (*c* 2·1), m. p. 165—166° alone or mixed with 14-acetoxydihydrocodeine prepared by catalytic hydrogenation of 14-acetoxycodeine, which afforded a diacetate, m. p. 180·5—181·5° alone or mixed with a specimen prepared by hydrogenation of 14-acetoxycodeine 6-acetate.

14-*Hydroxycodeinone from* 14-*Hydroxycodeine*.—14-Hydroxycodeine (0·5 g.) in chloroform (25 c.c.) was stirred at room temperature with active manganese dioxide (5 g.) for 20 min. 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°.

Dihydro-14-*hydroxydihydrocodeinone*.—(*a*) Dihydro-14-hydroxycodeine (0·5 g.) was oxidised with potassium t-butoxide and benzophenone under Rapoport's conditions.[4] The cooled solution was extracted with dilute hydrochloric acid, and the extract was washed with ether (2 × 30 c.c.), basified with ammonia (*d* 0·88), and shaken with chloroform (5 × 30 c.c.). The chloroform solution was washed with water (20 c.c.), dried (Na_2SO_4), and evaporated. The product (390 mg.) crystallised from ethanol, to give dihydro-14-hydroxycodeinone (265 mg., 53%), m. p. 218—219°, $[\alpha]_D$ −217° (*c* 1·3).

(*b*) Oxidation of dihydro-14-hydroxyisocodeine (150 mg.) by the same method gave dihydro-14-hydroxycodeinone (27·6 mg., 19%) as long blades, m. p. 217—218°.

14-*Hydroxycodeine* 6-*Toluene*-p-*sulphonate*.—14-Hydroxycodeine (5 g.) in pyridine (10 c.c.) was cooled to 0° and toluene-*p*-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°, then diluted with ice water (150 c.c.). The 6-*toluene*-p-*sulphonate* (6·4 g.) was isolated by means of chloroform and crystallised from chloroform–methanol 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* 6-*Toluene*-p-*sulphonate*.—(*a*) 14-Acetoxycodeine (5 g.) in pyridine (10 c.c.) was treated with toluene-*p*-sulphonyl 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 the *diester* (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. $C_{27}H_{29}O_7NS,C_6H_6$ requires C, 67·2; H, 6·0%).

(*b*) 14-Hydroxycodeine 6-toluene-*p*-sulphonate (0·1 g.) with acetic anhydride (2 c.c.) on the steam-bath (1 hr.) gave the same diester, m. p. and mixed m. p. 90—91°, $[\alpha]_D$ −128° (*c* 1·0).

14-*Acetoxydihydrocodeine* 6-*Toluene*-p-*sulphonate*.—(*a*) 14-Acetoxydihydrocodeine (5 g.) in pyridine (10 c.c.) was treated with toluene-*p*-sulphonyl chloride as described above. The crude product (6·6 g.) crystallised from chloroform–methanol, to give the *diester* 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 6-toluene-*p*-sulphonate (2 g.) in 50% aqueous acetic acid (50 c.c.) was shaken with hydrogen and platinum until 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 the preceding diester, m. p. and mixed m. p. 134°.

Dihydro-14-*hydroxycodeine* 6-*Toluene*-p-*sulphonate*.—(*a*) 14-Acetoxydihydrocodeine 6-toluene-*p*-sulphonate (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 2¾ hr. The product was isolated in the usual way and crystallised from chloroform–methanol to give *dihydro*-14-*hydroxycodeine* 6-*toluene*-p-*sulphonate* 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*) Dihydro-14-hydroxycodeine (1·25 g.) in pyridine (5 c.c.) was treated with toluene-*p*-sulphonyl chloride (1 g.) in pyridine (3 c.c.) at 0°. The ester crystallised from chloroform–methanol as prisms, m. p. 138°, identical with the compound obtained by method (*a*).

(*c*) 14-Hydroxycodeine toluene-*p*-sulphonate (1·8 g.) in 50% aqueous acetic acid (60 c.c.) was hydrogenated over platinum, giving the preceding product, m. p. and mixed m. p. 138°.

Acetylation of 14-hydroxydihydrocodeine 6-toluene-*p*-sulphonate in the usual way gave the 14-acetate 6-toluene-*p*-sulphonate, m. p. and mixed m. p. 134°.

Deoxy-14-*hydroxycodeine*.—14-Acetoxycodeine 6-toluene-*p*-sulphonate (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°. Stirring was continued at 0° for 2¾ hr. The excess of hydride was decomposed by 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 *deoxy-14-hydroxycodeine* (1·3 g.) as prisms, m. p. 125°, $[\alpha]_D$ −80° (*c* 2·0), $\nu_{max.}$ (in 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 6-toluene-*p*-sulphonate in dry tetrahydrofuran gave deoxy-14-hydroxycodeine in 60% yield. 40% of the ester was recovered.

Deoxydihydro-14-hydroxycodeine (VII).—Deoxy-14-hydroxycodeine (0·4 g.) in 50% aqueous acetic acid (50 c.c.) was hydrogenated over platinum at room temperature. Crystallisation of the product, *deoxydihydro-14-hydroxycodeine*, from chloroform–methanol gave prisms (0·35 g.), 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.—14-Hydroxydeoxycodeine (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, 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 (0·15 g.) was refluxed for 2 hr. with potassium hydroxide (1 g.) in water (5 c.c.) and ethanol (15 c.c.). Dilution with water (200 c.c.) and extraction with chloroform gave gummy deoxy-14-hydroxycodeine which crystallised from chloroform–methanol as prisms (0·12 g.), m. p. and mixed m. p. 125°.

14-Acetoxydeoxydihydrocodeine.—(*a*) 14-Acetoxydeoxycodeine (0·2 g.), when hydrogenated as above, gave *14-acetoxydeoxydihydrocodeine* which crystallised from chloroform–methanol 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*) Deoxydihydro-14-hydroxycodeine (0·5 g.) was heated on the steam-bath for 2·5 hr. with acetic anhydride (5 c.c.), affording the 14-acetate (0·5 g.), m. p. and mixed m. p. 124—126·5°.

14-Hydroxyisocodeine.—14-Hydroxycodeine 6-toluene-*p*-sulphonate (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%).

With acetic anhydride (3 c.c.) on the steam-bath (1 hr.) this product (0·1 g.) gave its *diacetate* (0·1 g.), prismatic needles (from chloroform–methanol), 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%).

The first chloroform–methanol mother-liquor from 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 (A), m. p. 230—240° (0·35 g.), and a more soluble fraction recrystallisation of which gave 14-acetoxyisocodeine acetate (0·25 g.) as prisms, m. p. and mixed m. p. 187°.

14-Hydroxyisocodeine 6-Acetate.—14-Acetoxyisocodeine 6-acetate (2 g.) in methanol (100 c.c.) was refluxed for 4 hr. on the steam bath. The solution was concentrated to 5—10 c.c., and the crystals separating on cooling were collected (m. p. 150—170°). Fractional crystallisation 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%), which with alcoholic potassium hydroxide gave 14-hydroxyisocodeine, m. p. and mixed m. p. 149—150°.

14-Hydroxycodeinone from 14-Hydroxyisocodeine.—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.

Dihydro-14-hydroxyisocodeine.—A solution of 14-hydroxyisocodeine (100 mg.) in 50% aqueous acetic acid (40 c.c.) 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 by using chloroform, and crystallised to give dihydro-14-hydroxyisocodeine which separated from chloroform–light petroleum as needles, m. p. and mixed m. p. 165—166°.

14-*Hydroxyallopseudocodeine* 8-*Acetate* (IX; R = H, R′ = Ac).—14-Hydroxycodeine 6-toluene-*p*-sulphonate (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* (IX; R = R′ = Ac).—Fraction A, m. p. 230—240°, obtained during the preparation of 14-acetoxyisocodeine acetate (method *b*) 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-hydroxyallopseudocodeine 8-acetate.

This diacetate (1 g.) in methanol (100 c.c.) was refluxed for 4 hr. The solution was concentrated to 10 c.c., and the solid which slowly separated was recrystallised from chloroform–methanol to give 14-hydroxyallopseudocodeine 8-acetate (0·75 g.) as needles, m. p. and mixed m. p. 194—195°.

14-*Hydroxyallopseudocodeine* (IX; R = R′ = H).—The preceding diacetate (1·0 g.) in ethanol (30 c.c.) was refluxed for 1 hr. with potassium hydroxide (2 g.) in water (10 c.c.). The solution was diluted with water, and the product isolated by using chloroform and crystallised from chloroform–light petroleum, to give 14-*hydroxyallopseudocodeine* (0·9 g.) 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* (X).—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-*hydroxy-pseudocodeinone* (0·1 g.) as prismatic needles, m. p. 186—187°, $[\alpha]_D$ −66° (*c* 1·1), $\nu_{max.}$ (in CCl_4) 3311 (OH) and 1695 cm.$^{-1}$ (C:C·C=O) (Found: C, 69·0; H, 5·8. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1%).

Dihydro-14-*hydroxypseudocodeinone* (XI).—14-Hydroxypseudocodeinone (0·6 g.) in 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 crystallised from chloroform–methanol to give *dihydro*-14-*hydroxypseudocodeinone* (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 gave a positive reaction with diazotised sulphanilic acid.

Dihydro-14-*hydroxyallopseudocodeine* (XII; R = R′ = H).—(*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 2N-sodium hydroxide (10 c.c.), the base was separated by using chloroform. Crystallisation of the product from chloroform–light petroleum gave *dihydro*-14-*hydroxyallopseudocodeine* (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*) Dihydro-14-hydroxypseudocodeinone (62 mg.) was hydrogenated (18 hr.) as above. The product, isolated by means of chloroform and crystallised from chloroform–light petroleum, was dihydro-14-hydroxyallopseudocodeine (52 mg.), m. p. and mixed m. p. 175—176°.

(*c*) 14-Hydroxyallopseudocodeine (0·75 g.) in acetic acid (47 c.c.) and hydrochloric acid (3 c.c.; *d* 1·15) was hydrogenated (1½ hr.) as above. Dihydro-14-hydroxyallopseudocodeine, crystallised six times from chloroform–methanol, gave prisms (0·2 g.), m. p. and mixed m. p. 175—176°.

14-*Acetoxydihydroallopseudocodeine.*—Dihydro-14-hydroxyallopseudocodeine (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%).

*Dihydro-*14-*hydroxyallopseudocodeine Acetate.*—(*a*) 14-Hydroxyallopseudocodeine acetate (0·5 g.) in 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) was added in portions with shaking. The chloroform layer was washed with water and dried (Na_2SO_4) and the chloroform evaporated *in vacuo*, to give a red gum which crystallised from chloroform–methanol yielding *dihydro-*14-*hydroxyallopseudocodeine 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 dihydro-14-hydroxyallopseudocodeine acetate (30 mg.) as needles, m. p. and mixed m. p. 154—156°. Hydrolysis of both 14-acetoxydihydroallopseudocodeine and 14-hydroxydihydroallopseudocodeine acetate by 5% ethanolic potassium hydroxide gave dihydro-14-hydroxyallopseudocodeine, m. p. and mixed m. p. 175—176°.

*Dihydro-*14-*hydroxypseudocodeinone from Dihydro-*14-*hydroxyallopseudocodeine.*—The diol (200 mg.) was oxidised with potassium t-butoxide and benzophenone under Rapoport's conditions.[4] Isolation in the usual way followed by crystallisation from chloroform–methanol gave dihydro-14-hydroxypseudocodeinone (140 mg., 70%) as needles, m. p. and mixed m. p. 155—156°.

We thank Dr. F. R. Smith of Messrs. T. and H. Smith Ltd., Edinburgh, for the gift of intermediates.

The Royal College of Science and Technology, Glasgow. [*Received, August 5th,* 1959.]