927. 14-*Hydroxynorcodeine and its Derivatives.*

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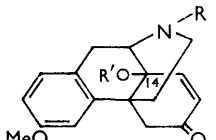
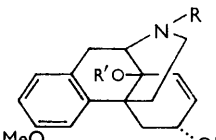
Reduction of 14-acyloxy-*N*-cyanonorcodeine derivatives by lithium aluminium hydride gives 14-hydroxynorcodeine. *N*-Acyl derivatives of the latter compound are prepared from the corresponding 14-acyloxy-*N*-cyano-compound by acyl migration. Reduction of the *N*-acyl compounds with lithium aluminium hydride gives the *N*-alkyl-14-hydroxynorcodeines.

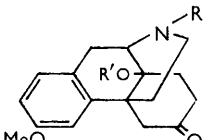
Reaction of 14-acetoxycodeinone (I; R = Me, R′ = Ac) with cyanogen bromide [1] affords 14-acetoxy-*N*-cyanonorcodeinone (I; R = CN, R′ = Ac) contrary to the claim [2] that *N*-cyano-14-hydroxynorcodeinone was so formed. Attempts to obtain the latter by the reaction between cyanogen bromide and 14-hydroxycodeinone gave a quaternary salt. However, 14-acetoxy- and 14-benzoyloxy-*N*-cyanonorcodeine 6-acetate (II; R = CN, R′ = Ac or Bz, R″ = Ac), 14-acetoxy-*N*-cyanodihydronorcodeinone (III; R = CN, R′ = Ac), *N*-cyano-14-propionyloxynorcodeinone (I; R = CN, R′ = Et·CO), and 14-n-butyryloxy-*N*-cyanonorcodeinone (I; R = CN, R′ = Pr·CO) were all prepared from the corresponding *N*-methyl compounds by treatment with cyanogen bromide.



(I)



(II)



(III)

14-Acetoxy-*N*-cyanonorcodeine (II; R = CN, R′ = Ac, R″ = H) was prepared from 14-acetoxy-*N*-cyanonorcodeinone by reduction with sodium borohydride. It was also formed in low yield by the action of this reagent or pyridine in methanol on 14-acetoxy-*N*-cyanonorcodeine 6-acetate.

Lithium aluminium hydride which converts the *N*-cyano-derivative of a secondary amine into the related amine,[3] when used for the reduction of 14-acetoxy-*N*-cyanonorcodeinone and 14-acetoxy-*N*-cyanonorcodeine 6-acetate yielded 14-hydroxynorcodeine (II; R = R′ = R″ = H) which was smoothly oxidised by activated manganese dioxide to 14-hydroxynorcodeinone (I; R = R′ = H), m. p. 185—187°. The compound, m. p. 218° (decomp.), obtained by hydrolysis of 14-acetoxy-*N*-cyanonorcodeinone with mineral acid and described as 14-hydroxynorcodeinone [4] was obtained in our hands as a gum and appears to be heterogeneous, its infrared spectrum showing weak bands in the *O*-acetyl region. Acetylation of the gum gives 14-acetoxy-*N*-acetylnorcodeinone (I; R = R′ = Ac), the acetylation product of 14-hydroxynorcodeinone, m. p. 185—187°. Hydrolysis of 14-acetoxy-*N*-cyanodihydronorcodeinone by mineral acid gave in poor yield 14-hydroxydihydronorcodeinone (III; R = R′ = H), m. p. 175—176°, previously described as an oil.[4] All the secondary amines described crystallise with difficulty and in very poor yield although the infrared spectra show the crude reaction products to be substantially homogeneous.

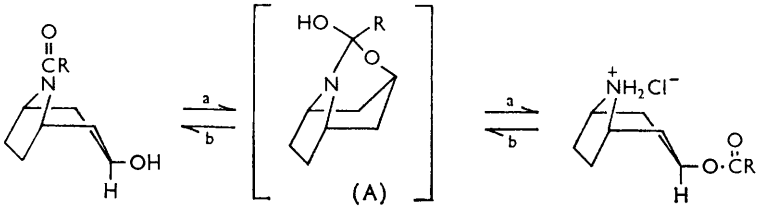
14-Acetoxy-*N*-cyanonorcodeine acetate in hot aqueous acetic acid gave a compound, m. p. 249—250°, also obtained by the action of acetic anhydride on 14-hydroxynorcodeine. This compound was unaffected by manganese dioxide and since its infrared spectrum shows bands in the hydroxyl, *O*-acetyl, and *N*-acetyl regions it must be *N*-acetyl-14-hydroxynorcodeine 6[6]-acetate (II; R′ = H, R = R″ = Ac). Both this compound and

[1] *Org. Synth.*, Coll. Vol. II, p. 150.
[2] Freund and Speyer, *J. prakt. Chem.*, 1916, **94**, 135.
[3] Prelog, McKusick, Merchant, Julia, and Wilhelm, *Helv. Chim. Acta*, 1956, **39**, 498.
[4] Speyer and Sarre, *Ber.*, 1924, **57**, 1427.

14-hydroxynorcodeine on more vigorous treatment with acetic anhydride yielded the triacetyl derivative (II; R = R′ = R″ = Ac), also obtained by refluxing 14-acetoxy-*N*-cyanonorcodeine acetate in glacial acetic acid. Attempts to hydrogenate 14-acetoxy-*N*-cyanonorcodeine acetate in acetic acid over platinum resulted in the formation of *N*-acetyl-14-hydroxynorcodeine 6-acetate which is also prepared by the action of aqueous propionic acid on the *N*-cyano-compound (II; R = CN, R′ = R″ = Ac).

Similarly 14-acetoxy-*N*-cyanonorcodeinone, when treated with aqueous propionic acid, gave *N*-acetyl-14-hydroxynorcodeinone (I; R = Ac, R′ = H), vigorous acetylation of which gave 14-acetoxy-*N*-acetylnorcodeinone. The latter was also obtained on refluxing a glacial acetic acid solution of 14-acetoxy-*N*-cyanonorcodeinone. *N*-Acetyldihydro-14-hydroxynorcodeinone (III; R = Ac, R′ = H) was prepared by the action of aqueous acetic or propionic acid on 14-acetoxy-*N*-cyanodihydronorcodeinone, and with glacial acetic acid the latter gave 14-acetoxy-*N*-acetyldihydronorcodeinone (III; R = R′ = Ac), the acetylation product of both *N*-acetyl-14-hydroxy- and 14-hydroxy-dihydronorcodeinone.

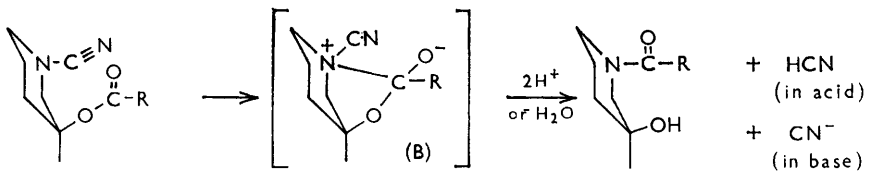
The mechanism of the formation of *N*-acetyl derivatives from 14-acetoxy-*N*-cyano-compounds must involve migration of the *O*-acetyl group. In contrast with this work, acyl groups are known to migrate from nitrogen to oxygen under acid catalysis [5] and studies of the mechanisms of the reactions have indicated that they probably proceed through cyclic intermediates.[6] Nickon and Fieser [5] postulate the intermediate (A) in the migrations in the tropine series.



a, HCl. b, K_2CO_3.

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 hydrolyses, mixtures of 14-acetoxy-*N*-cyano- and *N*-acetyl-14-hydroxy, but no >NH, compounds are formed it seems likely that the reaction takes place synchronously and probably through an intermediate (B), rather than by hydrolysis of the *N*-cyano-group to give, first, $>N\cdot CO_2H$ and then >NH, with subsequent acyl migration.

The reverse process of migration of the acetyl group, namely, from oxygen to nitrogen, proceeds under base catalysis [5] for the tropine alkaloids. Treatment of *N*-acetyl-14-hydroxynorcodeine acetate with base gave intractable material, the infrared spectrum



of which showed that this process may occur to some extent. However, treatment of 14-acetoxy-*N*-cyanodihydronorcodeinone (III; R = CN, R′ = Ac) with 1% potassium hydroxide in methanol gave *N*-acetyl-14-hydroxydihydronorcodeinone (III; R = Ac, R′ = H). That migration took place under basic conditions was confirmed by the action

[5] Nickon and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5566.
[6] Fodor and Kiss, *J. Amer. Chem. Soc.*, 1950, **72**, 3495; Welsh, *ibid.*, 1949, **71**, 3500; Philips and Baltzly, *ibid.*, 1947, **69**, 200; van Tamelen, *ibid.*, 1951, **73**, 5773.

of 1% potassium hydroxide in methanol on 14-acetoxy-*N*-cyanonorcodeine or its acetate, which gave *N*-acetyl-14-hydroxynorcodeine (II; R = Ac, R′ = R″ = H); manganese dioxide oxidation then gave *N*-acetyl-14-hydroxynorcodeinone. 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 demonstrates, for the first time experimentally, the close proximity of the nitrogen atom to the 14-oxygen atom in 14-hydroxycodeinone and provides a general route to *N*-acyl derivatives of 14-hydroxynorcodeine.

N-Cyano-14-propionyloxynorcodeinone, when refluxed with aqueous acetic or propionic acid, gave 14-hydroxy-*N*-propionylnorcodeinone (I; R = Et·CO, R′ = H). Reduction of the latter by sodium borohydride, followed by reaction with propionic anhydride, yielded *N*-propionyl-14-propionyloxynorcodeine 6-propionate (II; R = R′ = R″ = Et·CO) also prepared as follows: Treatment of 14-hydroxynorcodeine with, successively, propionic anhydride, sodium borohydride, and 1% methanolic potassium hydroxide gave a gum whose infrared spectrum shows bands in the *N*-acyl and hydroxyl regions; heating this gum with propionic anhydride afforded *N*-propionyl-14-propionyloxynorcodeine 6-propionate in good yield.

Similarly 14-butyryloxy-*N*-cyanonorcodeinone gave a gum (*N*-acyl and hydroxyl absorption), oxidised by active manganese dioxide to *N*-butyryl-14-hydroxynorcodeinone (I; R = Pr·CO, R′ = H), an amorphous powder, which was also obtained by refluxing an aqueous-butyric acid solution of 14-butyryloxy-*N*-cyanonorcodeinone.

Reduction of either *N*-acetyl-14-hydroxynorcodeine acetate or its 14-acetate (II; R = R″ = Ac, R′ = H or Ac) with lithium aluminium hydride afforded *N*-ethyl-14-hydroxynorcodeine (II; R = Et, R′ = R″ = H). The latter on mild acetylation yielded 14-acetoxy-*N*-ethylnorcodeine and on more vigorous acetylation gave the diacetate; both are hydrolysed by alkali to *N*-ethyl-14-hydroxynorcodeine. Oxidation of the latter acetate by manganese dioxide afforded *N*-ethyl-14-hydroxynorcodeinone (I; R = Et, R′ = H), the reverse change being effected by reduction with sodium borohydride. Similar reduction of 14-acetoxy-*N*-ethylnorcodeinone (I; 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.

Reduction of *N*-propionyl-14-propionyloxynorcodeine propionate by lithium aluminium hydride yielded 14-hydroxy-*N*-propylnorcodeine (II; R = Pr^n, R′ = R″ = H) which with activated manganese dioxide gave 14-hydroxy-*N*-propylnorcodeinone (I; R = Pr^n, R′ = H).

Experimental

Rotations were measured for chloroform solutions. Light petroleum, where unspecified, had b. p. 60—80°. Infrared spectra were determined for Nujol mulls, and identities were confirmed by infrared comparison.

14-*Acetoxy*-N-*cyanonorcodeine* 6-*Acetate*.—14-Acetoxycodeine acetate (6 g.) was heated with cyanogen bromide [1] (10 g.) for 3 min. at 100°. After cooling, 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* 6-*acetate* (5 g.) as prisms, 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. $C_{22}H_{22}N_2O_6$ requires C, 64·4; H, 5·4; N, 6·8%).

14-*Acetoxy*-N-*cyanonorcodeinone*.—(*a*) 14-Acetoxycodeinone (4 g.) was heated with cyanogen bromide (8 g.) for 6 min. at 100°. Addition of ethanol gave a solid which on crystallisation from chloroform–ethanol gave 14-*acetoxy*-N-*cyanonorcodeinone* (3·5 g.) as 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.$^{-1}$ (C:C·C=O) (Found: C, 65·9; H, 4·9. $C_{20}H_{18}N_2O_5$ requires C, 65·6; H, 4·95%).

(*b*) 14-Acetoxycodeinone (5 g.) in chloroform (400 c.c.) was refluxed for 2 hr. with cyanogen bromide (20 g.) in chloroform (200 c.c.). Evaporation 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 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. $C_{20}H_{20}N_2O_5$ 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 gave its 6-acetate and with manganese dioxide gave 14-acetoxy-*N*-cyanonorcodeinone.

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

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

N-*Cyano*-14-*propionyloxynorcodeinone* (from chloroform–light petroleum) as prisms, m. p. 220—221°, $[\alpha]_D$ −46·5° (*c* 0·8), $\nu_{max.}$ 2200 (C≡N) 1680 (C=C·C=O), 1725 cm.$^{-1}$ (ester C=O) (Found: C, 66·4; H, 5·3. $C_{21}H_{20}N_2O_5$ requires C, 66·3; H, 5·3%).

14-*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 (C=C·C=O), 1725 cm.$^{-1}$ (ester C=O) (Found: C, 67·3; H, 5·75. $C_{22}H_{22}N_2O_5$ 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. $C_{27}H_{24}N_2O_6$ requires C, 68·6; H, 5·1; N, 6·2%).

14-*Hydroxynorcodeine*.—(*a*) 14-Acetoxy-*N*-cyanonorcodeinone (478 mg.) was extracted from a Soxhlet thimble on to lithium aluminium hydride (500 mg.) in boiling ether (200 c.c.). After 66 hr. solution was complete, and the cooled solution was treated with water and chloroform to decompose the excess of lithium aluminium hydride, then filtered through kieselguhr, and the organic layer was evaporated to a gum which crystallised from chloroform–light petroleum–ethanol, giving 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. $C_{17}H_{19}NO_4,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 66·6; H, 6·8%).

Recrystallisation from chloroform–methanol gave prismatic needles of a different *solvate*, m. p. 203° (Found: C, 65·9; H, 6·8. $C_{17}H_{19}NO_4,\frac{1}{2}CH_3{\cdot}OH$ 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 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 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.$^{-1}$ (C:C·C=O) (Found: C, 68·7; H, 5·5. $C_{17}H_{17}NO_4$ requires C, 68·2; H, 5·7%).

Dihydro-14-*hydroxynorcodeinone*.—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 in chloroform. Removal

of the solvent under a vacuum at room temperature, followed by addition of methanol and concentration of the solution to low bulk under a vacuum, gave dihydro-14-hydroxynorcodeinone (1 g.) as 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.

Dihydro-14-hydroxynorcodeinone hydriodide (250 mg.), prepared as described by Speyer and Sarre,[4] was dissolved in water (200 c.c.), ammonia (*d* 0·88) added, and the base extracted with chloroform. The gum obtained crystallised from chloroform–methanol to give dihydro-14-hydroxynorcodeinone (35 mg.) as needles, m. p. and mixed m. p. 174—175°.

N-*Acetyl*-14-*hydroxynorcodeine* 6-*Acetate*.—(*a*) 14-Hydroxynorcodeine (100 mg.) was heated on the steam bath for 1 hr. with acetic anhydride (5 c.c.). The mixture was cooled, taken up in chloroform, and shaken with water and ammonia (*d* 0·88). The chloroform solution was washed with water and evaporated. The gum obtained crystallised from chloroform–methanol to give N-*acetyl*-14-*hydroxynorcodeine* 6-*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 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; this gave *N*-acetyl-14-hydroxynorcodeine 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 shaken with hydrogen and platinum oxide (150 mg.). In each case starting material (90%) was returned but the mother liquors yielded from chloroform–light petroleum *N*-acetyl-14-hydroxynorcodeine 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 crystallised from chloroform–methanol to give *N*-acetyl-14-hydroxynorcodeine acetate as needles, m. p. and mixed m. p. 249—250° (decomp.).

14-*Acetoxy*-N-*acetylnorcodeine* 6-*Acetate*.—(*a*) *N*-Acetyl-14-hydroxynorcodeine 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*-acetyl C=O) (Found: C, 63·8; H, 6·2. $C_{23}H_{25}NO_7,\frac{1}{2}CH_3{\cdot}OH$ 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 acetic acid (35 c.c.) and acetic anhydride (1 c.c.) was refluxed for 5 hr. After removal of the solvent under a vacuum the residue 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 (C:C·C=O), 1639 cm.$^{-1}$ (*N*-acetyl C=O) (Found: C, 65·4; H, 5·5. $C_{21}H_{21}NO_6$ requires C, 65·8; H, 5·5%).

(*b*) 14-Acetoxy-*N*-cyanonorcodeinone (1 g.) in 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 acetic acid (35 c.c.) and acetic anhydride (0·5 c.c.) was refluxed for 5 hr. After removal of the solvent, the gum 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 (12 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 crystallised from chloroform–light petroleum–ethanol to give 14-acetoxy-*N*-acetylnorcodeinone as needles, m. p. and mixed m. p. 174—176°.

N-*Acetyl*-14-*hydroxynorcodeinone*.—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 crystallised from chloroform–methanol to give N-*acetyl*-14-*hydroxynorcodeinone* (1·5 g.) as prisms, m. p. 222—223°, $[\alpha]_D$ −221° (*c* 0·25), $\nu_{max.}$ 3333 (OH), 1695 (C:C·C=O), 1600 cm.$^{-1}$ (*N*-acetyl C=O) (Found: C, 66·8; H, 5·6. $C_{19}H_{19}NO_5$ requires C, 66·85; H, 5·6%). This gives the 14-acetoxy-compound, 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 C=O) (Found: C, 66·0; H, 6·0. $C_{21}H_{23}NO_6$ requires C, 65·45; H, 6·0%).

N-*Acetyl*-14-*hydroxynorcodeine*.—(*a*) 14-Acetoxy-*N*-cyanonorcodeine acetate (1 g.) was refluxed for 6 hr. with 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 × 50 c.c.). The chloroform solution was washed with water (2 × 100 c.c.), dried (Na_2SO_4), and evaporated under a vacuum. The solid obtained was triturated with anhydrous ether to give amorphous N-*acetyl*-14-*hydroxynorcodeine* (700 mg.), m. p. 115—120°, $[\alpha]_D$ −113·5° (*c* 0·3), $\nu_{max.}$ 3333 (OH), 1618 cm.$^{-1}$ (*N*-acetyl C=O) (Found: C, 62·3; H, 6·7. $C_{19}H_{21}NO_5,H_2O$ requires C, 63·1; H, 6·4%). 14-Acetoxy-*N*-cyanonorcodeine (0·5 g.), similarly treated, gave the same product.

(*b*) *N*-Acetyl-14-hydroxynorcodeinone (135 mg.) in dioxan (10 c.c.) was stirred for 2 hr. with 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 amorphous *N*-acetyl-14-hydroxynorcodeine, m. p. and mixed m. p. 115—120°.

N-*Acetyl*-14-*hydroxynorcodeinone*.—*N*-Acetyl-14-hydroxynorcodeine (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 *N*-acetyl-14-hydroxynorcodeinone (100 mg.) as prisms, m. p. and mixed m. p. 222—223°.

N-*Acetyldihydro*-14-*hydroxynorcodeinone*.—(*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 evaporated in a vacuum to a gum which crystallised from chloroform–methanol, giving N-*acetyldihydro*-14-*hydroxynorcodeinone* (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*-acetyl C=O) (Found: C, 64·7; H, 6·1. $C_{19}H_{21}NO_5,\frac{1}{2}H_2O$ requires C, 64·8; H, 6·3%). Use of 70% propionic acid gave the same product.

(*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, crystallised from chloroform–light petroleum, to give 14-acetoxy-*N*-acetyldihydronorcodeinone (150 mg.) as prisms, m. p. and mixed m. p. 254—258°.

Dihydro-N-*propionyl*-14-*propionyloxynorcodeinone*.—Dihydro-14-hydroxynorcodeinone (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, dried (Na_2SO_4), and evaporated. The resulting gum crystallised from chloroform–light petroleum to give the *dipropionyl-ketone* (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. $C_{23}H_{27}NO_6$ requires C, 66·8; H, 6·6%).

14-*Hydroxy*-N-*propionylnorcodeinone*.—(*a*) *N*-Cyano-14-propionyloxynorcodeinone (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, from chloroform–methanol, gave 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 (C:C·C=O), 1612 cm.$^{-1}$ (*N*-propionyl C=O) (Found: C, 67·9; H, 5·6. $C_{20}H_{21}NO_5$ requires C, 67·6; H, 6·0%). Use of 70% acetic acid gave the same product.

N-*Propionyl*-14-*propionyloxynorcodeine* 6-*Propionate*.—(*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 filtered in benzene through alumina. After elution with benzene (500 c.c.), and removal of the solvent, the gum obtained crystallised from chloroform–light petroleum to give the *tripropionyl derivative* (1·5 g.), prisms, m. p. 157—158°, $[\alpha]_D$ −145° (*c* 2·0), $\nu_{max.}$ 1724 (ester C=O), 1640 cm.$^{-1}$ (*N*-propionyl C=O) (Found: C, 66·35; H, 6·7. $C_{26}H_{31}NO_7$ 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 anhydride under a vacuum gave a gum which crystallised from chloroform–light petroleum to give the preceding product.

(*c*) *N*-Cyano-14-propionyloxynorcodeinone (400 mg.) was similarly reduced to a gum that was refluxed for 12 hr. with potassium hydroxide (250 mg.) in methanol (25 c.c.) and water (0·5 c.c.). The solid product (230 mg.), $\nu_{max.}$ 3333 (OH), 1612 cm.$^{-1}$ (*N*-propionyl), was heated on the steam bath for 3 hr. with propionic anhydride (5 c.c.), and the resulting gum crystallised from chloroform–light petroleum to give the tripropionyl derivative (130 mg.), prisms, m. p. and mixed m. p. 157—158°.

N-*Butyryl*-14-*hydroxynorcodeinone*.—(*a*) 14-Butyryloxy-*N*-cyanonorcodeinone (0·6 g.) in 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 amorphous *N*-butyryl-14-hydroxynorcodeinone (0·6 g.), m. p. 185—190°, $[\alpha]_D$ −162° (*c* 0·2), $\nu_{max.}$ 3333 (OH), 1685 (C:C·C=O), 1613 cm.$^{-1}$ (*N*-acyl C=O). A satisfactory analysis was not obtained.

(*b*) 14-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 being worked 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 × 50 c.c.). The bulked chloroform layers yielded a gum (1·8 g.), $\nu_{max.}$ 3333 (OH), 1613 cm.$^{-1}$ (*N*-butyryl), which was stirred in chloroform (20 c.c.) for 1 hr. with active manganese dioxide (4·5 g.). The filtered solution was evaporated and the residue on trituration with anhydrous ether gave amorphous *N*-butyryl-14-hydroxynorcodeinone (1·5 g.), m. p. and mixed m. p. 185—190°.

N-*Ethyl*-14-*hydroxynorcodeine*.—(*a*) *N*-Acetyl-14-hydroxynorcodeine 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., then cooled, and the excess of hydride destroyed by chloroform and ice. The filtered solution was shaken with water and the chloroform–ether layer separated. After removal of the solvent, the gum crystallised from chloroform–light petroleum to give N-*ethyl*-14-*hydroxynorcodeine* (90 mg.), prisms, m. p. 128°, $[\alpha]_D$ −105° (*c* 0·3), $\nu_{max.}$ 3448, 3226 cm.$^{-1}$ (OH) (Found: C, 69·75; H, 7·3. $C_{19}H_{23}NO_4$ requires C, 69·3; H, 7·0%). 14-Acetoxy-*N*-acetylnorcodeine and its acetate, when treated with lithium aluminium hydride as above, yielded the same alcohol, m. p. and mixed m. p. 128°.

N-*Ethyl*-14-*hydroxynorcodeinone*.—*N*-Ethyl-14-hydroxynorcodeine (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 N-*ethyl*-14-*hydroxynorcodeinone* (50 mg.), prisms, m. p. 230° (decomp.), $[\alpha]_D$ −220° (*c* 1·0), $\nu_{max.}$ 3257 (OH), 1669 cm.$^{-1}$ (C:C·C=O) (Found: C, 68·7; H, 6·7. $C_{19}H_{21}NO_4,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 68·55; H, 6·9%).

N-*Ethyl*-14-*hydroxynorcodeine*.—*N*-Ethyl-14-hydroxynorcodeinone (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., water (500 c.c.) was added, and the solid extracted with chloroform. The gum left

on removal of the solvent crystallised from chloroform–light petroleum to give *N*-ethyl-14-hydroxynorcodeine (100 mg.), prisms, m. p. and mixed m. p. 128°.

With acetic anhydride this gave its *acetate*, prisms (from chloroform–light petroleum–ethanol), m. p. 183—185°, $[\alpha]_D$ −115° (*c* 0·2), $\nu_{max.}$ 1730 (ester C=O), 1684 cm.$^{-1}$ (C:C·C=O) (Found: C, 68·0; H, 6·3. $C_{21}H_{23}NO_5$ requires C, 68·3; H, 6·3%).

14-*Acetoxy*-N-*ethylnorcodeine*.—*N*-Ethyl-14-hydroxynorcodeine with acetic anhydride at 100° for 1 hr. gave its 14-*acetate*, needles (from chloroform–methanol), 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. $C_{21}H_{25}NO_5$ requires C, 67·9; H, 6·8%).

14-Acetoxy-*N*-ethylnorcodeinone (350 mg.) in dioxan (20 c.c.) was reduced by sodium borohydride (200 mg.) in water (5 c.c.) to the same product.

14-*Acetoxy*-N-*ethylnorcodeine* 6-*Acetate*.—*N*-Ethyl-14-hydroxynorcodeine (100 mg.) in acetic anhydride (10 c.c.) was refluxed for 1 hr. The product was the *diacetate*, prisms (80 mg.) (from chloroform–light petroleum–ethanol), 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. $C_{23}H_{27}NO_6$ requires C, 66·8; H, 6·6%).

14-*Acetoxy*-N-*cyanonorcodeine* 6-*Acetate*.—14-Acetoxy-*N*-ethylnorcodeine 6-acetate (100 mg.) was heated with cyanogen bromide (1 g.) for 3 min. at 100°. Crystals separated on cooling and were filtered off, washed with ethanol, and recrystallised from chloroform–methanol, giving 14-acetoxy-*N*-cyanonorcodeine acetate as prisms, m. p. and mixed m. p. 190°.

14-*Hydroxy*-N-*propylnorcodeine*.—*N*-Propionyl-14-propionyloxynorcodeine 6-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 of hydride was destroyed by chloroform (100 c.c.) and ice, and the mixture filtered through kieselguhr. The chloroform–ether layer was separated. The product, isolated in the usual way, 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. $C_{20}H_{25}NO_4$ requires C, 69·95; H, 7·3%).

14-*Hydroxy*-N-*propylnorcodeinone*.—14-Hydroxy-*N*-propylnorcodeine (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.$^{-1}$ (C:C·C=O) (Found: C, 70·4; H, 7·0. $C_{20}H_{23}NO_4$ requires C, 70·4; H, 6·8%). Its 14-*acetate* formed needles (chloroform–light petroleum–ethanol), m. p. 178°, $[\alpha]_D$ −102° (*c* 1·1), $\nu_{max.}$ 1686) C:C·C=O) and 1730 cm.$^{-1}$ (ester C=O) (Found: C, 68·8; H, 6·8. $C_{22}H_{25}NO_5$ requires C, 68·9; H, 6·6%).

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