Studies on Morphine Alkaloids. Part X.[1] Some Reactions of 14β-Bromocodeine Derivatives with Various Substituents At C-6

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In the solvolysis of 14β-bromocodeine (1), an important contribution by the hydroxy-group at C-6 has been assumed. In order to investigate this assumption further solvolytic reactions were carried out on several compounds obtained by changing the functional group at C-6 and correlating the products and the reactivity with the different substituents.

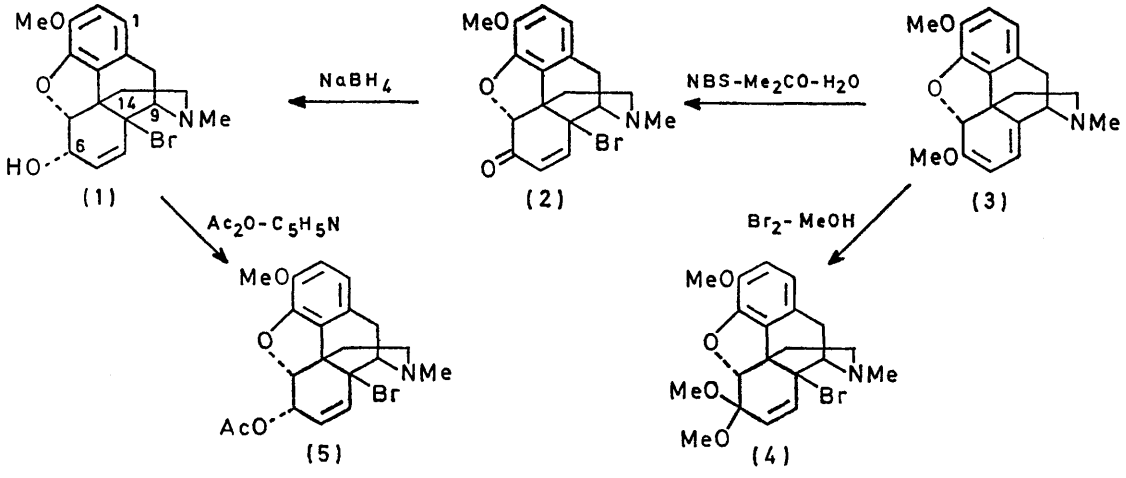
WE reported previously[2] that 14β-bromocodeine (1) was more reactive than related compounds and showed various interesting reactions. It was assumed that this was due to the presence of the 6-hydroxy-group in compound (1).

In the present work, derivatives of compound (1) with various 6-substituents have been synthesized and solvolysed under the same conditions as for (1), in order to confirm this assumption. Structure elucidation of the products has been carried out, together with correlations of the products and reactivity with the different substituents.

The 6-oxo-compound (2) was obtained by bromination of thebaine (3) with *N*-bromosuccinimide (N.B.S.) in aqueous acetone,[3] while direct bromination of (3) with bromine in anhydrous methanol afforded the dimethyl acetal (4) in good yield. Acetylation of (1) with acetic anhydride–pyridine gave the 6-acetate (5). Compounds (2), (4), and (5) were solvolysed under various conditions.

14β-Bromocodeinone (2) is known[4] to undergo a change in strong alkali and a hydroxy-group is introduced into C-7; however, compound (2) is generally much more stable than (1) and hardly changes even under drastic solvolytic conditions.

14β-Bromocodeinone dimethyl acetal (4)[5] was less labile than 14β-bromocodeine (1) and no reaction resulted under the same conditions as for the solvolysis of (1). Prolonging the reaction time or raising the temperature gave a styrene-type compound (6)[6] in good yield, together with compounds corresponding to the products from (1) [(7)—(9)]. For example, treatment of compound (4) in aqueous acetone † with sodium carbonate under reflux afforded, besides (6) (40%), three products [(10)—(12)] in 21, 9, and 5%, respectively. The structures of these compounds were distinguishable from their n.m.r. spectra. Neopine type compounds have a one-proton signal in the olefinic region, the coupling constant of which shows the configuration of the 7-substituent.[2] Indolinocodeine and codeine compounds show signals for two vinyl protons in this region, but in the former, signals for 5-H and one of the 6-OMe groups shift to higher field (Table).



SCHEME 1

† Acetone was used to increase the solubility of compound (4).

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[3] H. Conroy, *J. Amer. Chem. Soc.*, 1955, **77**, 5960.

[4] D. E. Rearick and M. Gates, *Tetrahedron Letters*, 1970, 507; W. Fleischhacker, F. Vieböck, and F. Zeidler, *Monatsh.*, 1970, **101**, 1215.

[5] Some reactions of compound (4) have been reported recently; (*a*) G. Heinisch, V. Klintz, and F. Vieböck, *Monatsh.*, 1971, **102**, 530; (*b*) W. Fleischhacker, *ibid.*, 1971, **102**, 558; (*c*) W. Fleischhacker and H. Markut, *ibid.*, 1971, **102**, 569, 587; (*d*) R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1971, 1121.

[6] (*a*) R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1970, 1346; (*b*) W. Reusser and F. Vieböck, *Monatsh.*, 1971, **102**, 1101.

Diagnostic n.m.r. signals (δ; *J*/Hz)

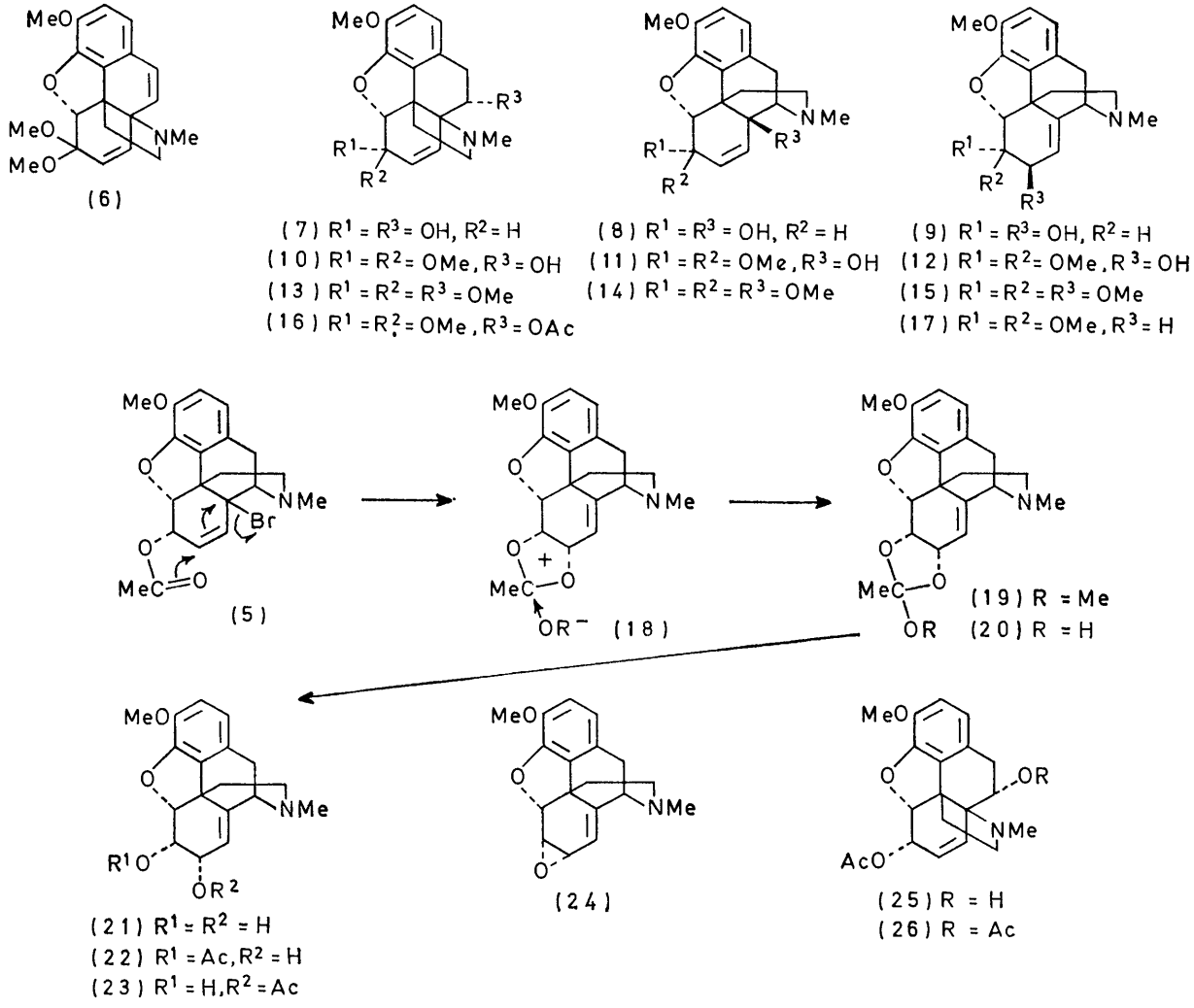
Compound	5-H	6-OMe		7-H	8-H (olefinic)
(10)	4·57	3·57	3·00	6·01	6·16 (ABq, *J* 10)
(13)	4·56	3·55	3·00	6·01	6·15 (ABq, *J* 10)
(16)	4·57	3·55	3·03	5·90 (s)	
(4)	4·65	3·46	3·18	5·67	6·01 (ABq, *J* 10)
(11)	4·74	3·48	3·25		5·80 (s)
(12)	4·91	3·50	2·97		5·78 (d, *J* 6)
(17) [5e]	4·74	3·50	2·92		5·23 (q, *J* 6 and 1)

In strongly basic solutions such as potassium hydroxide, sodium methoxide, or sodium borohydride in methanol, compound (6) was obtained as the main product instead of the expected methoxy-substituted compounds [(13)[5d]—(15)]. It seems possible that at the same time as the C–N bond rearranges to form indolinocodeine type compounds,* an elimination occurs between C-9 and -10 to form compound (6).

Treatment of compound (4) with potassium acetate in methanol gave 9-substituted indolinocodeine (16) [6a] as the main product with little formation of other compounds. Such a reactivity pattern is approximately the same as for (1).

In the case of 14β-bromocodeine 6-acetate (5), compound (19) was obtained as the main product for solvolysis in methanol. Compound (19) was an oil which did not crystallize. Its mass spectrum showed M^+ 371·1758 corresponding to $C_{21}H_{25}NO_5$. There were no absorptions for a hydroxy or an acetyl group in its i.r. spectrum. The n.m.r. spectrum exhibited absorptions due to 9α- and 10β-H at δ 3—4 and one due to a vinyl proton at δ 5·46 (d, *J* 1·0 Hz), indicating that (19) is a neopine-type compound with a α-substituent at C-7. There was no signal for an acetoxy methyl group but signals for a tertiary methyl and a methoxy-group are present at δ 1·00 and 3·25 respectively. From these spectral data, the structure of (19) was presumed to be as shown in Scheme 2.

Hydrolysis of compound (19) with dilute hydrochloric acid gave a diol (21) whose n.m.r. spectrum



SCHEME 2

* The indolinocodeine products have been presumed to be derived *via* an aziridinium intermediate,[2,6a] the structure of which has been deduced recently.[5d]

indicated that the 7-hydroxy-group has the α-configuration. This proved that the 7-substituent of (19) also has the α-configuration.

We suggested that, in the solvolysis of (5), the 6-acetyl group attacks C-7, forming an intermediate such as (18) which is attacked by methoxide ion, giving compound (19). This corresponds to compound (24) obtained in the solvolysis of 14β-bromocodeine (1).

The hydrolysis of (5) progresses similarly. Two compounds (22) and (23) were obtained as the neopine-type products with a 7-substituent. The position and configuration of the substituents were determined from the n.m.r. spectra of compounds deuteriated at C-6. Since the 7-substituent has the α-configuration, this hydrolysis is also thought to progress through an intermediate (20), which is less stable than (19), followed by cleavage to form compounds (22) and (23).

Since this reaction involves the participation of the 6-substituent attacking from the α-side of C-7, the solvolysis of (5) may be considered as analogous to the solvolysis of (1) reported previously.

In the hydrolysis of compound (5) the indolinocodeine-type compound (25) was also obtained in small yield but codeine-type compounds were not obtained at all. Acetylation of compound (25) gave a diacetate (26) which was also obtained in good yield by treatment of (5) with potassium acetate in methanol.

EXPERIMENTAL

M.p.s were determined on a micro hot-stage. I.r. spectra were recorded on JASCO model IR-G spectrometer for chloroform or carbon tetrachloride solutions. N.m.r. spectra were measured on a Varian T-60 spectrometer for deuteriochloroform solution using tetramethylsilane as an internal reference. Chemical shifts are given in δ values and coupling constants (*J*) in Hz. Mass spectra were determined on a JEOL JMS-O1S mass spectrometer with a direct sample inlet system, ionizing potential 70 eV.

14β-*Bromocodeinone Dimethyl Acetal* (4).—Compound (4) was prepared as previously reported [2] and was obtained as needles, m.p. 167—168°.

14β-*Bromocodeine* 6-*Acetate* (5).—Acetylation of 14β-bromocodeine (1) [3] was carried out as reported.[2] Recrystallization from acetone–water gave needles, m.p. 148—150°.

Hydrolysis of 14β-*Bromocodeinone Dimethyl Acetal* (4).—A solution of compound (4) (1 g) in acetone–water (2 : 1; 50 ml) with sodium carbonate (1 g) was refluxed for 2 h. After evaporation of the organic solvent *in vacuo*, the mixture was extracted with chloroform, washed with water, and dried (Na_2SO_4). After evaporation of the solvent *in vacuo*, the oily residue (948 mg) was dissolved in benzene and chromatographed on neutral alumina (Woelm; grade III) (50 g). The first fraction, eluted with benzene, gave 9α-hydroxyindolinocodeinone dimethyl acetal (10) (53 mg, 6·2%), which was recrystallized from ether–light petroleum to give plates, m.p. 118—119°, $\nu_{max.}$ ($CHCl_3$) 3500 cm^{-1} (OH), δ 6·72 (2H, s, 1- and 2-H), 6·10 (2H, ABq, *J* 10, 7- and 8-H), 4·57 (1H, s, 5-H), 4·05br (1H, OH), 3·92 (3-OMe), 3·57, 3·00 (6-OMe), and 2·52 (NMe) (Found: M^+, 359·1701. Calc. for $C_{20}H_{25}NO_5$: *M*, 359·1733). The second fraction, eluted with benzene, gave an oil (516 mg) which showed two spots on t.l.c. After preparative t.l.c. on silica gel plates (0·5 mm) using benzene–ethyl acetate (1 : 1) as solvent, the zones with R_F 0·6 and 0·35 were collected and eluted with chloroform respectively. The material with R_F 0·6 (125 mg, 15%) was crystallized from ether–light petroleum to give compound (10) as fine needles, m.p. 118—119°. The slower running fraction gave 9,10-dehydroindolinocodeinone dimethyl acetal (6) [6] (340 mg, 40%) as fine needles, m.p. 77—78° (from n-hexane), δ 6·60 (2H, s, 1- and 2-H), 6·42 (1H, d, *J* 9·5, 10-H), 5·80 (2H, s, 7- and 8-H), 5·67 (1H, d, *J* 9·5, 9-H), 4·80 (1H, s, 5-H), 3·90 (3-OMe), 3·36, 3·16 (6-OMe), and 2·46 (NMe) (Found: M^+, 341·1652. Calc. for $C_{20}H_{23}NO_4$: *M*, 341·1627). The third fraction from the column chromatography, eluted with ether, gave 14β-hydroxycodeinone dimethyl acetal (11) (76·5 mg, 9%), which was recrystallized from ether to give prisms, m.p. 151—152°, $\nu_{max.}$ (CCl_4) 3400 cm^{-1} (OH), δ 6·60 (2H, ABq, *J* 8, 1- and 2-H), 5·80 (2H, s, 7- and 8-H), 4·74 (1H, s, 5-H), 4·10br (1H, OH), 3·88 (3-OMe), 3·48, 3·25 (6-OMe), and 2·47 (NMe) (Found: M^+, 359·1754. Calc. for $C_{20}H_{25}NO_5$: *M*, 359·1733). Hydrolysis of the acetal (11) with 5% hydrochloric acid gave the corresponding enone, m.p. 271°, identical with an authentic sample of 14β-hydroxycodeinone by mixed m.p. The last fraction, eluted with methanol, afforded 7β-hydroxyneopinone dimethyl acetal (12) [5b] (43 mg, 5%), which was recrystallized from acetone–n-hexane to give prisms, m.p. 156—157°, $\nu_{max.}$ (CCl_4) 3570 cm^{-1} (OH), δ 6·65 (2H, ABq, *J* 8, 1- and 2-H), 5·78 (1H, d, *J* 6, 8-H), 4·91 (1H, s, 5-H), 4·18 (1H, d, *J* 6, 7-H), 3·85 (3-OMe), 3·50, 2·97 (6-OMe), and 2·45 (NMe) (Found: M^+, 359·1749. Calc. for $C_{20}H_{25}NO_5$: *M*, 359·1733).

9α-*Acetoxyindolinocodeinone Dimethyl Acetal* (16).[6a]—14β-Bromocodeinone dimethyl acetal (4) (1 g) and potassium acetate (1 g) were dissolved in methanol (20 ml) and the solution was refluxed for 5 h. After evaporation of the solvent *in vacuo*, the mixture was diluted with water and extracted with chloroform. After the usual work-up, the resulting oil (923 mg) was passed through alumina (Woelm; grade III; 10 g). The first fraction (820 mg), eluted with benzene, was recrystallized from ether–light petroleum to give prisms of compound (16) (595 mg, 62%), m.p. 138—139°, $\nu_{max.}$ (CCl_4) 1730 cm^{-1} (OAc), δ 6·65 (2H, ABq, *J* 10, 1- and 2-H), 5·90 (2H, s, 7- and 8-H), 5·18 (1H, t, *J* 3, 9-H), 4·57 (1H, s, 5-H), 3·96 (3-OMe), 3·55, 3·03 (6-OMe), 2·55 (NMe), and 1·80 (OAc) (Found: M^+, 401·1796. Calc. for $C_{22}H_{27}NO_6$: *M*, 401·1838). The second fraction (72 mg), eluted with ethyl acetate, was recrystallized from ether to give needles of compound (10) (23 mg), m.p. 117—118°, identical with an authentic sample.

Methanolysis of 14β-*Bromocodeine* 6-*Acetate* (5).—A solution of compound (5) (500 mg) in methanol (10 ml) was refluxed for 4 h. After concentration of the solvent *in vacuo*, the residue was diluted with water, made alkaline with 5% ammonium hydroxide, extracted with chloroform, washed with water, and dried (Na_2SO_4). After evaporation of the solvent *in vacuo*, oily residue (470 mg) was dissolved in benzene and chromatographed on neutral alumina (Woelm; grade III; 10 g). The first eluate with benzene was purified on a silica gel column (Davison; No. 923; 100—200 mesh; 20 g) to give an oil (19) (290 mg, 66%), R_F 0·40 [silica gel; benzene–ethyl acetate (1 : 1)], $\nu_{max.}$ ($CHCl_3$) 1605 (aromatic) and 1630 cm^{-1} (C=C) (Found:

M^+, 371·1758. Calc. for $C_{21}H_{25}NO_5$: M, 371·1733), δ 6·66 (2H, ABq, J 8, 1- and 2-H), 5·46 (1H, d, J 1·0, 8-H), 4·80br (3H, 5-, 6-, and 7-H), 3·93 (3-OMe), 3·27 (OMe), 2·42 (NMe), and 1·00 (Me).

Hydrolysis of Compound (19).—A solution of compound (19) (100 mg) in 10% hydrochloric acid (1 ml) was heated on a steam-bath for 30 min. The mixture was made alkaline with aqueous ammonia and extracted with chloroform. After the usual work-up, the crystalline residue (82 mg) was recrystallized from acetone to give needles (37·5 mg) of 7α-hydroxyneopine (21), m.p. 173—174°, $\nu_{max.}$ ($CHCl_3$) 3550 cm^{-1} (OH), δ 6·65 (2H, ABq, J 8, 1- and 2-H), 5·38 (1H, d, J 1·0, 8-H), 4·65 (1H, d, J 4·0, 5-H), 4·30 (1H, q, J 1 and 3, 7-H), 4·15 (1H, m, 6-H), 3·85 (3-OMe), 2·84 (OH), and 2·42 (NMe) (Found: M^+, 315·1443. Calc. for $C_{18}H_{21}NO_4$: M, 315·1471).

Hydrolysis of 14β-*Bromocodeine* 6-*Acetate* (5).—A solution of compound (5) (1 g) in acetone–water (3 : 2; 100 ml) was stirred overnight at room temperature. After evaporation of the organic solvent *in vacuo*, the mixture was made alkaline with 5% ammonium hydroxide and extracted with chloroform. After the usual work-up, the oily residue (872 mg) was chromatographed on neutral alumina (Woelm; grade III; 30 g). The first fraction (60 mg), eluted with benzene, was recrystallized from ether to give fine needles of 9α-hydroxyindolinocodeine 6-acetate (25) (38 mg, 4%), m.p. 134—135°, $\nu_{max.}$ ($CHCl_3$) 3540 (OH) and 1740 cm^{-1} (OAc) (Found: M^+, 357·1602. Calc. for $C_{20}H_{23}NO_5$: M, 357·1576), δ 6·73 (2H, s, 1- and 2-H), 6·26 (2H, ABq, J 8, 7- and 8-H), 5·70, (1H, m, 6-H), 4·57 (1H, d, J 4·5, 5-H), 3·8br (1H, 9-H), 3·90 (OMe), 2·50 (NMe), and 2·13 (OAc). Hydrolysis with 5% methanol–potassium hydroxide gave prisms, m.p. 193—194°, identical with an authentic sample of 9α-hydroxyindolinocodeine. The second fraction, eluted with ether–ethyl acetate (1 : 1), gave an oil (630 mg). Crystallization from ether gave 7α-hydroxyneopine 6-acetate (22) (190 mg, 23%), which was recrystallized from ether–light petroleum to give needles, m.p. 166—168°, $\nu_{max.}$ (CCl_4) 3470 (OH) and 1730 cm^{-1} (OAc) (Found: M^+, 357·1587. Calc. for $C_{20}H_{23}NO_5$: M, 357·1576), δ 6·66 (2H, s, 1- and 2-H), 5·58br (1H, 6-H), 5·46 (1H, d, J 1, 8-H), 4·80 (1H, d, J 4·5, 5-H), 4·56 (1H, q, J 1·0 and 2·5, 7-H), 3·87 (3-OMe), 2·47 (NMe), and 1·52 (OAc). The n.m.r. spectrum of the 6β-deuterio-derivative of 7α-hydroxyneopine 6-acetate showed signals at δ 4·80 (s) and 4·56 (d, J 1·0) and none at 5·58. The combined mother liquors of crystallization of the two fractions were submitted to preparative t.l.c. on silica gel plates 1 mm) using chloroform–methanol (4 : 1) as developing solvent. The zones of R_F 0·6 and 0·3 were collected and eluted with chloroform respectively. The former (90 mg, 11%) gave 7α-acetoxyneopine (23), an oil which did not crystallize, $\nu_{max.}$ ($CHCl_3$) 3400 (OH) and 1715 cm^{-1} (OAc) (Found: M^+, 357·1487. Calc. for $C_{20}H_{23}NO_5$: M, 357·1576), δ 6·66 (2H, ABq, J 8, 1- and 2-H), 5·50 (1H, d, J 1·0, 8-H), 5·40 (1H, q, J 1·0 and 2·5, 7-H), 4·73 (1H, d, J 4·5, 5-H), 4·35 (1H, m, 6-H), 3·88 (OMe), 2·47 (NMe), and 2·10 (OAc). The n.m.r. spectrum of the 6-deuterio-analogue showed signals at δ 5·40 (d, J 1) and 4·73 (s) and none at 4·35. Hydrolysis of compound (23) with methanol–potassium hydroxide gave needles of compound (21), m.p. 173°, identical with an authentic sample. The zone of R_F 0·3 gave compound (22) (270 mg, 31%), m.p. 165°. The third fraction (90 mg), eluted with methanol, was recrystallized from ether to give compound (21) (51 mg), needles, m.p. 169—171°.

9α-*Acetoxyindolinocodeine* 6-*Acetate* (26).—14β-Bromocodeine 6-acetate (5) (1 g) and potassium acetate (1 g) were dissolved in methanol and the solution was refluxed for 40 min. After evaporation of the solvent *in vacuo*, the mixture was diluted with water and extracted with chloroform. After the usual work-up, the resulting oil (996 mg) was dissolved in benzene and chromatographed on alumina (Woelm; grade III; 50 g). The first fraction, eluted with benzene, afforded 9α-acetoxyindolinocodeine 6-acetate (26) (246 mg, 27%), which was recrystallized from n-hexane to give needles, m.p. 123—125°, $\nu_{max.}$ (CCl_4) 1736 cm^{-1} (OAc) (Found: M^+, 399·1722. Calc. for $C_{22}H_{25}NO_6$: M, 399·1682), δ 6·70 (2H, s, 1- and 2-H), 6·13 (2H, ABq, J 8, 7- and 8-H), 5·50 (1H, m, 6-H), 5·28 (1H, t, J 1·5, 9-H), 4·60 (1H, d, J 5·5, 5-H), 3·90 (OMe), 2·58 (NMe), 1·74, and 1·60 (OAc). The next fraction, eluted with ether, gave the oil (19) (430 mg).

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