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VILSMEIER* REACTIONS WITH CYCLIC KETALS OF 14-HYDROXYDIHYDROCODEINONE AND SOME NEW CYCLIC DERIVATIVES OF 14-HYDROXY-DIHYDROCODEINONE

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Abstract—The reaction of cyclic ketals derived from 14-hydroxydihydrocodeinone with a Vilsmeier reagent is described. The reactions of 14-hydroxydihydrocodeinone with dimethylsulphoxonium methylide, dimethylsulphonium methylide and amyl nitrite have been examined.

Structures are proposed for the various products formed.

OUR investigations of the Vilsmeier reaction with 14-hydroxydihydrocodeinone (I; R = Me, R′ = OH, X = O) and derived enol ethers[1] were extended to cyclic ketals of this compound.

Reaction of 14-hydroxydihydrocodeinone with ethane-1,2-diol in the presence of toluene-*p*-sulphonic acid gave a high yield of the required ketal (Ia, R = Me, R′ = OH), when slightly more than 1 molar proportion of the sulphonic acid was used in the reaction.

Routine biological screening of the ethylene ketal somewhat surprisingly revealed that it was a more potent analgesic when administered orally than was morphine by injection.[2] In view of this significant result, further ketals were prepared from 14-hydroxydihydrocodeinone by reaction with propane-1,3-diol and butylene-2,3-diol to yield the derivatives Ib (R = Me, R′ = OH) and Ic (R = Me, R′ = OH) respectively. The dithioketal (Id; R = Me, R′ = OH) was obtained by reaction of 14-hydroxydihydrocodeinone with ethane-1,2-dithiol using boron trifluoride etherate as catalyst. Additionally, the ethylene ketal (Ia; R = H, R′ = OH) was prepared from 14-hydroxydihydromorphinone (I; R = H, R′ = OH, X = O) and converted into the 3-β-hydroxyethyl ether (Ia; R = $HO{\cdot}CH_2{\cdot}CH_2$, R′ = OH) by reaction with ethylene carbonate in the presence of potassium carbonate. The 3-ethyl ether (Ia; R = Et, R′ = OH) was prepared directly from the 3-ethoxy-6-keto compound (I; R = Et, R′ = OH, X = O). Finally, to check the effect of substitution at position 7 on analgesic activity, 14-hydroxydihydrocodeinone was converted into the 7-methyl derivative by alkylation with methyl iodide and sodamide in liquid ammonia–tetrahydrofuran, and thence in high yield into the required 6-ethylene ketal.

A Vilsmeier reaction was carried out on the trimethylene ketal (Ib; R = Me, R′ = OH) using the reagent prepared from phosphorus oxychloride and dimethylformamide and leaving the mixture at 65° for 7 hours. Opening of the ketal ring occurred as expected and two products were isolated. (a) 14-Chloro-6-(3′-chloropropoxy)-Δ^6-dihydrodeoxycodeine (II; R = $Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}O$, R′ = H, R^2 = Cl) and (b) 6-(3′-

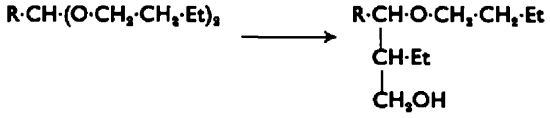
* See Houben-Weyl, *Methoden der Organische Chemie* (4th Edition) Vol. 7 (1), 29 (1954); also, H. H. Bosshard and Hch. Zollinger, *Helv. Chim. Acta* **42**, 1659 (1959); Z. Arnold, *Coll. Czech. Chem. Comm.* **24**, 4048 (1959).

[1] M. G. Lester, V. Petrow and O. Stephenson, *Tetrahedron* **20**, 1407 (1964).

[2] D. I. Barron, P. L. Hall and D. K. Vallance, *to be published.*

chloropropoxy)-7-formyl-14-hydroxy-Δ^6-dihydrodeoxycodeine (II; R = Cl·CH_2·CH_2·CH_2·O, R′ = CHO, R^2 = OH). The structures of both compounds were confirmed by IR spectral data. Vilsmeier reaction with the corresponding ethylene ketal (Ia; R = Me, R′ = OH) gave a mixture of 14-chloro-6,6-ethylenedioxydihydrodeoxycodeine; (Ia; R = Me, R′ = Cl) and 14-chloro-6-(2′-chloroethoxy)-Δ^6-dihydrodeoxycodeine (II; R = Cl·CH_2·CH_2·O, R′ = H, R^2 = Cl). Chromatography of the mother liquors from the reaction revealed no signs of a 7-formyl derivative despite the long reaction time (20 hr) and the fact that some cleavage of the ketal to the enol ether had occurred. Enol ethers are normally readily formylated under these conditions but we have noted previously that the presence of a chlorine atom at position-14 inhibits formylations and 14-chlorodihydrocodeinone-Δ^6-methyl enol ether (II; R = MeO, R′ = H, R^2 = Cl) was not formylated under the experimental conditions employed.[1] It is worth noting here that the Vilsmeier reagent does provide a convenient method of preparation of 14-chlorodihydrocodeinone, a compound which is normally difficult to obtain. Thus, Lutz and Small,[3] have shown that successive treatment of 14-hydroxydihydrocodeine-B with thionyl chloride and phosphorus pentachloride yields a 1,6-dichloro-14-hydroxydihydrocodeine derivative (compare Small and Turnbull[4]) and that, in general, compounds of the 14-hydroxycodeinone series usually yield intractable substances after treatment with chlorinating agents.

Mastagli *et al.*[5] have recently shown that some acetals are converted into ethers on treatment with titanium tetrachloride, thus:



It was thought worthwhile to see if an analogous reaction occurred with the ethylene ketal (Ia; R = Me, R′ = OH) to yield an oxirane of type (Ie; R = Me, R′ = OH). However, reaction of the ketal with titanium tetrachloride in methylene chloride gave a product which, from analytical and IR spectral data is tentatively assigned the structure If (R = Me, R′ = OH). Rather surprisingly, however, this compound is unattacked by hot aqueous ethanolic potassium hydroxide and is unreactive towards potassium cyanide, lithium aluminium hydride and ethylmagnesium iodide. It was stable to cold dilute mineral acid but on heating yielded the parent ketone (I; R = Me, R′ = OH, X = O). An analogous reaction occurred with the trimethylene ketal (Ib; R = Me, R′ = OH) with formation of 6-chloro-14-hydroxy-6-(3′-hydroxypropoxy)-dihydrodeoxycodeine (Ig; R = Me, R′ = OH).

The high analgesic activity of the ethylene ketal (Ia; R = Me, R′ = OH) mentioned earlier prompted further work on the preparation of related compounds containing a small ring at position 6. Accordingly, 14-hydroxydihydrocodeinone was reacted with diazomethane when a very small yield of the expected 6,6-methyleneoxy derivative (Ih; R = Me, R′ = OH) was obtained. Later this same compound was obtained in ca. 90% yield by reaction of 14-hydroxydihydrocodeinone with dimethylsulphoxonium methylide in dimethyl sulphoxide solution using procedures described

[3] R. E. Lutz and L. F. Small, *J. Org. Chem.* **4**, 220 (1939).
[4] L. F. Small and S. G. Turnbull, *J. Amer. Chem. Soc.* **59**, 1541 (1937).
[5] D. Mastagli, C. Gnanadickam and C. Hirigoyen, *C.R. Acad. Sci. Paris* **254**, 1445 (1962).

by Corey and Chaykovsky.[6] Reduction of this 6,6-methyleneoxy derivative with LAH yielded 14-hydroxy-6-methyldihydrocodeine (Ij; R = Me, R′ = OH) whilst reaction with warm 2 N HCl gave 6-chloromethyl-14-hydroxydihydrocodeine (Ik; R = Me, R′ = OH, A = Cl). Reaction of the latter compound with aqueous ethanolic ammonia solution under pressure furnished the aminomethyl derivative (Ik; R = Me, R′ = OH, A = NH_2) converted into the original 6,6-methyleneoxy derivative by treatment with nitrous acid. Examination of the IR spectra of the latter material revealed only traces of ketonic material which contrasts with the observation of Corey and Chaykovsky[6] that reactions of an analogous aminomethyl derivative with nitrous acid led to ketone formation with ring expansion. Finally, reaction of the chloromethyl derivative with sodium azide yielded the azidomethyl derivative (Ik; R = Me, R′ = OH, A = N_3) which was resistant to attempted reduction with hydrogen–Raney nickel or with LAH.

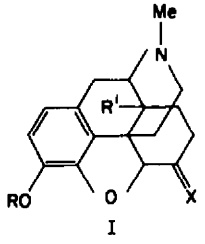
A further attempt to prepare the oxirane (Ih; R = Me, R′ = OH) was made by reacting 14-hydroxydihydrocodeinone with the dimethylsulphonium methylide reagent, described in a second paper by Corey and Chaykovsky.[7] The *product*, isolated in only 20% yield proved to be an isomeric 6,6-methyleneoxy compound, tentatively assigned the structure Il (R = Me, R′ = OH). In view of the similarity between the dimethylsulphonium methylide reagent and the Wittig reagent, triphenylphosphonium methylide, it was first thought that the product might be the 6-methylene compound (Im; R = Me, R′ = OH). A separate synthesis of the latter by an improved Wittig reaction showed, however, that this was not the case. The low yield of the isomeric oxirane was thought to be due to the instability of the reagent used. Attempts were made to improve this yield by reacting 14-hydroxydihydrocodeinone with an excess of dimethylsulphonium methylide reagent. In this case however a new product was obtained which contained no hydroxy and no carbonyl grouping. Its analysis confirmed that it contained one methylene group more than the original oxirane and hence we suggest that it is best represented by formula III.

14-Hydroxy-3-methoxymethyldihydromorphinone (I; R = CH_2·OMe, R′ = OH, X = O), prepared from the morphinone (I; R = H, R′ = OH, X = O) by standard means was converted into the oxirane (Ih; R = CH_2·O·Me, R′ = OH) by reaction with dimethylsulphoxonium methylide and thence to the morphine derivative (Ih; R = H, R′ = OH) by mild hydrolysis with dilute hydrochloric acid. Additionally, 14-hydroxycodeinone was converted into 14-hydroxy-6-methyleneoxydeoxycodeine (IV) by reaction with dimethylsulphonium methylide reagent.

Reaction of 14-hydroxydihydrocodeinone with amyl nitrite in ethanolic hydrogen chloride gave a 33% yield of 14-hydroxy-7-hydroxyiminodihydrocodeinone (Va). This yield was increased to 63% by using chloroform as the main solvent and working at about 0°. The amount of amyl nitrite used in the reaction (1·1 to 1·5 mole equiv) was critical and use of higher proportions of this reagent yielded other unidentified products. Reaction of the hydroxyimino ketone with ethane-1,2-diol and toluene *p*-sulphonic acid yielded the ketal (Vb) which was heated with pyruvic acid in acetic acid in the presence of sodium acetate in an attempt to prepare the 7-keto-6-ketal (Vc), which was obtained in only 21% yield accompanied by a somewhat higher yield of the Δ^8 analogue (VIa) formed by loss of the elements of water across the 8–14 bond. The

[6] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.* **84**, 867 (1962).
[7] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.* **84**, 3782 (1962).

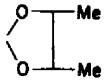
two products were separated fairly readily by chromatography on alumina. The latter compound, 6,6-ethylenedioxy-7-oxo-Δ^8-dihydrodeoxycodeine (VIa) was reacted, as described earlier, with both the dimethylsulphoxonium methylide and dimethylsulphonium methylide reagents to yield isomeric 7-methyleneoxy derivatives (designated VIb and VIc) in 45 and 33% yields respectively. This is contrary to the findings of Corey and Chaykovsky[7] that dimethylsulphoxonium methylide reacted with $\alpha:\beta$-unsaturated ketones to give cyclopropane derivatives. In our case the lower yields of the isomeric oxiranes are probably due to the adverse steric effect of the 6-ketal group. Reaction of 6,6-ethylenedioxy-14-hydroxy-7-oxo-dihydrodeoxycodeine was studied only with the dimethylsulphoxonium methylide reagent and a 54% yield of the expected oxirane (Va) was obtained.



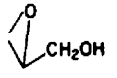
I

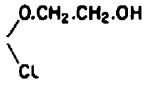
X = (a) 

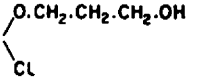
(b) 

(c) 

(d) 

(e) 

(f) 

(g) 

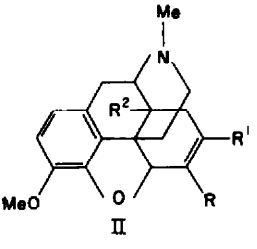
(h) 

(j) 

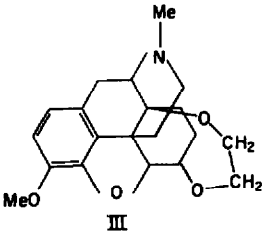
(k) 

(l) 

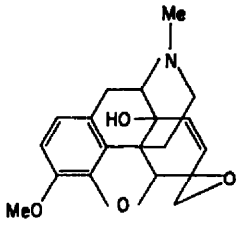
(m) 



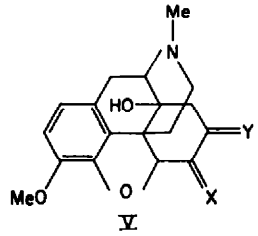
II



III



IV



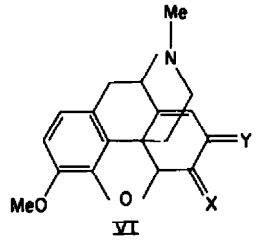
V

(a) X = O, Y = NOH

(b) X =  , Y = NOH

(c) X =  , Y = O

(d) X =  , Y = 



VI

(a) X =  , Y = O

(b) X =  , Y = 

(c) X =  , Y = 

EXPERIMENTAL

IR measurements were made for Nujol mulls with a Perkin–Elmer Infracord Spectrophotometer; no calibration corrections were applied.

6,6-*Ethylenedioxy*-14-*hydroxydihydrodeoxycodeine*. A mixture of 14-hydroxydihydrocodeinone (12 g) and toluene-*p*-sulphonic acid (8 g) was dissolved in ethane-1,2-diol (50 ml) and the solution heated at 70–80° for 2 hr at 0·1 mm press. to remove water and some ethane-1,2-diol. The solution was cooled and poured with stirring into excess 2 N NaOH when the *product* was collected and washed with water. It (11·8 g) had m.p. 196–196·5° (from EtOH). (Found: C, 67·0; H, 6·9; N, 4·1. $C_{20}H_{25}NO_5$ requires: C, 66·8; H, 7·0; N, 3·9%.) The *hydrochloride* had m.p. 230–234° (dec) from EtOH aq. (Found: C, 60·4; H, 7·1; Cl, 8·6; N, 3·6. $C_{20}H_{26}ClNO_5$ requires: C, 60·7; H, 6·6; Cl, 9·0; N, 3·5%.)

14-Hydroxy-6,6-(propylene-1',3'-dioxy)-dihydrodeoxycodeine, was prepared as in the foregoing experiment using propane-1,3-diol in place of ethane-1,2-diol. It (76% yield), had m.p. 157–159° from EtOH. (Found: C, 66·9; H, 7·0; N, 3·7. $C_{21}H_{27}NO_5$ requires: C, 67·5; H, 7·3; N, 3·75%.) *6,6-(Butylene-2',3'-dioxy)-14-hydroxydihydrodeoxycodeine*, had m.p. 186° from EtOH. (Found: N, 3·9. $C_{22}H_{29}NO_5$ requires: N, 3·6%.)

6,6-Ethylenedithio-14-hydroxydihydrodeoxycodeine. 14-Hydroxydihydrocodeinone (2 g) was mixed with ethane-1,2-dithiol (2 ml) and treated with cooling and stirring with BF_3-etherate (2 ml). The mixture was allowed to stand at room temp for 1 hr and was then stirred with excess of 2 N NaOH. The *product* (1·85 g) had m.p. 183–184° from MeOH. (Found: C, 61·1; H, 6·7; N, 3·6; S, 16·2. $C_{20}H_{25}NO_3S_2$ requires: C, 61·35; H, 6·4; N, 3·6; S, 16·4%.)

6,6-Ethylenedioxy-14-hydroxydihydrodeoxymorphine-3-ethyl ether. A stirred solution of 14-hydroxydihydromorphinone hydrochloride trihydrate (4 g) in the minimum of water was added with stirring to 1 N NaOH (40 ml). Ethyl iodide (5 ml) was then added and the mixture warmed gradually to 60–65° during 4 hr. The mixture was cooled and the 3-ethyl ether collected and washed with water. It (2·55 g), (m.p. 150–151° from EtOH) was dissolved in ethane-1,2-diol (20 ml), treated with toluene-*p*-sulphonic acid (2 g) and the mixture heated at 60–70° at 0·1 mm press. for 2 hr. The *product* (2·6 g) isolated as described earlier, had m.p. 154–155° from EtOH. (Found: C, 67·3; H, 7·2; N, 3·8. $C_{21}H_{27}NO_5$ requires: C, 67·5; H, 7·3; N, 3·8%.)

14-Hydroxy-7-methyldihydrocodeinone. A solution of 14-hydroxydihydrocodeinone (5 g) in tetrahydrofuran (130 ml) was added to a solution of sodamide (prepared from 0·4 g Na) in liquid ammonia (150 ml). The mixture was stirred for 3 hr when a solution of methyl iodide (1 ml) in tetrahydrofuran (10 ml) was added. The ammonia was allowed to evaporate overnight, the solvent was distilled off at red. press. when the residual solid was triturated with water and collected (4·8 g). Crystallization from EtOH yielded the *product* (1·67 g), m.p. 226–228° (dec). (Found: C, 69·3; H, 7·2; N, 3·8. $C_{19}H_{23}NO_4$ requires: C, 69·3; H, 7·0; N, 4·25%.) Concentration of the ethanolic mother liquors yielded 2 g 14-hydroxydihydrocodeinone.

6,6-Ethylenedioxy-14-hydroxy-7-methyldihydrodeoxycodeine, obtained in 88% yield by reaction of the foregoing ketone with ethane-1,2-diol, had m.p. 204–205° from EtOH. (Found: C, 67·6; H, 7·2; N, 3·6. $C_{21}H_{27}NO_5$ requires: C, 67·6; H, 7·3; N, 3·8%.)

Vilsmeier reaction on 6,6-ethylenedioxy-14-hydroxydihydrodeoxycodeine. A solution of 6,6-ethylenedioxy-14-hydroxydihydrodeoxycodeine (4·4 g) in 1,2-dichloroethane (25 ml) was added to a Vilsmeier reagent prepared from phosphorus oxychloride (4 ml) and dimethylformamide (8 ml) in 1,2-dichloroethane (48 ml). The mixture was heated to 70–75° for 20 hr. It was then cooled and stirred with Na_2HPO_4 aq, the pH of the mixture being maintained at 9·5 by the periodic addition of NaOH aq. The mixture was extracted with chloroform 4 times and the extracts washed with water twice. Evaporation of the chloroform yielded a gum which solidified on stirring with EtOH. Crystallization from this solvent gave *14-chloro-6,6-ethylenedioxydihydrodeoxycodeine* (2·05 g), m.p. 156–158°. (Found: C, 63·4; H, 6·3; Cl, 9·3; N, 3·5. $C_{20}H_{24}ClNO_4$ requires: C, 63·6; H, 6·4; Cl, 9·4; N, 3·7%.) Concentration of the ethanolic mother-liquor yielded *14-chloro-6-(β-chloroethoxy)-Δ⁸-dihydrodeoxycodeine* (0·3 g), m.p. 186–188° from EtOH. (Found: C, 60·8; H, 5·8; Cl, 18·1; N, 3·8. $C_{20}H_{23}Cl_2NO_3$ requires: C, 60·6; H, 5·85; Cl, 17·9; N, 3·5%.)

Vilsmeier reaction on 14-hydroxy-6,6-(propylene-1',3'-dioxy)-dihydrodeoxycodeine was carried out on the 6,6-(propylene-1',3'-dioxy)-derivative (6 g) [using reagent prepared from phosphorus oxychloride (6 ml) and dimethylformamide (12 ml) in 1,2-dichloroethane (75 ml)] at 65° for 7 hr. After hydrolysis and chloroform extraction the extracts were evaporated at red. press. and finally at 0·1 mm press. to give a gum which was crystallized from EtOH to yield *14-chloro-6-(γ-chloropropoxy)-Δ⁸-dihydrodeoxycodeine*, m.p. 150–151° (1·2 g), ν_{max} (in Nujol), 1670 (C=C), 1630, 1600, 1500 cm^{-1} (aromatic). (Found: C, 61·9; H, 6·1; Cl, 17·1; N, 3·6. $C_{21}H_{25}Cl_2NO_3$ requires: C, 61·5; H, 6·2; Cl, 17·3; N, 3·4%.) Concentration of the ethanolic mother liquors deposited *6-(γ-chloropropoxy)-7-formyl-14-hydroxy-Δ⁸-dihydrodeoxycodeine* (0·5 g), m.p. 152–153° from EtOH. ν_{max} (in Nujol), 3300 (OH), 1650 (C=C), 1610 (C=O), 1510 cm^{-1} (aromatic). (Found: C, 62·7; H, 6·1; Cl, 8·3; N, 3·5. $C_{22}H_{24}ClNO_5$ requires: C, 63·0; H, 6·3; Cl, 8·5; N, 3·35%.)

6-Chloro-14-hydroxy-6-(β-hydroxyethoxy)-dihydrodeoxycodeine. A solution of 6,6-ethylenedioxy-14-hydroxydihydrodeoxycodeine (0·5 g) in methylene chloride (10 ml) was added slowly with shaking to a solution of titanium tetrachloride (0·5 ml) in methylene chloride (10 ml). An orange-red solid was precipitated and the mixture was allowed to stand overnight with the exclusion of moisture. It was

then poured with stirring into excess of 2 N NaOH. Isolation with chloroform furnished the *product* (0·35 g) m.p. 245° (dec) from EtOH. (Found: C, 60·3; H, 6·5; Cl, 9·2; N, 3·4. $C_{20}H_{26}ClNO_6$ requires: C, 60·7; H, 6·6; Cl, 9·0; N, 3·5%.)

6-*Chloro*-14-*hydroxy*-6-(3′-*hydroxypropoxy*)-*dihydrodeoxycodeine* was obtained by reaction of 14-hydroxy-6,6-(propylene-1′,3′-dioxy)-dihydrodeoxycodeine with titanium tetrachloride as described in the foregoing experiment. It had m.p. 230° from EtOH. (Found: C, 61·6; H, 6·5; N, 3·7. $C_{21}H_{28}ClNO_6$ requires: C, 61·5; H, 6·9; N, 3·4%.)

14-*Hydroxy*-6,6-*methyleneoxydihydrodeoxycodeine*. A solution of trimethylsulphoxonium iodide (2·5 g) in dimethyl sulphoxide (30 ml) was stirred at room temp under N_2 and treated with a 50% dispersion in oil of NaH (0·55g). When the evolution of H_2 had ceased, 14-hydroxydihydrocodeinone (3·25 g) was added and the mixture stirred at room temp for 1 hr then at 50° for the same period. The mixture was filtered and the cooled filtrate poured with stirring into excess of water. The solids were collected and crystallized from EtOH to yield the product (3·1 g), m.p. 193–194°. (Found: C, 69·1; H, 7·1; N, 3·9. $C_{19}H_{23}NO_4$ requires: C, 69·3; H, 7·0; N, 4·3%.)

6-*Chloromethyl*-14-*hydroxydihydrocodeine* was obtained in 88% yield when the foregoing 6,6-methyleneoxy compound was heated on the steam-bath for 1 hr with excess of 2 N HCl, followed by cooling and basification with NaOH aq. It had m.p. 166–167° from EtOH. (Found: C, 62·6; H, 6·6; Cl, 9·95; N, 4·1. $C_{19}H_{24}ClNO_4$ requires: C, 62·4; H, 6·6; Cl, 9·7; N, 3·8%.)

6-*Aminomethyl*-14-*hydroxydihydrocodeine*. 6-chloromethyl-14-hydroxydihydrocodeine (2 g) was heated with a 50:50 mixture of EtOH and ammonia solution (d = 0·880; 200 ml) in a sealed vessel for 10 hr at 100°. Evaporation of the liquid yielded the hydrochloride of the product. This was dissolved in water, basified with conc. Na_2CO_3 aq and extracted with chloroform. Concentration of the chloroform yielded the *product* (1·2 g), m.p. 150–152° from ether. (Found: C, 66·4; H, 7·9; N, 8·3. $C_{19}H_{26}N_2O_4$ requires: C, 65·9; H, 7·6; N, 8·1%.)

6-*Azidomethyl*-14-*hydroxydihydrocodeine*. A solution of 6-chloromethyl-14-hydroxydihydrocodeine (1 g) in MeOH (20 ml) was treated with a solution of sodium azide (1 g) in the minimum of water and the mixture was heated under reflux for 48 hr. The MeOH was boiled off and the solids collected and washed with hot water to yield the *product* (0·9 g), m.p. 141–142° from EtOH. (Found: C, 61·5; H, 6·5; N, 14·7. $C_{19}H_{24}N_4O_4$ requires: C, 61·3; H, 6·5; N, 15·05%.)

14-*Hydroxy*-6-*methyldihydrocodeine*. A solution of 14-hydroxy-6,6-methyleneoxydihydrodeoxycodeine (2 g) in tetrahydrofuran (30 ml) was treated gradually with a slight excess LAH when the mixture was heated under reflux for 3 hr. It was then cooled, decomposed carefully with water and the *product* isolated with chloroform. It (1·4 g) had m.p. 199–201° from EtOH. (Found: C, 68·6; H, 7·6; N, 4·2. $C_{19}H_{25}NO_4$ requires: C, 68·8; H, 7·6; N, 4·2%.)

14-*Hydroxy*-6,6-*methyleneoxydihydrodeoxycodeine*. A solution of trimethylsulphonium iodide (1·5 g) in dimethyl sulphoxide (20 ml) was stirred at room temp under N_2 and treated with a 50% dispersion in oil of NaH (0·34 g). After 1 hr, 14-hydroxydihydrocodeinone (2 g) was added to the mixture which was stirred for 1 hr and then heated to 50° for a further hr. The mixture was filtered, the filtrate poured into water and the resultant oil isolated with chloroform. Evaporation of the chloroform and crystallization of the residue from cyclohexane furnished the *product* (0·4 g), m.p. 150–151°. (Found: C, 69·1; H, 7·0; N, 4·0. $C_{19}H_{23}NO_4$ requires: C, 69·3; H, 7·0; N, 4·3%.) When the foregoing reaction was repeated using 4 times as much trimethylsulphonium iodide reagent, the product (37% yield) had m.p. 146–149° (from ether) and the m.p. was strongly depressed on admixture with the foregoing material. It is tentatively formulated as 6,14-*dimethylenedioxydihydrodeoxycodeine*. (Found: C, 69·9; H, 7·4; N, 3·9. $C_{20}H_{25}NO_4$ requires: C, 69·9; H, 7·4; N, 4·1%.)

14-*Hydroxy*-6-*methylenedihydrodeoxycodeine*. A 50% dispersion in oil of NaH (0·61 g) was added to dimethyl sulphoxide (40 ml) under N_2, and the mixture stirred at 65–70° for 2 hr. Triphenylmethylphosphonium bromide (4·5 g) was then added at the same temp followed, 1 hr later, by 14-hydroxydihydrocodeinone (1 g) and stirring was continued for a further 3 hr. The mixture was then cooled, diluted with 3 vol of water, acidified with dil. HCl aq and extracted with chloroform. The chloroform extracts were rejected. The aqueous layer was then basified to pH 9 and the *product* isolated with chloroform. It (0·4 g) had m.p. 148–148·5° from EtOH. ν_{max} (in Nujol), 3350 (OH), 1650 (C=C), 1630, 1610 and 1510 cm^{-1} (aromatic). (Found: C, 72·9; H, 7·6; N, 4·9. Calc. for $C_{19}H_{23}NO_3$: C, 72·8; H, 7·4; N, 4·5%.)

14-*Hydroxy*-3-*methoxymethyldihydrodeoxymorphine*. A solution of 14-hydroxydihydromorphinone (3 g) in EtOH (100 ml) was treated with a solution of EtONa prepared from Na (0·23 g) in EtOH

(5 ml). The EtOH was distilled off and the residual dry solid was suspended in chloroform (100 ml), treated with chlorodimethyl ether (1 ml) and the mixture stirred for 8 hr under N_2. It was then treated with an equal volume of water and the chloroform layer washed 3 times with dil. NaOH aq then with water. Evaporation of the chloroform yielded the *product* (2·3 g), m.p. 200–201° from EtOH. (Found: C, 65·9; H, 7·0; N, 3·6 $C_{19}H_{23}NO_5$ requires: C, 66·1; H, 6·7; N, 4·1%.)

14-*Hydroxy*-3-*methoxymethyl*-6-*methyleneoxydihydrodeoxymorphine*, obtained by reaction of the foregoing compound with dimethylsulphoxonium methylide, had m.p. 142·5–143·5° from EtOH. (Found: C, 67·2; H, 7·1; N, 3·5. $C_{20}H_{25}NO_5$ requires: C, 66·8; H, 7·0; N, 3·9%.)

14-*Hydroxy*-6-*methyleneoxydihydrodeoxymorphine*. A solution of the foregoing compound (1 g) in N-HCl (20 ml) was allowed to stand at room temp for 1 hr and was then brought to pH 9·5 with ammonia. Five extractions with chloroform yielded a crude solid (0·75 g) which furnished the *product* (0·37 g) from EtOH. (Found: C, 68·4; H, 6·9; N, 4·3. $C_{18}N_{21}NO_4$ requires: C, 68·6; H, 6·7; N, 4·4%.)

14-*Hydroxy*-6,6-*methyleneoxydeoxycodeine* was prepared by reaction of 14-hydroxycodeinone with dimethylsulphonium methylide by the method described earlier. It had m.p. 198–200° from EtOH. (Found: C, 69·4; H, 6·6; N, 4·0. $C_{19}H_{21}NO_4$ requires: C, 69·7; H, 6·5; N, 4·3%.)

14-*Hydroxy*-7-*hydroxyiminodihydrocodeinone*. A solution of 14-hydroxydihydrocodeinone (10 g) in dry chloroform (50 ml) was treated with a solution of anhydrous HCl (3 g) in EtOH (15 ml). The mixture was cooled to 0° and treated with amyl nitrite (5 ml) and allowed to stand overnight at 0–3°. It was then shaken with 2 N NaOH (50 ml) and the alkaline layer was re-extracted with chloroform. The combined chloroform extracts were evaporated to yield the *product* (6·9 g), m.p. 226° (dec). (Found: C, 62·8; H, 6·1; N, 8·1. $C_{18}H_{20}N_2O_5$ requires: C, 62·7; H, 5·9; N, 8·1%.)

6,6-*Ethylenedioxy*-14-*hydroxy*-7-*hydroxyiminodihydrodeoxycodeine*. A solution of the foregoing compound (3 g) in ethane-1,2-diol (25 ml) was treated with toluene-*p*-sulphonic acid (1·7 g) and the mixture heated at 60° and 0·1 mm press with slow distillation of the diol. until a sample of the reaction mixture showed no carbonyl absorption on IR examination. The mixture was then cooled, treated with Na_2CO_3 aq and extracted at pH 10 with chloroform. Evaporation of the chloroform extracts yielded the *product* (2·4 g), m.p. 250° (dec). from EtOH or ethyl acetate. (Found: C, 61·8; H, 6·6; N, 7·2. $C_{20}H_{24}N_2O_6$ requires: C, 61·8; H, 6·2; N, 7·2%.)

6,6-*Ethylenedioxy*-7-*oxo*-Δ^8-*dihydrodeoxycodeine*. A solution of 6,6-ethylenedioxy-14-hydroxy-7-hydroxyiminodihydrodeoxycodeine (2 g) in acetic acid (15 ml) containing pyruvic acid (2 ml) was treated with a solution of hydrated sodium acetate (1·5 g) in water (5 ml) and the mixture heated under reflux for 5 hr. It was then cooled, basified strongly with NaOH aq and extracted with chloroform. Evaporation of the chloroform yielded a crude mixture which was separated by chromatography on alumina. Elution with chloroform gave the *product* in the first fraction. It (0·5 g) was obtained as needles, m.p. 220–222° from EtOH. (Found: C, 67·6; H, 6·0; N, 3·8. $C_{20}H_{21}NO_5$ requires: C, 67·6; H, 6·0; N, 3·9%.) The later chloroform fractions yielded 6,6-*ethylenedioxy*-14-*hydroxy*-7-*oxo*-*dihydrodeoxycodeine* (0·4 g), plates, m.p. 245–246° from EtOH. Found: C, 64·4; H, 6·4; N, 3·8. $C_{20}H_{23}NO_6$ requires: C, 64·3; H, 6·2; N, 3·75%.)

6,6-*Ethylenedioxy*-7-*methyleneoxy*-Δ^8-*dihydrodeoxycodeine*. Dimethylsulphoxide (15 ml) was heated to 65° under N_2 and treated with stirring with a 50% dispersion in oil of NaH (0·26 g). When H_2 evolution had ceased the mixture was diluted with tetrahydrofuran (15 ml), cooled to 0° and treated successively with trimethylsulphonium iodide (1 g) and 6,6-ethylenedioxy-7-oxo-Δ^8-dihydrodeoxycodeine (1 g). The mixture was stirred for 1 hr at 0° and was then allowed to rise to room temp when it was filtered to remove insoluble material. The filtrate was diluted with water (200 ml) and the *product* was isolated with chloroform. It (0·35 g) had m.p. 144–145° from EtOH. (Found: C, 68·4; H, 6·5; N, 3·7. $C_{21}H_{23}NO_5$ requires: C, 68·3; H, 6·3; N, 3·8%.)

The *isomeric* 6,6-*ethylenedioxy*-7-*methyleneoxy*-Δ^5-*dihydrodeoxycodeine* was obtained in 45% yield, m.p. 173–174° from EtOH. (Found: C, 68·2; H, 6·6; N, 3·7%) by reaction of 6,6-ethylenedioxy-7-oxo-Δ^5-dihydrodeoxycodeine (1 g) with trimethylsulphoxonium iodide (0·67 g) and a 50% dispersion in oil of NaH (0·16 g).

6,6-*Ethylenedioxy*-14-*hydroxy*-7-*methyleneoxydihydrodeoxycodeine*, m.p. 183–185° from EtOH. (Found: C, 64·6; H, 6·8; N, 3·8. $C_{21}H_{25}NO_6$ requires: C, 65·1; H, 6·5; N, 3·6%), was obtained in 54% yield by reaction of 6,6-ethylenedioxy-14-hydroxy-7-oxodihydrodeoxycodeine (1 g) with trimethylsulphoxonium iodide (0·63 g) and a 50% dispersion in oil of NaH (0·14 g).