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VILSMEIER REACTIONS WITH 14-HYDROXY-DIHYDROCODEINONE AND DERIVED ENOL ETHERS

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Abstract—The reaction of 14-hydroxydihydrocodeinone and some of its derived 6-enol ethers with a Vilsmeier reagent, are described. Structures are proposed and reaction mechanisms suggested for the various products formed. The reaction of one of these products, 7-formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine, with certain organic bases is discussed.

THE reaction of a Vilsmeier reagent[1] with 14-hydroxydihydrocodeinone (I) and enol ethers derived therefrom (II; R = O-alkyl, R′ = OH, X = H) was investigated in attempts to prepare compounds of potential chemotherapeutic interest. Lower, enol ethers of 14-hydroxydihydrocodeinone were readily prepared by heating a mixture of ketone (I), the appropriate alcohol, its orthoformate and slightly more than one equivalent of toluene *p*-sulphonic acid (compare[2]). With methanol, appreciable amounts of the ketal (III) were formed along with the enol ether (II; R = OMe, R′ = OH, X = H). This mixture (though readily separable into its components by extraction with ether), was itself satisfactory for use in the Vilsmeier reaction. Higher enol ethers were more difficult to prepare by this route and the cyclohexyl ether (II; R = O·C_6H_{11}, R′ = OH, X = H) was obtained by refluxing a mixture of the ketone (I), tricyclohexylorthoformate, cyclohexanol and toluene-*p*-sulphonic acid in toluene, with azeotropic removal of water. The IR spectrum of the enol ethers showed bands at 1600, 1630 and an intense C=C stretching absorption at near 1670 cm^{-1} which was absent in the ketal (III).

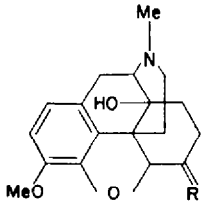
The general procedure adopted for the Vilsmeier reaction was to add a solution of the alkaloid in 1,2-dichloroethane to the Vilsmeier reagent prepared from phosphorus oxychloride and formdimethylamide in the same solvent at 0°. The mixture was then heated to the appropriate temperature and finally hydrolysed in aqueous solution buffered to the required pH. With the ketal (III) reaction at room temperature merely yielded the enol ether (II; R = OMe, R′ = OH, X = H) but at 50° formylation of the tertiary hydroxyl group occurred to yield the formate ester (II; R = OMe, R′ = O·CHO, X = H). At 60–70°, C-formylation occurred at the 7-position to yield the formate ester (II; R = OMe, R′ = O·CHO, X = CHO) as a syrup, smoothly converted into the crystalline tertiary alcohol (II; R = OMe, R′ = OH, X = CHO) by heating with methanol. Chromatography of reaction residues on alumina yielded as by-products the 14-chloro enol ether (II; R = OMe, R′ = Cl, X = H) the 6-chloro-7-formyl derivative (II; R = Cl, R′ = OH, X = CHO) and traces of thebaine.

[1] O. Fischer, A. Müller and A. Vilsmeier, *J. Prakt. Chem.* **109,** 69 (1925); A. Vilsmeier and A. Haack, *Chem. Ber.* **60,** 119 (1927).

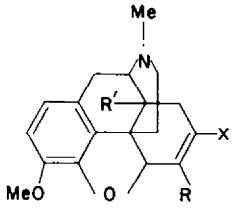
[2] C. A. Mackenzie and J. H. Stocker, *J. Org. Chem.* **20,** 1695 (1955).

The latter compound is presumably formed from the formyl ester (II; R = OMe, R′ = O·CHO, X = H) by elimination of formic acid across the 8:14 position on the faintly alkaline alumina column. The 6-chloro-7-formyl by-product (II; R = Cl, R′ = OH, X = CHO), was readily converted into the required 7-formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (II; R = OMe, R′ = OH, X = CHO) by heating with sodium acetate in methanol. The structure of this latter compound was confirmed by spectral and chemical data. Thus, the IR spectrum showed two intense absorption bands near 1660 and 1625 cm^{-1} (cf. Ref. 3) and the position of the main maximum at 277 mμ in the UV spectrum agrees closely with that expected from calculations based on Woodward's empirical rules.[4] Reduction of the 7-formyl derivative with lithium borohydride yielded the corresponding primary alcohol (II; R = OMe, R′ = OH, X = CH_2OH) which on treatment with acetic anhydride in pyridine was converted into the 7-acetoxy derivative (II; R = OMe, R′ = OH, X = CH_2·OAc). Acid hydrolysis of the 7-formyl-6-enol ethers yielded the α-hydroxymethylene ketone (IV) as an amorphous alkali-soluble compound which gave a characteristic purple coloration with ferric chloride. The same compound was obtained as its sodium salt by hydrolysis of the enol ether in aqueous-ethanolic sodium hydroxide solution.

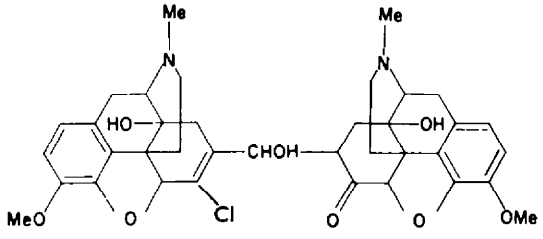
The IR spectrum of IV was typical of that of an enolic β-dicarbonyl compound.[5] Reaction of IV with methyl iodide–sodium methoxide in methanol furnished 14-hydroxy-7-methyl-dihydrocodeinone (compare[6]).



I, R = O
III, R = $(OMe)_2$



II



XIII

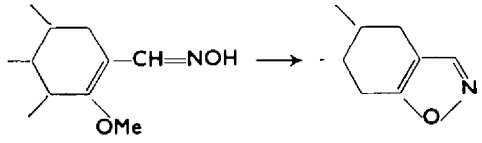
[3] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Edition) p. 268. Methuen, London (1958).

[4] L. F. Fieser and M. Fieser, *Steroids* pp. 16–21. Reinhold (1959).

[5] R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1068 (1949).

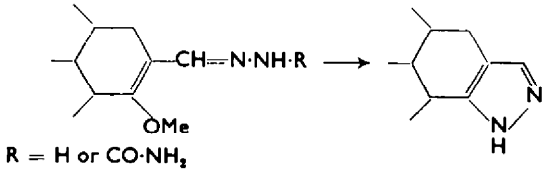
[6] H. T. Ringold and G. Rosenkranz, *J. Org. Chem.* **21**, 1333 (1956).

7-Formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (II; R = OMe, R′ = OH, X = CHO) formed an oxime and a semicarbazone. The former was dehydrated to the 7-cyano derivative (II; R = OMe, R′ = OH, X = CN) on boiling with acetic anhydride and was cyclized to the iso-oxazole (V) on heating with hydrochloric acid.



V

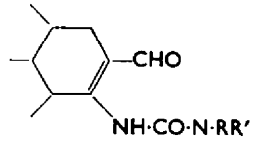
The semicarbazone on heating with hydrochloric acid yielded the pyrazole (VI), also obtained by heating the 7-formyl-6-enol ether with hydrazine sulphate in ethanol.



VI

The structure (V) proposed for the iso-oxazole is based upon the following facts. It is insoluble in aqueous sodium hydroxide solution and the IR spectrum confirms that no hydroxyl group is present other than at position 14. In addition, the C=N band present at 1650 cm^{-1} in the IR spectrum of the oxime is replaced by a composite band of C=N with aromatic C=C at 1600 cm^{-1} which suggests that the C=N is part of a conjugated ring.[3]

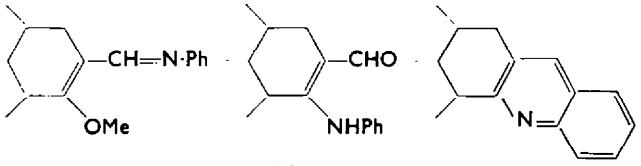
Displacement of the methoxy group in 7-formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine occurred with remarkable ease when this compound was heated with ureas in acid solution. The products are the 6-ureido derivatives (VII) and since the simple enol ether (II; R = OMe, R′ = OH, X = H) does not react under these conditions the activating effect of the 7-formyl group is apparent.



VII

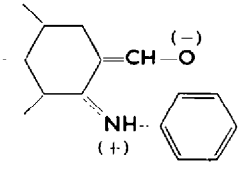
The IR spectra of these ureas (VII) show an intense band near 1550 cm^{-1} due to modification of the formyl carbonyl group by a β-nitrogen atom.[4,5] A further interesting feature of the IR spectra is a strong band near 1690 cm^{-1} when both groups R and R′ (VII) are alkyl. This band shifts to near 1740 cm^{-1} when one of the alkyl groups R or R′ (VII) is replaced by hydrogen but the cause of this shift is not apparent. The UV spectra of all these urea derivatives show a characteristic maximum in the region 325–350 mμ.

Reaction of 7-formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine with aniline yielded three distinct products according to the conditions used. The normal anil (VIII) was formed when equimolar quantities of reactants were refluxed in methanolic solution for 30 minutes. Longer heating with an excess of aniline gave the 6-anilino-7-formyl derivative (IX) whilst more vigorous conditions, especially in the presence of acid, yielded the quinoline (X). The IR spectrum of the anil (VIII) showed no band



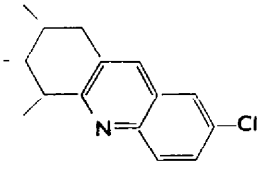
VIII IX X

in the 3500–3000 cm^{-1} region (other than that associated with the 14-hydroxy group), and a strong band at 1635 cm^{-1} due to the C=N bond in addition to the C=C stretching absorption in this region. The UV spectrum showed a main maximum at 283 mμ, consistent with the system, RO—C=C—CH=N—Ph. The IR spectrum of the anilino compound (IX) showed the characteristic strong band at 1540 cm^{-1} associated with the β-amino-α:β-unsaturated aldehyde grouping (see earlier), as well as an NH-band at 3300 cm^{-1}. The UV spectrum showed an intense maximum at 376 mμ, somewhat higher than those already encountered and probably due to resonance in the molecule leading to extended conjugation with the aromatic ring, viz.



The third compound (X) was stable towards mineral acid, and the absence of a band near 1640 cm^{-1} in the IR made the presence of an acyclic C=N group unlikely. Additionally the absence of any NH-stretching vibration suggested that the second nitrogen atom was tertiary. Confirmation of the quinoline structure (X) was afforded by the UV spectrum which showed maxima at 280, 298 and 311 mμ characteristic of this system.[7]

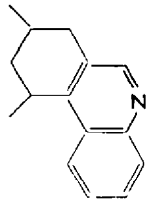
The anil (VIII) was recovered unchanged after boiling in ethanol for several hours but was converted into the anilino derivative (IX) by heating with aniline. The anilino compound (IX) was converted into the quinoline (X) by heating in ethanol, the transformation being accelerated in the presence of acid. Finally, the anil (VIII) yielded the chloroquinoline (XI) on extended heating with an ethanolic solution of



XI

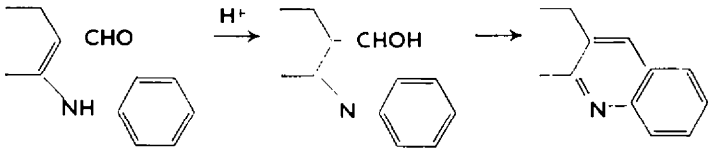
[7] *Organic Electronic Spectral Data*, Vol. 1; p. 238. Interscience (1946–1952).

p-chloroaniline and its hydrochloride. The alternative structure for the quinoline (XII) by direct cyclization from the anil (VIII) is therefore eliminated. The formation

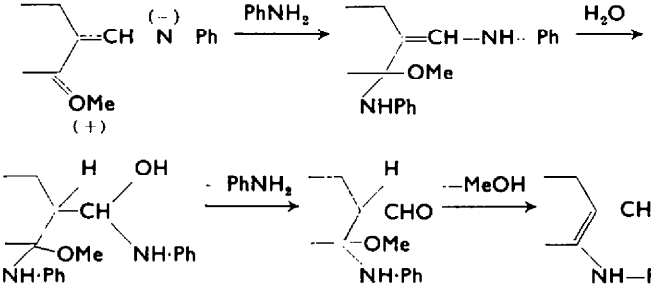


XII

of the quinoline can therefore be represented by the following scheme where the presence of acid assists enolization of the aldehyde. The suggested mechanism for the conversion of the anil (VIII) into the anilino derivative (IX) involves attack by the



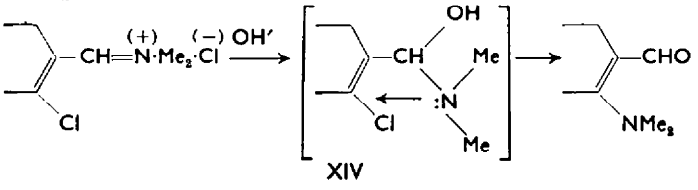
nucleophilic Ph·NH–group at the 6-position of a mesomeric form of the anil, followed by addition of the elements of water to an unstable vinylamine with subsequent elimination of aniline and methanol, viz:



The reaction of 14-hydroxydihydrocodeinone (I) itself with a Vilsmeier reagent was next studied since it has been shown[8] that saturated methylene ketones yield β-chloro-α:β-unsaturated aldehydes under these conditions. When the reaction was carried out for 6 to 7 hours at 70° three products were isolated. These were the expected 6-chloro-7-formyl derivatives (II; R = Cl, R′ = OH, X = CHO) accompanied by 6-dimethylamino-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine (II; R = NMe_2, R′ = OH, X = CHO) and a bimolecular compound (XIII). The yields of the 6-chloro- and of the bimolecular compound were about the same whether the reaction hydrolysis was carried out at pH 4–6 or pH 10 but the 6-dimethylamino compound was not isolated when acid hydrolysis was used. Secondly, the yield of bimolecular compound (XIII) was increased at the expense of the other two products when 14-hydroxydihydrocodeinone was added to the reaction mixture immediately before hydrolysis. Attempts to convert the 6-chloro- into the 6-dimethylamino-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine by reaction with dimethylamine under a variety

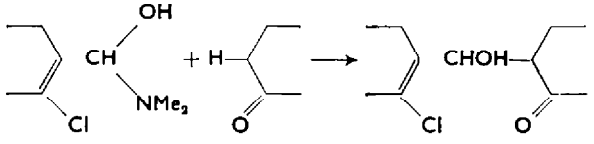
[8] Z. Arnold and J. Žemlicka, *Proc. Chem. Soc.* 227 (1958).

of conditions, failed completely, and further, addition of dimethylamine at the hydrolysis stage of the reaction did not increase the yield of the 6-dimethylamino-7-formyl derivative. It is therefore concluded that the dimethylamino group at position 6 results from an intramolecular nucleophilic displacement involving an intermediate hydrolysis product (XIV) and this reaction competes with the normal formation of the 6-chloro compound, viz:

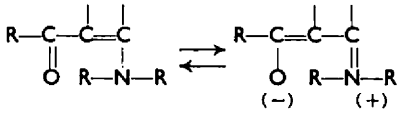


XIV

The reaction of such an intermediate (XIV) with 14-hydroxydihydrocodeinone with elimination of dimethylamine would also explain the formation of the bimolecular product (XIII), viz:



The structure of 6-chloro-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine is supported by its conversion into an oxime, its reduction to the 7-hydroxymethyl derivative with lithium borohydride and, as mentioned earlier, its conversion into the 6-methoxy derivative by reaction with alkaline methanol. The IR spectrum shows the normal carbonyl stretching vibration at 1695 cm^{-1} since here the halogen atom does not offer the possibility of mesomeric forms such as exists with an alkoxy or alkylamino group in the position β to the unsaturated aldehyde. On the other hand, 6-dimethylamino-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine shows a remarkable IR spectrum. Intense bands near 1650 and 1550 cm^{-1} seem to be due to the formyl group since they were absent after reduction with lithium borohydride. Large carbonyl shifts have been reported in such systems[4,5] and are attributed by the authors to resonance between the structures:



Final confirmation of the structure was obtained when it was found possible to synthesize compounds containing this system by Vilsmeier formylation of enamines of type II (R = NR″, R′ = OH, X = H). The enamines themselves were prepared by heating 14-hydroxydihydrocodeinone with high boiling secondary amines in toluene solution in the presence of toluene-*p*-sulphonic acid with azeotropic distillation of the water formed.

The structure of the bimolecular product (XIII) was demonstrated by its cleavage in acid solution or on fusion to yield an equimolar mixture of 6-chloro-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine and 14-hydroxydihydrocodeinone.

The IR spectrum of the product after fusion showed carbonyl absorption of equal intensity at 1730 and 1690 cm^{-1}. The IR spectrum of the compound itself showed

only one carbonyl absorption of approximately half normal intensity at 1725 cm^{-1}, suggesting that the unsaturated aldehyde carbonyl group was involved in the formation of XIII. In addition the spectrum showed a new hydroxyl band at 3300 cm^{-1} as well as that due to the 14-hydroxyl group at 3410 cm^{-1}.

Final confirmation of structure XIII was obtained when the compound was prepared by reaction of 6-chloro-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine with 14-hydroxydihydrocodeinone in methanol containing sodium methoxide, at room temperature.

EXPERIMENTAL

Optical rotations were measured for chloroform or ethanol solutions (ca. 1% concentration) at temps between 20° and 25°. UV absorption spectra (in ethanol) were kindly determined by Mr. M. T. Davies, B.Sc. IR measurements were made for Nujol mulls with a Perkin–Elmer Infracord Spectrophotometer; no calibration corrections were applied.

6,6-Dimethoxy-14-hydroxydihydrodeoxycodeine and 14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine

A solution of 14-hydroxydihydrocodeinone (12 g) and toluene-*p*-sulphonic acid (8 g) in methanol (40 ml) was adjusted to pH 2 by addition of more toluene-*p*-sulphonic acid if necessary. Trimethyl orthoformate (12 ml) was then added and the mixture heated under reflux for 2 hr when it was cooled and poured with stirring into 1 N NaOH aq. The solids were collected, washed with water and dried. Extraction of this material with ether (500 ml) gave insoluble 14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine, m.p. 196–197° from ethanol, $[\alpha]_D$ −228° (chloroform, ν_{max} 3380(OH), 1660 cm^{-1} (C=C). (Found: C, 69·6; H, 7·3; N, 4·3. $C_{19}H_{23}NO_4$ requires: C, 69·3; H, 7·0; N, 4·3%).

Evaporation of the ether yielded 6,6-dimethoxy-14-hydroxydihydrodeoxycodeine, m.p. 121–122° from ethanol, $[\alpha]_D$ −179° (ethanol), ν_{max} 3300 cm^{-1} (OH). (Found: C, 66·4; H, 7·1; N, 4·1. $C_{20}H_{27}NO_5$ requires: C, 66·5; H, 7·5; N, 3·9%).

6-Ethoxy-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This was prepared from 14-hydroxydihydrocodeinone (6 g), toluene-*p*-sulphonic acid (4 g) and trimethyl orthoformate (6 ml) in ethanol (50 ml) at reflux temp for 4 hr, giving the *product* (5·5 g), m.p. 182–184° from ethanol, $[\alpha]_D$ −231° from ethanol. (Found: C, 69·5; H, 7·1; N, 4·0. $C_{20}H_{25}NO_4$ requires: C, 69·95; H, 7·3; N, 4·1%).

6-n-Butoxy-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained in 63% yield, had m.p. 121–122° from ethanol, $[\alpha]_D$ −228° (ethanol), ν_{max} 3360(OH), 1670 cm^{-1} (C=C). (Found: C, 71·0; H, 7·9; N, 3·8. $C_{22}H_{29}NO_4$ requires: C, 71·1; H, 7·9; N, 3·8%).

6-Cyclohexyloxy-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained in 68% yield from 14-hydroxydihydrocodeinone (1·0 g), toluene-*p*-sulphonic acid (0·66 g) and tricyclohexyl orthoformate (5 ml) containing a trace of cyclohexanol, by heating under reflux in toluene for 4 hr, with azeotropic distillation of water and had m.p. 160·5–161·5° from ethanol, $[\alpha]_D$ −220° (ethanol), ν_{max} 3360 (OH), 1660 cm^{-1} (C=C). (Found: C, 72·2; H, 7·6; N, 3·3. $C_{24}H_{31}NO_4$ requires: C, 72·5; H, 7·9; N, 3·5%).

14-Hydroxy-6-morpholino-$\Delta^{6,7}$-dihydrodeoxycodeine

A mixture of 14-hydroxydihydrocodeinone (9 g), morpholine (4 ml) and toluene-*p*-sulphonic acid (3 g) in toluene (100 ml) was heated for 2 hr with azeotropic distillation of water. The toluene was distilled off at red. press. and the residue, treated with excess 1 N NaOH aq furnished the *product* (9·2 g) m.p. 201–202° from ethanol, $[\alpha]_D$ −282° (ethanol), ν_{max} 3400 (OH), 1650 cm^{-1} (C=C). (Found: C, 68·6; H, 7·4; N, 7·3. $C_{23}H_{28}N_2O_4$ requires: C, 68·7; H, 7·3; N, 7·3%).

14-Hydroxy-6-pyrrolidino-$\Delta^{6,7}$-dihydrodeoxycodeine

This had m.p. 190–191° from ethanol, $[\alpha]_D$ −300° (ethanol), ν_{max} 3400 (OH), 1650 cm^{-1} (C=C). (Found: C, 71·5; H, 7·3; N, 7·6. $C_{23}H_{28}N_2O_3$ requires: C, 71·7; H, 7·7; N, 7·6%).

14-Hydroxy-6-methylanilino-$\Delta^{6,7}$-dihydrodeoxycodeine

This had m.p. 195–196° from ethanol, $[\alpha]_D$ −58° (chloroform). (Found: C, 74·0; H, 6·9; N, 7·0. $C_{25}H_{28}N_2O_3$ requires: C, 74·2; H, 7·0; N, 6·9%).

7-Formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine

A mixture of dimethylformamide (20 ml) and anhydrous 1,2-dichloroethane (20 ml) contained in a 500 ml 3-necked flask fitted with sealed stirrer, drying tube and dropping funnel, was stirred during the slow addition of a solution of phosphoryl chloride (12 ml) in anhydrous 1,2-dichloroethane (100 ml) with cooling to below 20°.

The mixture was allowed to stand for 15 min, when a mixture of 6,6-dimethoxy-14-hydroxy-dihydrodeoxycodeine and 14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (12 g, prepared as described earlier), dissolved in 1,2-dichloroethane (100 ml), was added at once. The mixture was heated at 65–70° for 7 hr, then was cooled to room temp and added slowly with stirring to an ice-cold solution of disodium hydrogen phosphate (40 g) in water (1 l.), whilst the pH of the solution was kept between 8 and 9·5 by the periodic addition of 2 N NaOH aq. When the addition was complete the mixture was stirred for 30 min when the organic layer was separated and the aqueous layer was extracted with 3 200 ml portions of chloroform. The combined organic layers were dried and evaporated at red. press. leaving a dark viscous residue which was boiled with methanol (50 ml) for 15 min. The product, which at this stage contained about 20% of *6-chloro-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine*, was collected, dissolved in hot methanol and heated under reflux for 6 hr with an equal weight of anhydrous sodium acetate. The methanol was distilled off at red. press. and the residue treated with excess Na_2CO_3 aq. to yield the *product* (6·5 g), m.p. 185–186° from ethanol, λ_{max} 277 mμ (ε 11,250), ν_{max} 3410 (OH), 1660 (C=C), 1625 cm^{-1} (CO). (Found: C, 67·2; H, 6·7; N, 4·2. $C_{20}H_{23}NO_5$ requires: C, 67·2; H, 6·5; N, 3·9%).

The methanolic mother liquor from the crystallization of the crude product before sodium acetate–methanol treatment was poured into water. The resultant crude solid was dried and chromatographed on alumina. Elution with benzene–chloroform yielded:

(i) *14-Chloro-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine*, m.p. 164–165° from ethanol, $[\alpha]_D$ −235° (ethanol), ν_{max} 1675 cm^{-1} (C=C). (Found: C, 65·2; H, 6·4; Cl, 10·5; N, 3·8. $C_{19}H_{22}ClNO_3$ requires: C, 65·6; H, 6·4; Cl, 10·2; N, 4·0%).

(ii) *Thebaine*, m.p. 192° from ethanol, not depressed in admixture with an authentic specimen.

(iii) *6-Chloro-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine*, m.p. 173–174° from ethanol, $[\alpha]_D$ −307° (ethanol), λ_{max} 252 mμ (ε 8,250), ν_{max} 3380 (OH), 1690 (CO), 1620 cm^{-1} (C=C and aromatic). (Found: C, 63·0; H, 5·8; Cl, 9·8; N, 3·8. $C_{19}H_{20}ClNO_4$ requires: C, 63·1; H, 5·6; Cl, 9·8; N, 3·9%).

14-Formyloxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine

A solution of 14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (6 g) in 1,2-dichloroethane (50 ml) was added in one portion to Vilsmeier reagent prepared from phosphoryl chloride (2 ml) and dimethylformamide (4 ml) in 1,2-dichloroethane (24 ml). The mixture was warmed at 40° for 2 hr, then was cooled and poured into an ice-cold solution of disodium hydrogen phosphate (7 g) in water (150 ml). 2 N NaOH aq was added to bring the pH to 9 then the mixture was extracted with 3 50 ml portions of chloroform. Evaporation of the extracts gave the *product* (3·7 g), m.p. 178–180° (dec) (from n-hexane), ν_{max} 1720 (CO), 1660 cm^{-1} (C=C). (Found: C, 66·8; H, 6·5; N, 4·0. $C_{20}H_{23}NO_5$ requires: C, 67·2; H, 6·5; N, 3·9%).

6-Ethoxy-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained in 64% yield by Vilsmeier reaction on 6-ethoxy-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine, had m.p. 220–221° from ethanol, $[\alpha]_D$ −387° (chloroform). (Found: C, 67·5; H, 6·8; N, 3·8. $C_{21}H_{25}NO_5$ requires: C, 67·9; H, 6·8; N, 3·8%).

6-n-Butoxy-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained in 46% yield, m.p. 144–144·5° from ethanol, $[\alpha]_D$ −317·4 (ethanol). (Found: C, 68·8; H, 7·4; N, 3·7. $C_{23}H_{29}NO_5$ requires: C, 69·1; H, 7·3; N, 3·5%).

7-Formyl-14-hydroxy-6-morpholino-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained in 50% yield by reaction of 14-hydroxy-6-morpholino-$\Delta^{6,7}$-dihydrodeoxycodeine with the Vilsmeier reagent and had m.p. 174–175° from hexane, $[\alpha]_D$ −286° (chloroform). (Found: C, 66·9; H, 7·1; N, 6·7. $C_{22}H_{28}N_2O_5$ requires: C, 66·95; H, 6·8; N, 6·8%).

7-Formyl-14-hydroxy-6-pyrrolidino-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained in 54% yield, had m.p. 241–243° (dec) from ethanol, $[\alpha]_D$ −567° (ethanol), λ_{max} 347 mμ (ε 14,200), ν_{max} 3430 (OH), 1630 (C=C) 1570 cm^{-1} (CO). (Found: C, 69·3; H, 7·5; N, 7·3. $C_{23}H_{28}N_2O_4$ requires: C, 69·7; H, 7·1; N, 7·1%).

Vilsmeier reaction on 14-hydroxydihydrocodeinone

A solution of 14-hydroxydihydrocodeinone (12 g) in 1,2-dichloroethane was added to the Vilsmeier reagent prepared from phosphoryl chloride (12 ml) and dimethylformamide (20 ml) in the same solvent and the mixture heated at 70° for 7 hr. After hydrolysis as described earlier the following products were obtained:

(i) *6-Chloro-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine* (2·4 g), identical with authentic material.

(ii) *6-Dimethylamino-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine* (1·8 g), m.p. 258° (dec) from ethanol, $[\alpha]_D$ −2° (ethanol), λ_{max} 345 mμ (ε 10,410), ν_{max} 3420 (OH), 1655 (C=C), 1550 cm^{-1} (CO). (Found: C, 68·1; H, 7·0; N, 7·6. $C_{21}H_{26}N_2O_4$ requires: C, 68·1; H, 7·1; N, 7·6%).

(iii) A dimeric compound (1·2 g), m.p. 192–193° (dec) from methanol–chloroform, $[\alpha]_D$ −290° (chloroform), ν_{max} 3450 (shoulder) (OH), 3330 (OH), 1730 cm^{-1} (CO). (Found: C, 65·1; H, 6·3; Cl, 5·7; N, 3·8. $C_{37}H_{41}ClN_2O_8$ requires: C, 65·6; H, 6·1; Cl, 5·2; N, 4·1%).

14-Hydroxy-7-hydroxymethyl-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained in 85% yield by reduction of the corresponding 7-formyl compound (20 g) in tetrahydrofuran (100 ml) with lithium borohydride (3 g), had m.p. 164–165° from ethanol, $[\alpha]_D$ −251° (ethanol), ν_{max} 3400 (14-OH and 7-CH_2OH), 1680 cm^{-1} (C=C). (Found: C, 66·6; H, 6·9; N, 4·3. $C_{20}H_{25}NO_5$ requires: C, 66·8; H, 7·0; N, 3·9%).

6-Ethoxy-14-hydroxy-7-hydroxymethyl-$\Delta^{6,7}$-dihydrodeoxycodeine

This had m.p. 122–123° from ethanol, $[\alpha]_D$ −246° (ethanol), ν_{max} 3420 (14-OH and 7-CH_2OH), 1675 cm^{-1} (C=C). (Found: C, 67·6; H, 7·0; N, 3·8. $C_{21}H_{27}NO_5$ requires: C, 67·5; H, 7·3; N, 3·8%).

6-Chloro-14-hydroxy-7-hydroxymethyl-$\Delta^{6,7}$-dihydrodeoxycodeine

This had m.p. 208–209° from ethanol, ν_{max} 3400 (14-OH and 7-CH_2OH), 1675 cm^{-1} (shoulder) (C=C). (Found: C, 62·5; H, 6·3; Cl, 10·1; N, 4·0. $C_{19}H_{22}ClNO_4$ requires: C, 62·7; H, 6·1; Cl, 9·7; N, 3·85%).

6-Dimethylamino-14-hydroxy-7-hydroxymethyl-$\Delta^{6,7}$-dihydrodeoxycodeine, borane adduct

This had m.p. ca. 300° (dec) from ethanol, ν_{max} 3600 (OH), 3400 (OH), 2400, 2350 (shoulder) and 2300 cm^{-1} (B—H). (Found: C, 64·9; H, 8·4; N, 6·9. $C_{21}H_{31}BN_2O_4$ requires: C, 65·3; H, 8·1; N, 7·25%).

7-Acetoxymethyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained by reaction of the corresponding 7-hydroxymethyl compound (0·5 g) with acetic anhydride (0·16 ml) in pyridine (3 ml) at room temp for 16 hr. It (0·32 g) had m.p. 154·5–156° from ethanol, ν_{max} 3350 (OH), 1730 (CO), 1680 cm^{-1} (C=C). (Found: C, 65·3; H, 6·5; N, 3·4. $C_{22}H_{27}NO_6$ requires: C, 65·8; H, 6·8; N, 3·5%). Other esters prepared similarly were the *7-diethylacetate*, m.p. 91–92° from ethanol. (Found: C, 68·0; H, 7·6; N, 3·5. $C_{26}H_{34}NO_6$ requires: C, 68·4; H, 7·5; N, 3·1%). The 7-o-*toluate* had m.p. 123–124° from ethanol. (Found: C, 70·1; H, 6·5; N, 3·3. $C_{29}H_{31}NO_6$ requires: C, 70·4; H, 6·5; N, 2·9%). The *7-phenyldiethylacetate* had m.p. 128–129° from ethanol. (Found: C, 71·7; H, 7·3; N, 2·7. $C_{32}H_{39}NO_6$ requires: C, 72·1; H, 7·9; N, 2·6%). The *7-propionate* had m.p. 108–109° from ethanol. (Found: C, 66·3; H, 7·1; N, 3·7. $C_{23}H_{29}NO_6$ requires: C, 66·6; H, 6·8; N, 3·4%).

7-Benzoyloxy-6-ethoxy-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This had m.p. 128–128·5° from ethanol. (Found: C, 70·1; H, 6·9; N, 2·8. $C_{38}H_{31}NO_6$ requires: C, 70·4; H, 6·5; N, 2·9%). The corresponding *7-furoate*, had m.p. 100–101° from ethanol. (Found: C, 66·5; H, 6·7; N, 3·1. $C_{36}H_{29}NO_7$ requires: 66·8; H, 6·25; N, 3·0%).

14-Hydroxy-6-methoxy-7-phenyliminomethyl-$\Delta^{6,7}$-dihydrodeoxycodeine

A solution of 7-formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (1 g) and aniline (0·26 ml) in the minimum of methanol was heated on the steam bath, with evaporation of the methanol, for 30 min. The residual oil solidified on trituration with ether to yield the product (0·78 g), m.p. 176–177° from ether–light petroleum (b.p. 60–80°), λ_{max} 283 mμ (ε 16,500), ν_{max} 3350 (OH), 1625, 1600 and 1575 cm^{-1} (aromatic and C=N). (Found: C, 72·4; H, 6·7; N, 6·3. $C_{30}H_{30}N_2O_4$ requires: C, 72·3; H, 6·5; N, 6·5%).

6-Anilino-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

(i) A solution of the foregoing 7-phenyliminomethyl compound (0·5 g) in methanol with aniline (0·13 ml) was heated under reflux for 16 hr. After evaporation of the solvent, the *product* (0·32 g) had m.p. 280° (dec) from ethanol, λ_{max} 376 mμ (ε 18,940), ν_{max} 3390 (OH) 3280 (NH), 1660, 1640 and 1600 (aromatic and C=C), 1550 (shoulder) and 1530 cm^{-1} (CO). (Found: C, 71·3; H, 6·4; N, 6·6. $C_{25}H_{26}N_2O_4$ requires: C, 71·7; H, 6·3; N, 6·7%).

(ii) 7-Formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (1 g) was heated for 4 hr with aniline sulphate (1 g) in ethanol (100 ml) when solvent was distilled off and the residue was triturated with water. The *product* (0·83 g), m.p. 280° (dec), was identical with that prepared in (i).

Quinolino-(6,7-b)-14-hydroxydihydrodeoxycodeine

14-Hydroxy-6-methoxy-7-phenyliminomethyl-$\Delta^{6,7}$-dihydrodeoxycodeine (0·5 g) was heated with aniline (0·13 ml) and a trace of aniline hydrochloride in ethanol for 16 hr. The *product* (0·38 g) had m.p. 280° (dec) from ethanol, λ_{max} 280 mμ (ε 5,200), 298 mμ (ε 4,280), 311 mμ (ε 4,605), 325 mμ (ε 4,965), ν_{max} 3400 (OH), 1630, 1600, 1550 and 1500 cm^{-1} (aromatic C=N and C=C). (Found: C, 75·2; H, 6·0; N, 7·0. $C_{25}H_{24}N_2O_3$ requires: C, 75·0; H, 6·0; N, 7·0%).

6'-Chloroquinolino-(6,7-b)-14-hydroxydihydrodeoxycodeine

This was obtained in 74% yield and was prepared like the foregoing compound but using *p*-chloroaniline in place of aniline. It had m.p. 285° (dec) from chloroform–ethanol. (Found: C, 68·7; H, 5·6; Cl, 7·8; N, 6·3. $C_{25}H_{23}ClN_2O_3$ requires: C, 69·0; H, 5·3; Cl, 8·15; N, 6·4%).

14-Hydroxy-7-hydroxyiminomethyl-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This was obtained in 96% yield from the corresponding 7-formyl derivative and had m.p. 242–243° (dec) from ethanol $[\alpha]_D$ −216° (ethanol), λ_{max} 255 mμ (ε 14,670), ν_{max} 3260 (oxime OH and 14-OH), 1650 (C=N), 1630 (shoulder) and 1610 cm^{-1} (aromatic). (Found: C, 64·0; H, 6·3; N, 7·6. $C_{20}H_{24}N_2O_5$ requires: C, 64·5; H, 6·5; N, 7·5%).

Isoxazolyl-(6,7-d)-14-hydroxydihydrodeoxycodeine

This was obtained in 88% yield when the foregoing oxime (1 g) was heated with conc. HCl (4 ml) at 60° for 20 min. It had m.p. 189–190° from ethanol, $[\alpha]_D$ −336° (chloroform), ν_{max} 3380 (OH), 1630 (aromatic), 1605 cm^{-1} (cyclic C=N and aromatic). (Found: C, 66·8; H, 6·0; N, 7·8. $C_{19}H_{20}N_2O_4$ requires: C, 67·0; H, 5·9; N, 8·2%).

Pyrazolinyl-(6,7-c)-14-hydroxydihydrodeoxycodeine

(i) A mixture of 7-formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (1 g) and hydrazine hydrochloride (0·3 g) in ethanol (50 ml) was heated under reflux for 2 hr when solvent was distilled off at red. press. The residual mass was dissolved in dil. HCl and filtered after the addition of charcoal. The *product* (0·62 g) obtained by basification with dil. Na_2CO_3 aq had m.p. 290° (dec) from ethanol, $[\alpha]_D$ −384° (ethanol), ν_{max} 3300 (OH and NH) 1630 (aromatic), 1605 cm^{-1} (cyclic C=N and aromatic). (Found: C, 67·4; H, 6·3; N, 12·2. $C_{19}H_{21}N_3O_3$ requires: C, 67·2; H, 6·2; N, 12·4%).

(ii) The 7-formyl derivative was converted to the semicarbazone (82% yield), m.p. 268–270° (dec) from ethanol. (Found: C, 60·5; H, 6·3; N, 13·2. $C_{21}H_{27}N_4O_5$ requires: C, 60·7; H, 6·55; N, 13·5%), which (0·5 g) was heated with dil. HCl at 100° for 2 hr to yield the pyrazole (0·3 g) m.p. 290° (dec) from ethanol, identical with the compound prepared above.

6-n-Butylureido-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

A mixture of 7-formyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (1 g) and n-butyl urea (0·33 g) in ethanol (50 ml) containing glacial acetic acid (2 ml) was heated under reflux for 2 hr when the solvent was distilled off at red. press. The residue was diluted with water, basified to pH 10 with Na_2CO_3 aq when the solids were collected and stirred with hot water (50 ml). The *product* (0·9 g) had m.p. 250–252° (dec) from ethanol, $[\alpha]_D$ −486° (ethanol), λ_{max} 324 mμ (ε 17,130), ν_{max} 3400 (OH), 3350 (shoulder) (NH), 1740 (amide CO), 1675 (C=C), 1530 cm^{-1} (formyl CO). (Found: C, 65·0; H, 7·3; N, 9·4. $C_{24}H_{31}N_3O_5$ requires; C, 65·3; H, 7·1; N, 9·5%).

6-t-Butylureido-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This had m.p. 268° from ethanol. (Found: C, 65·6; H, 7·2; N, 9·5%).

6-(N,N-Diethylureido)-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine

This had m.p. 220° (dec) from ethanol, λ_{max} 330 mμ (ε 14,450), ν_{max} 3400 (OH), 1680 (amide CO), 1650 (C=C), 1560 cm^{-1} (formyl CO). (Found: C, 65·2; H, 7·2; N, 9·3%).

7-Cyano-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine

7-Hydroxyiminomethyl-14-hydroxy-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine (4 g) was heated under reflux with acetic anhydride (25 ml) for 1 hr when it was cooled, poured onto ice and basified with NaOH aq. *14-Acetoxy-7-cyano-6-methoxy-$\Delta^{6,7}$-dihydrodeoxycodeine* (2·9 g) had m.p. 176–176·5; from ethanol, $[\alpha]_D$ −305° (ethanol), ν_{max} 2210 (C=N), 1730 (CO), 1640 cm^{-1} (C=C). (Found: C, 66·7; H, 6·0; N, 7·3. $C_{23}H_{24}N_2O_5$ requires: C, 66·65; H, 6·1; N, 7·1%). Hydrolysis of the foregoing acetate for 10 min with one equivalent of ethanolic NaOH aq furnished the *product*, m.p. 233–235° from ethanol, $[\alpha]_D$ −311° (ethanol), ν_{max} 3390 (OH), 2210 (C=N), 1640 cm^{-1} (C=C). (Found: C, 68·3; H, 6·4; N, 7·6. $C_{20}H_{22}N_2O_4$ requires: C, 67·8; H, 6·3; N, 7·9%).

Hydrolysis of 6-alkoxy-7-formyl-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeines

(a) The compound (0·15 g) was dissolved in conc. HCl (0·5 ml) with external cooling, allowed to stand at room temp for 15 min and then basified to pH 9·5 with NaOH aq. Extraction with 50% ethanol–chloroform gave amorphous 14-hydroxy-7-hydroxymethylene-dihydrocodeinone, ν_{max} 3400–2650 (continuous band) (14-OH and CHOH), 1630 (aromatic), 1600 cm^{-1} (aromatic and enolic β-keto aldehyde). The product was soluble in water and ethanol but insoluble in chloroform. It gave a deep purple colour with ferric chloride solution.

(b) The compound (0·5 g) was dissolved in ethanol, treated with 2N NaOH aq (1 ml) and allowed to stand at room temp for a few min. The solution was then diluted with water and brought to pH 9·5 by addition of dil. HCl. Extraction with 50% ethanol–chloroform furnished the 7-hydroxymethylene compound identical with that obtained in (a).

14-Hydroxy-7-methyldihydrocodeinone

A solution of the foregoing hydroxymethylene compound (1 g) in water (50 ml) containing slightly more than one equivalent of NaOH was stirred with methyl iodide (2 ml) at room temp for 48 hr. The *product* (0·4 g), had m.p. 226–228° (dec) from ethanol, $[\alpha]_D$ −187° (chloroform). (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%). It was identical with the compound obtained by methylation of 14-hydroxydihydrocodeinone with methyl iodide–sodamide in liquid ammonia solution.

Hydrolysis of 6-dialkylamino-7-formyl-14-hydroxydihydrodeoxycodeinone derivatives

(a) The compounds (0·5 g) were dissolved in excess of 5 N HCl and allowed to stand at room temp for 30 min when the solution was basified to pH 9·5 and the solids collected, washed with water, dried and chromatographed on alumina. Three fractions were obtained:

(i) Starting material.

(ii) 6-Dialkylamino-14-hydroxy-$\Delta^{6,7}$-dihydrodeoxycodeine.

(iii) 14-Hydroxydihydrocodeinone, m.p. 218–219° from ethanol, identical with an authentic specimen. This latter was the only compound obtained from more vigorous treatment with HCl aq.

(b) When the compound was heated in a slight excess of ethanolic NaOH for 30 min, the only product was the amorphous 14-hydroxy-7-hydroxymethylenedihydrocodeinone.