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Note

On the Configuration of 14-Hydroxylated Codeine Analogues

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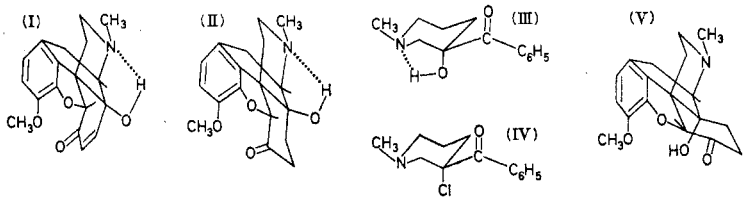
Recent investigations and rationalizations of structure activity relationships among codeine-type analgetics depend upon configurational and conformational specificity of the pharmacophore and/or directophore.[1] There appears to be no rational basis for the significant pharmacological differences between 14-hydroxylated codeines and their codeine counterparts. In order to be able to rationalize these trends, the relative and thus the absolute configuration of the C_{14}-OH group of 14-hydroxycodeinone (I) and 14-hydroxydihydrocodeinone (II) was determined.

Optical rotatory dispersion data for (+)-3-benzoyl-3-hydroxy-1-methylpiperidine (III) and (−)-3-chloro-3-benzoyl-1-methylpiperidine (IV) indicated the presence of an O—H···N hydrogen bond in III.[2,3] This prediction was confirmed and led to current interest in 14-hydroxylated codeines which are also 3-piperidinols.

The infrared spectra of 14-hydroxycodeinone (I) and 14-hydroxydihydrocodeinone (II) show single intramolecular hydroxyl absorptions at 3385 cm^{-1} and 3414 cm^{-1} respectively. This proves unequivocally what previously had been strongly suspected by others, namely that the C_{14}-OH group is β to the ethylenimine bridge.[4,5] The O—H···N bonding can only arise from I and II, i.e. not V. The shift of the O—H absorption to higher frequency in going from I to II is in line with the earlier noted acid strengthening effect of the carbonyl group of α-hydroxy ketones (*cf.* III);[2] I is a vinylogous α-hydroxy ketone. As expected, the H···N bonds in these compounds are weaker than in the non-vinylogous, yet conformationally less rigid III which absorbs at 3350 cm^{-1}.

If, as has been suggested,[6] some of the pharmacological actions of codeine analogues are dependent upon oxidative *N*-dealkylation

of these drugs, then the observed gradations in pharmacological response between the C_{14}-hydroxylated compounds and the corresponding C_{14}-deoxy analogues may be a function of hydrogen bonding which would facilitate such metabolic reactions. Correlations are now being sought in these laboratories.



Experimental

Melting points were obtained in a Hershberg-type silicone-filled melting-point apparatus equipped with Anschütz immersion thermometers. The samples were placed in the circulating bath 10° below the reported melting points and heated at the rate of 2° per minute.

The infrared spectra were determined in the region 3100–3800 cm^{-1} in carbon tetrachloride solution using a Beckman IR–7 spectrophotometer operating on a double beam with a sodium chloride prism and replica grating. The compounds were examined at concentrations of $3 \cdot 2 \times 10^{-3}$ and $6 \cdot 4 \times 10^{-4}$ molar in 1·00 and 5·00-cm silica cells respectively. The band positions and peak heights were independent of concentration. Thus, none of the broad absorption bands was due to intermolecular hydrogen bonding. No non-bonded hydroxyl absorptions were present in these spectra. Observed spectral bands are believed reliable to within ± 5 cm^{-1}.

14-Hydroxycodeinone (I) prepared from thebaine by the method of Fel'dman and Lyutenberg[7] was obtained in 85 per cent yield, m.p. 268–269° (d.). A pure, white crystalline compound, m.p. 273–274° (d.) [lit. m.p. 275–276° (d.)],[7] which was sensitive to light and air, could be obtained only after several recrystallizations from acetone and decolorizations with carbon.

14-Hydroxydihydrocodeinone (II) was prepared by catalytic reduction of 14-hydroxycodeinone (2·50 g, 0·008 moles) with

$PdCl_2$ (50 mg) in 10 per cent acetic acid (85 ml) at over 800 mm hydrogen pressure. After 3 h, uptake of hydrogen was quantitative. The solution was filtered, made basic with ammonia, and extracted with chloroform. Evaporation of the solvent and recrystallization from absolute alcohol gave 2·13 g (0·0068 moles, 85 per cent) of product, m.p. 220–221° (d.) [lit. m.p. 219–221° (d.)].[7]

(±)-*3-Benzoyl-3-hydroxy-1-methylpiperidine* was prepared as described in a previous publication,[3] m.p. 53–53·5°.

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