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DERIVATIVES OF MORPHINE. VII[1]. CONSTITUTION OF A PRESUMED ISOMER OF 5-BENZYLDIHYDROCODEINONE.

Surendra P. Bhatnagar and Ulrich Weiss*

Laboratory of Chemical Physics, National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Maryland 20014, U.S.A.

Work by Small et al. (1938) has shown that Zeisel-demethylation of 5-benzyldihydrocodeinone (1) yields an alkali-insoluble product (3) in addition to the expected, alkali-soluble 5-benzyldihydromorphinone (2). The hitherto unknown structure of the alkali-insoluble compound is now determined by spectroscopic methods, and it is shown to be a secondary product formed from (2) during the demethylation.

During their investigation of the compounds produced in the reaction of dihydrothebaine[2a] or the enol acetate of dihydrocodeinone[2b] with Grignard

reagents, Small and coworkers prepared a series of 5-alkyldihydrocodeinones† and converted them to the corresponding morphine derivatives by Zeisel-demethylation with boiling conc. HBr. Usually, this last-named reaction yielded the desired phenol as the only isolated product. However, in the case of 5-benzyldihydrocodeinone (1), the expected morphine derivative (2) was accompanied by substantial amounts of an alkali-insoluble by-product of mp. 166-167.5°. On the basis of an elementary analysis and of the lack of manifest phenolic properties, Small et al. concluded that this unexpected product is an isomer of (1), "probably formed by a rearrangement of unknown nature."[2b] No structure was proposed.

It seemed worth while to examine this presumed rearrangement, and to establish the structure of the compound of mp. 166-167.5° by modern instrumental techniques. A sample of material still remaining from the work of Small et al., kindly made available by Drs. E. L. May and L. J. Sargent, served for this investigation. It had the mp. given in the literature,[2b]

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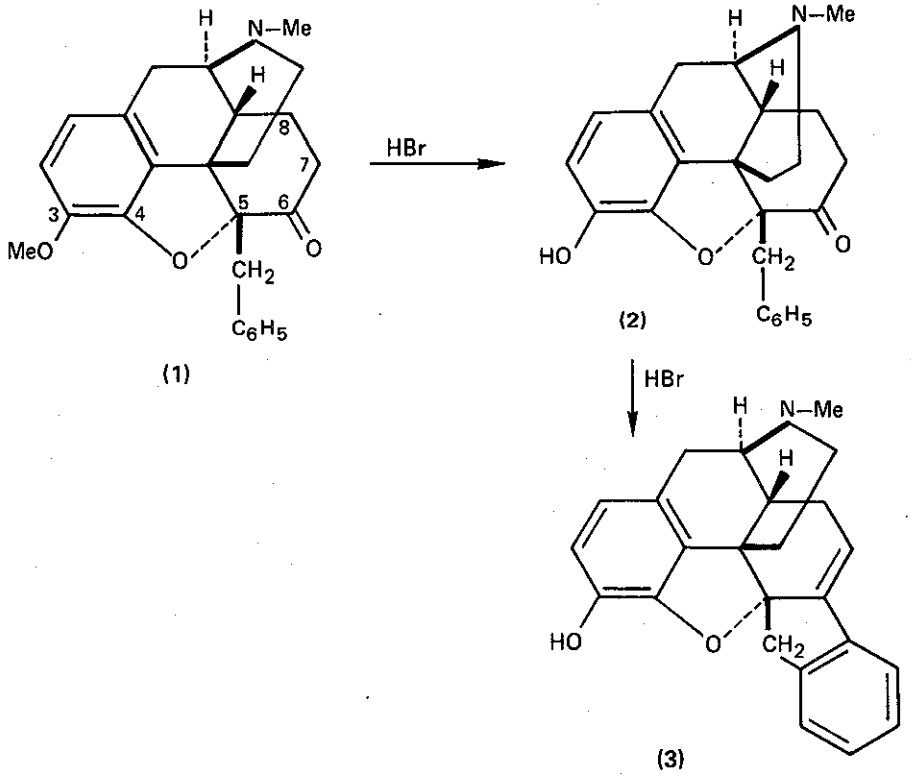
†Actually, Small and coworkers were unable to decide, with the methods available to them, whether the alkyl groups introduced by the various Grignard reagents became attached to C-5 or C-7 of the morphine skeleton. Attachment of C-5 was subsequently demonstrated by Stork and Bauer[3] for the methyl derivative. That both methyldihydrocodeinone and (1) are indeed the 5-alkyl derivatives follows from their ^{1}H nmr spectra, which lack the highly characteristic, isolated (1H) singlet at $\delta \sim 4.7$ ppm produced by the proton at C-5 in dihydrocodeinone [(1), H instead of benzyl] and its relatives.

was insoluble in aqueous NaOH, and gave no color with $FeCl_3$ in aqueous medium; morphine and analogous phenols give a blue color under those conditions.

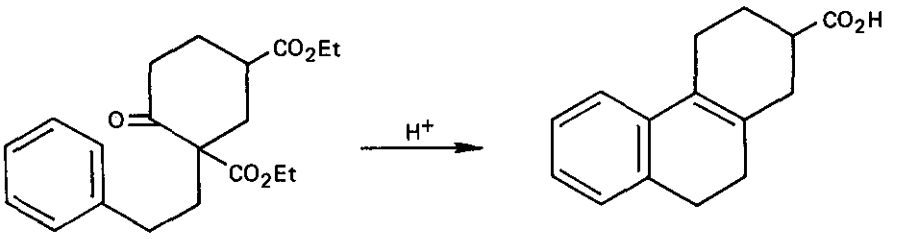
The compound showed a mass-spectrometric molecular weight of 357; it is thus not an isomer of (1) (mol. wt. 389), but is evidently formed from it by loss of both the oxygen-bound methyl and one molecule of water, and must have the empirical formula $C_{24}H_{23}NO_2$. That O-demethylation had indeed occurred was shown by the absence of the methoxyl signal in the ^1H nmr occurring at δ 3.8 ppm in codeine derivatives such as (1), and by the marked shift of the uv maximum due to the phenolic chromophore from λ_{max} 285 nm to 300 nm on addition of alkali to the alcoholic solution of the compound, which is thus cryptophenolic rather than non-phenolic.



Examination of the uv, ir, and nmr spectra permitted formulation of the compound as (3). Thus, the ir spectrum conclusively proves the absence of the carbonyl and the presence of hydroxyl. The uv spectrum, measured in ethanol, shows a band with λ_{max} at 245-248 nm, compatible with a styrene chromophore, in addition to the usual band at 285 nm produced by the phenolic ring. In the ^{1}H nmr spectrum, the singlet (5H) at δ 7.25 ppm, caused by the aromatic protons of the benzyl group of (1) and its congeners, is replaced by a complex multiplet (4H) between δ 7.15 and 7.6 ppm, and the presence of a new olefinic proton is indicated by a doublet with fine-structure (1H) centered at δ 5.7 ppm; $J = 6.9$ and <1. The methylene group of the benzyl residue shows as a broad doublet (2H) at 3.5 ppm; in (2), this group causes a multiplet at δ 3.4. The remaining nmr signals were not significantly different from those of (2). The coupling constants of the signal from the vinylic proton are in satisfactory agreement with those calculated by the Karplus relation from the bond angles measured on a Dreiding model of (3). Such a model can be constructed with only moderate strain.

Structure (3) suggests that the compound may be a secondary transformation product of (2). This interpretation was shown to be correct by refluxing a sample of (2) with conc. HBr, as described by Small et al.[2b] for preparation of (2) and (3) from (1); the reaction was monitored by tlc on silica gel plates ($MeOH/CHCl_3$ 1:1). After about 1 hr., a new spot developed, having an R_f value identical with that of authentic (3). This compound, isolated by preparative tlc with the same solvent system, gave a mass-spectrum identical with that of (3).

Precedent for the formation of (3) from (2) is available; cf., e.g., the conversion of (4) into (5) under the influence of HCl-AcOH, which has been observed by Ghatak et al.[4]



The failure of (3) to dissolve in aqueous NaOH may be due to formation of an insoluble Na salt. The negative color test with $FeCl_3$ remains surprising; low solubility of the compound in the aqueous medium might be responsible.

ACKNOWLEDGMENT

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