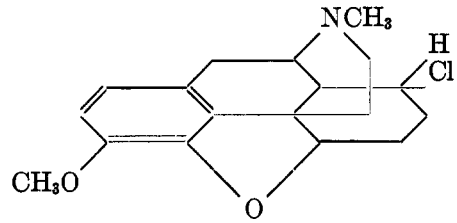
[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH AND THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

DESOXYCODEINE STUDIES. VI. DESOXYCODEINE-D (DESOXYNEOPINE)[1]

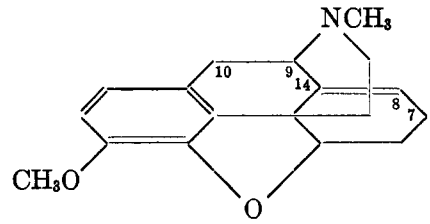
LYNDON SMALL AND JAMES E. MALLONEE[2]

Received January 6, 1940

In the preceding communication (1) it was pointed out that the action of phosphorus pentachloride on dihydropseudocodeine and on dihydroallopseudocodeine resulted in the same 8-chlorodihydrocodide (I). This chloro compound is exceedingly resistant to reduction, but we find that prolonged treatment with sodium in boiling cyclohexanol results in loss of hydrogen chloride, with formation of a new desoxycodeine that we shall designate as desoxycodeine-D. The structure II that we propose for the compound represents it also as the desoxy derivative of the rare opium alkaloid neopine (2). The new desoxycodeine might be logically named desoxyneopine, but this leads to embarrassment in selecting a name for the morphine analog.



I. 8-Chlorodihydrocodide

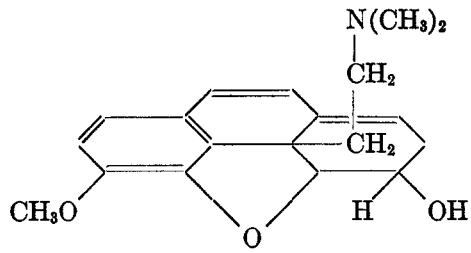


II. Desoxycodeine-D

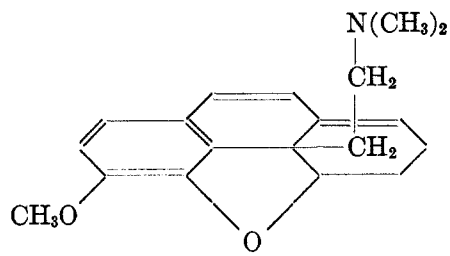
[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. P. H. S.

[2] Mallinckrodt Fellow in Alkaloid Chemistry 1937–39.

Desoxycodeine-D adds one mole of hydrogen on catalytic reduction, to give the well-known dihydrodesoxycodeine-D in nearly quantitative yield. This simple relationship demonstrates unequivocally the desoxycodeine nature of the compound, but leaves open the alternative position of the double bond, between carbons 7 and 8. The structure II that we favor is based on negative but fairly convincing evidence. In the methylmorphimethine series, α- and γ- methylmorphimethines, derived respectively from codeine and isocodeine and having the 7,8-unsaturation, undergo with ease a rearrangement (to β- and δ- methylmorphimethines) that consists in a shift of the unsaturated linkage into the 8,14-position, *i.e.*, into conjugation with the 9,10-double bond. We find that desoxycodeine-D-methine cannot be caused to rearrange in this fashion, whence it may be concluded that the methine already has the stable β-methylmorphimethine (neopinemethine) arrangement of double linkages. We were unable to devise any method of preparing desoxy-β-methylmorphimethine for a direct comparison.



III. β-Methylmorphimethine



IV. Desoxycodeine-D-methine

Further support for our conception of the structure of desoxycodeine-D has been obtained through the von Braun cyanogen bromide degradation (3). Von Braun has shown by numerous examples that cyanogen bromide reacts with morphine derivatives having the 7,8-unsaturation, to replace methyl on nitrogen by a cyano group. When, on the other hand, an unsaturated center is located in the β,γ-position to nitrogen, *i.e.* 8,14-, the attachment of nitrogen to an adjacent carbon is so loosened that this

linkage is more easily broken than the N-methyl linkage, and addition of cyanogen bromide takes place with rupture of the cyclic nitrogen structure. We first convinced ourselves of the applicability of the first type of reaction to the desoxycodeine series by an experiment with a compound of known structure. Desoxycodeine-C (4) was converted smoothly by cyanogen bromide to the expected cyanonordesoxycodeine-C. Desoxycodeine-D, on the other hand, reacted to yield an amorphous, bromine-containing product, as would be expected from rupture of the nitrogen-containing ring through cyanogen bromide addition. The result is reminiscent of that obtained by von Braun with thebaine, and, like von Braun's product, our desoxycodeine-D degradation-product behaved as though it slowly lost hydrogen bromide (5).

We may mention, further, that desoxycodeine-D behaves pharmacologically more like thebaine than like a codeine type, a fact that is suggestive of a structural similarity, *i.e.*, the 8,14-unsaturation. We know of no other instance where morphine derivatives of this type have been tested, so that one can scarcely formulate any general connection between physiological action and the presence of the 8,14-unsaturation. Saturation of the 8,14-double bond of thebaine (to dihydrothebaine), and conversion of desoxycodeine-D to dihydrodesoxycodeine-D, results in a marked change in the pharmacological picture, specifically in a two-fold or greater increase in analgesic power, and a moderate reduction in convulsant action (6).

As a by-product in the dehalogenation of 8-chlorodihydrocodide, a small amount (11% yield) of the demethylation product, desoxymorphine-D, was obtained. This was identified by methylation with diazomethane. In one experiment, desoxymorphine-D was obtained as a by-product from heating dihydroallopseudocodeine with phosphorus tribromide. It seems probable that dihydroallopseudocodeine was first converted to 8-bromodihydrocodide, and that this compound suffered loss of hydrogen bromide and demethylation.

EXPERIMENTAL

Desoxycodeine-D. A solution of 5.0 g. of 8-chlorodihydrocodide in 500 cc. of cyclohexanol was brought to boiling, and 55 g. of sodium was added over a period of three hours, while the solution was stirred mechanically and maintained in ebullition under reflux. Addition of 600 cc. more of cyclohexanol was necessary to keep the mixture liquid. The solution was cooled, and made acid with 6 *N* hydrochloric acid. The cyclohexanol was removed by steam distillation, since the alkaloidal material could not be extracted from it with acid. The resulting aqueous solution was made strongly alkaline with sodium hydroxide and extracted thoroughly with ether. Desoxymorphine-D, described in a later paragraph, remained in the alkaline solution. Concentration of the ether solution gave 3.5 to 4.5 g. of liquid base, which was converted to the acid tartrate with saturated aqueous *d*-tartaric acid solution.

The salt was purified from water, yield 4 to 4.5 g. (59–66%). It melted at 204–206° (evac. tube, foaming) and had $[\alpha]_D^{25}$ 0° (water, c = 1.17).

Anal. Calc'd for $C_{22}H_{27}NO_8$: C, 60.9; H, 6.3.
Found: C, 60.8; H, 6.3.

The desoxycodeine-D base obtained from the tartrate was a viscous liquid, and could be purified to some extent by distillation in a high vacuum at 110°. Like most of the compounds of the series, it gave low carbon values on analysis.

Anal. Calc'd for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.5.
Found: C, 75.0, 75.0; H, 7.4, 7.1.

The hydrochloride was prepared with alcoholic hydrogen chloride, and was precipitated crystalline with absolute ether. It could be purified from butanone, m.p. 234–235° (evac. tube); $[\alpha]_D^{28}$ −12.1° (water, c = 0.21).

Anal. Calc'd for $C_{18}H_{22}ClNO_2$: C, 67.6; H, 6.6.
Found: C, 66.5, 66.9; H, 6.7, 6.8.

The acid oxalate was prepared with alcoholic oxalic acid and absolute ether, and was recrystallized from 95% alcohol; m.p. 220–221° (evac. tube, decomp.).

Anal. Calc'd for $C_{20}H_{23}NO_6$: C, 64.3; H, 6.2.
Found: C, 63.5, 63.6; H, 6.4, 6.0.

Bromodesoxycodeine-D. Saturated bromine water was added to a solution of desoxycodeine-D in normal hydrochloric acid until precipitation of the insoluble yellow perbromide was complete. By addition of sulfur dioxide water, excess bromine was destroyed and the perbromide was brought back into solution. The brominated base separated in crystalline form when dilute ammonia was added; yield quantitative. The compound crystallized in six-sided plates from 60% alcohol; m.p. 125–126°. In analogy with bromocodeine (7), this compound may be assumed to be 1-bromodesoxycodeine-D.

Anal. Calc'd for $C_{18}H_{20}BrNO_2$: C, 59.6; H, 5.6; Br, 22.1.
Found: C, 59.0; H, 5.2; Br, 22.2.

After sublimation in a high vacuum, Found: C, 59.4; H, 5.1.

Hydrogenation of desoxycodeine-D. In spite of the analytical difficulty experienced with desoxycodeine-D and its derivatives, the result of hydrogenation appears to establish the empirical formula proposed. A solution of 1 g. of desoxycodeine-D acid tartrate in 35 cc. of water, with 50 mg. of platinum oxide absorbed one mole of hydrogen in 7 hours. Removal of the solvent under diminished pressure resulted in 0.8 g. of white crystals, m.p. 153–155°, which proved to be dihydrodesoxycodeine-D acid tartrate (4b). The base obtained from the salt had the melting point 102–105°, and did not depress the melting point of dihydrodesoxycodeine-D.

Desoxycodeine-D-methine. Reaction of desoxycodeine-D with methyl iodide in alcohol gave a quantitative yield of the methiodide, m.p. 204–206° (evac. tube). One and three-tenths grams of the methiodide was boiled for 10 minutes with 10 cc. of 20% sodium hydroxide solution. The partly crystalline mass was extracted into ether, from which 0.8 g. of crystals was obtained. The methine crystallized from dilute alcohol in lustrous six-sided plates of melting point 76–77°.

Anal. Calc'd for $C_{19}H_{23}NO_2$: C, 76.7; H, 7.8.
Found: C, 76.9; H, 7.6.

A solution of 0.3 g. of the methine in 2.5 cc. of alcohol with 0.35 g. of potassium hydroxide and 1.5 cc. of water was boiled under reflux for two hours. Desoxycodeine-D-methine was regained quantitatively.

Desoxycodeine-D and cyanogen bromide. Following the procedure of von Braun, we extracted into chloroform the base liberated from 1.5 g. of desoxycodeine-D acid tartrate, dried the solution over sodium carbonate, and concentrated it to 5 cc.

After addition of 0.6 g. of cyanogen bromide, the solution was boiled under reflux for two hours, and poured into 150 cc. of ether. The red precipitate that formed was identified after basification as desoxycodeine-D. The ether was concentrated in a vacuum until all odor of cyanide was gone. The reddish oily product contained much halogen, and was slowly transformed to an ether-insoluble substance, probably as a result of splitting out hydrogen bromide and formation of a hydrobromide.

Cyanonordesoxycodeine-C. Desoxycodeine-C differs in structure from the proposed desoxycodeine-D formula only in having the unsaturated linkage in a position other than β,γ- to nitrogen. A solution of 1 g. of desoxycodeine-C in 3 cc. of chloroform with 0.4 g. of cyanogen bromide was boiled under reflux for 2 hours, and then boiled to dryness. The oily product was treated with water and extracted into ether, from which 0.7 g. of crystals was obtained. After recrystallization from alcohol, the compound melted at 159.5–161°.

Anal. Calc'd for $C_{18}H_{18}N_2O_2$: C, 73.4; H, 6.2; N, 9.5.
Found: C, 72.9; H, 6.0; N, 9.7.

Desoxymorphine-D. The alkaline mother liquors from the preparation of desoxycodeine-D were acidified with hydrochloric acid and concentrated. After sodium chloride was removed, ammonia was added and the precipitate was brought into ether. The yield was 0.5 g. (11% of the calculated) of desoxymorphine-D. The base was purified from alcohol, m.p. 254–255° (evac. tube, decomp.); strongly phenolic. It sublimed in a high vacuum at 130–140°. Desoxymorphine-D was also obtained in one experiment when dihydroallopseudocodeine was heated for 7 hours at 120° with phosphorus tribromide. Desoxymorphine-D was converted easily to desoxycodeine-D by the action of diazomethane.

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1.
Found: C, 74.7, 75.0; H, 6.9, 7.0.

SUMMARY

The preparation of desoxycodeine-D and desoxymorphine-D from 8-chlorodihydrocodide is described. Desoxycodeine-D appears to have its unsaturation at the 8,14-position and hence represents the desoxy derivative of neopine. Desoxycodeine-D-methine behaves like β-methylmorphimethine in resisting rearrangement.

WASHINGTON, D. C.

REFERENCES

(1) SMALL, FARIS, AND MALLONEE, *J. Org. Chem.*, **5**, 334 (1940).
(2) VAN DUIN, ROBINSON, AND SMITH, *J. Chem. Soc.*, **1926**, 903.
(3) VON BRAUN, *Ber.*, **47**, 2312 (1914).
(4) (a) SMALL AND COHEN, *J. Am. Chem. Soc.*, **53**, 2214, 2227 (1931).
(b) SMALL AND MORRIS, *J. Am. Chem. Soc.*, **55**, 2874 (1933).
(5) *Cf.*, SPEYER AND ROSENFELD, *Ber.*, **58**, 1125 (1925).
(6) N. B. EDDY, unpublished results.
(7) SMALL AND TURNBULL, *J. Am. Chem. Soc.*, **59**, 1541 (1937).