[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

SOME REACTIONS OF NEOPINE

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The rare opium alkaloid neopine was first described in the form of salts and methiodide by Dobbie and Lauder (1), who believed it to be a hydroxycodeine through misinterpretation of their analytical results; they presented no evidence for two hydroxyl groups. The base was obtained crystalline by van Duin, Robinson, and Smith (2), who demonstrated that it was an isomer of codeine, differing from this alkaloid only in the position of the hydroaromatic unsaturation.

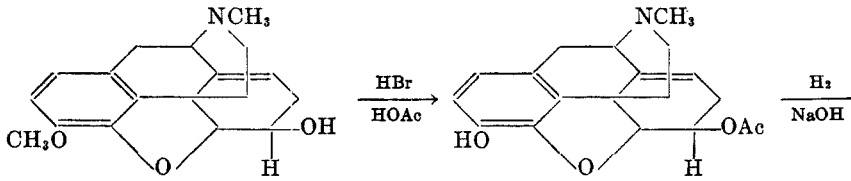
Through the courtesy of Dr. V. H. Wallingford and Dr. A. H. Homeyer, of the Mallinckrodt Chemical Works, a quantity of highly purified neopine hydrobromide has been supplied for investigation, and I present herewith some of the reactions of this neglected alkaloid. In confirmation of Robinson's work, analysis shows the formula to be $C_{18}H_{21}NO_3$. Although there is not the slightest reason to doubt the results of the English investigators, the important transformation of neopine methohydroxide to β-methylmorphimethine in a single step has been verified. The low rotatory power of neopine derivatives (mostly around $\pm 20°$) and the extraordinary effect of opening the nitrogen-containing ring ($+414°$) are of theoretical interest.

In contrast to codeine, neopine can be demethylated in excellent yield with hydrogen bromide in glacial acetic acid; at the same time, acetylation of the 6-hydroxyl group takes place, as observed by Mosettig (3) in the parallel demethylation of dihydro-β-methylmorphimethine, so that the product is 6-acetylneomorphine, a strongly phenolic, sparingly water-soluble base. It is probable that the primary demethylation product is diacetylneomorphine, which undergoes half-hydrolysis during isolation, for if the diacetylneomorphine described below is dissolved in dilute acetic acid and recovered by a parallel procedure, it is regained as the monoacetyl derivative. The demethylation can also be accomplished with 48% aqueous hydrobromic acid but the product (neomorphine) is difficult to isolate in good yield because of its water-solubility.

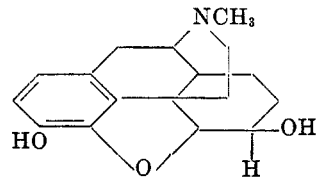
By hydrogenation, 6-acetylneomorphine is converted to 6-acetyldihydromorphine, identical with the compound obtained by half-hydrolysis of diacetyldihydromorphine with hydroxylamine hydrochloride. The 6-acetyldihydromorphine *ex* neopine can be hydrolyzed easily to dihydromorphine. This confirms in a slightly different way the relationship established by Robinson between neopine and dihydrocodeine.

6-Acetylneomorphine is hydrolyzed readily by hot dilute alkali, yielding neomorphine, whose unexpected water-solubility causes some difficulty in the separation from inorganic material. Neomorphine crystallizes best from chloroform, in coffin-shaped prisms containing one molecule of chloroform. That no change in structure took place in the demethylation reaction is shown

by the above-mentioned hydrogenation of 6-acetylneomorphine, and by the transformation of neomorphine·$CHCl_3$ back to neopine in quantitative yield by the action of diazomethane.



Neopine 6-Acetylneomorphine



Dihydromorphine

6-Acetylneomorphine, with acetic anhydride in pyridine, yields diacetylneomorphine, the analog of heroin. Other reactions of neopine and neomorphine will be discussed in a later publication.

The analgesic action of neopine, neomorphine, 6-acetylneomorphine, and diacetylneomorphine has been studied by Dr. N. B. Eddy, using the Woolfe-Macdonald (4) technique. The analgesic effectiveness of all four compounds is definitely less than that of their morphine analogs, the latter being 2 to 6 times more effective. There is not a consistent difference in toxicity; neopine and neomorphine are about one-half as toxic as codeine and morphine respectively, while 6-acetyl- and diacetyl-neomorphine are more toxic than their morphine analogs. It is remarkable that with all four compounds the Straub reaction is entirely absent, and in the main, convulsant action is less marked.

I am indebted to C. A. Kinser and Betty Mount of this Laboratory for the microanalyses.

EXPERIMENTAL

Neopine. The material used in this investigation was in part alkaloid of m.p. 127.5–128.5°, $(\alpha)_D^{30}$ −28.13°, and in part hydrobromide of $(\alpha)_D^{27}$ +16.99°, as described by Homeyer and Schilling (5). The composition of the alkaloid was verified.

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.2; H, 7.23.

Found: C, 72.4; H, 7.30.

Neopine hydrochloride shows $(\alpha)_D^{20}$ +18.2° (water, *c*, 1.04). Neopine methiodide has $(\alpha)_D^{20}$ +23.5° (alcohol, *c*, 0.62).

Degradation to β-methylmorphimethine. Boiling neopine methiodide with 30% KOH for 10 min. resulted largely in unchanged methiodide. One gram of neopine in 10 ml. of benzene was treated dropwise with dimethyl sulfate. In contrast to Robinson's description, the methomethyl sulfate crystallized immediately in sparkling white flakes. The isolated salt was, however, too hygroscopic for further characterization. It was added immediately to 10 ml. of 30% KOH and boiled gently for 3 min., when separation of pale yellow granu-

lar crystals was complete. These were filtered on a glass-wool mat and washed well with water; 0.95 g., m.p. 131–133°. It was recrystallized from ethyl acetate and from alcohol, 0.6 g., m.p. 136°, $(\alpha)_D^{20}$ +414° (95% alcohol, *c*, 1.03).

For purest β-methylmorphimethine *ex* codeine, m.p. 136°, $(\alpha)_D^{20}$ +413° (95% alcohol, *c*, 1.02). Knorr (6) reported m.p. 134–135°, $(\alpha)_D^{17}$ +438° in 97% alcohol.

Equal amounts of the "neopinemethine" and authentic β-methylmorphimethine were mixed and recrystallized from alcohol; m.p. 136°.

Demethylation of neopine: 6-acetylneomorphine. A suspension of 10 g. of neopine hydrobromide in 60 ml. of 15% hydrogen bromide in gl. acetic acid was heated slowly in the oil-bath. At 115° (bath-t.) vigorous evolution of gas began. The bath was raised to 145° in the course of an hour. The cooled, colorless solution was diluted with an equal volume of water and made alkaline with ammonia, scratching or seeding near the neutral point.

After 2 hrs. at 0°, the crystalline product was washed with a small amount of ice-water (fairly soluble); faintly pink crystals, 7.6 g. (88%).

From 73 ml. of alcohol, 5.1 g. (59%) was obtained; m.p. 243–251° (evac. tube, decomp.), $(\alpha)_D^{20}$ +27.6° (alcohol, *c*, 1.07).

Anal. Calc'd for $C_{19}H_{21}NO_4 + 1.5\ H_2O$: C, 64.4; H, 6.78.
Found: C, 64.5, 64.3; H, 6.66, 6.47.

The hydrate water could not be determined directly because of slight sublimation.

The hydrochloride was prepared with alcoholic HCl, and purified from absolute alcohol; it is extremely soluble in water. It had the m.p. 238–245° (evac. tube, decomp.), $(\alpha)_D^{20}$ +8.8° (water, *c*, 1.02).

Anal. Calc'd for $C_{19}H_{22}ClNO_4$: C, 62.7; H, 6.09.
Found: C, 62.9; H, 6.46.

Diacetylneomorphine. Five grams of 6-acetylneomorphine in 20 ml. of pyridine and 10 ml. of acetic anhydride was allowed to stand 24 hours. Liquid was removed as far as possible under diminished pressure, then over sulfuric acid in a high vacuum. Sat'd NaCl solution and sodium bicarbonate were added, and the emulsion extracted with ether. This left a syrup, which slowly crystallized, 5.6 g. It was very soluble in most media, quite soluble in hot water, 1% in cold water, but crystallized poorly. It was purified from ligroin (90–100°), 3.2 g., m.p. 127–127.5°, mixed m.p. with neopine 98–102°. In 95% alcohol it showed $(\alpha)_D^{20}$ +17.5° (*c*, 1.08).

Anal. Calc'd for $C_{21}H_{23}NO_5$: C, 68.3; H, 6.28.
Found: C, 68.4; H, 6.46.

Neomorphine. Ten grams of 6-acetylneomorphine was boiled for 10 min. with 40 ml. of 2 *N* NaOH. The solution was saturated with CO_2 (remained clear and colorless), and taken to dryness in the vacuum desiccator; it was necessary to break up frequently a tough surface skin. The dry powder was digested thoroughly with two 100-ml. portions of chloroform (filtering through "Supercel"). The acidified residue gave only a faint Mayer's test. The chloroform was distilled to about 30 ml., where crystals separated, 9 g., m.p. 103° (frothing). It was purified from chloroform, 5 g., m.p. 107° (±2°, the m.p. is difficult to determine accurately, as the froth is as white as the crystals). The crystals have a very characteristic "coffin shape"; in U.S.P. chloroform $(\alpha)_D^{20}$ −18.2° (*c*, 1.04); in 95% alcohol $(\alpha)_D^{20}$ −9.2° (*c*, 1.09).

Anal. Calc'd for $C_{17}H_{19}NO_3 + CHCl_3$: $CHCl_3$, 29.5.
Found: loss in wght., 100°/0.1 mm.: 29.5.
Calc'd for $C_{17}H_{19}NO_3$: C, 71.6; H, 6.71.
Found: C, 71.5; H, 6.85.

The solvent-free base has the m.p. 240–241° (evac. tube, decomp.). Both the dried and solvated product were readily soluble in water; ferric chloride test blue-green, Marquis' reagent red-violet, indistinguishable from that of morphine.

The *hydrochloride* was prepared with alcoholic HCl and purified from 95% alcohol containing HCl, granular, glassy crystals, m.p. 295–298° (evac. tube, decomp.); in water $(\alpha)_D^{20}$ +22.6° (*c*, 1.02).

Anal. Calc'd for $C_{17}H_{20}ClNO_3$: Cl, 11.0. Found: Cl, 10.5.

The salt tends to lose hydrogen chloride, and after two crystallizations from alcohol had the approximate composition $B_2 \cdot HCl$ (calc'd: C, 67.2; H, 6.66. Found: C, 68.2; H, 6.54); $(\alpha)_D^{20}$ +19.7° (water, *c*, 1.06).

Conversion of 6-acetylneomorphine to dihydromorphine. 6-Acetylneomorphine in 0.2 *N* HCl with platinum oxide absorbed the calculated amount of hydrogen in 40 min. Treatment with sodium carbonate precipitated the base crystalline; from alcohol, glassy needles of *6-acetyldihydromorphine*, m.p. 245° (evac. tube); $(\alpha)_D^{20}$ −117° (95% alcohol, *c*, 1.04). Authentic 6-acetyldihydromorphine, obtained by half-hydrolysis of diacetyldihydromorphine with warm aqueous hydroxylamine hydrochloride, had the m.p. 246° (evac. tube), $(\alpha)_D^{20}$ −117° (95% alcohol, *c*, 1.04). Both specimens were instantly soluble in dil. NaOH; ferric chloride reaction deep pure blue. 6-Acetyldihydromorphine hydrochloride has $(\alpha)_D^{20}$ −110.5° (water, *c*, 1.78).

Anal. Calc'd for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.04.

Found (base *ex* neopine): C, 69.2; H, 7.18.

Brief treatment of either product with hot 3 *N* NaOH gave dihydromorphine hydrate, purified from alcohol; both specimens, slow heating (2°/min.), gave an opaque melt at 135°, resolidifying and melting at 207°. With rapid heating the literature m.p. 155–157° (7) was observed. These melting point phenomena of dihydromorphine were first described by D. E. Morris (8).

SUMMARY

The degradation of neopine to β-methylmorphimethine in a single step has been verified. Neopine can be demethylated smoothly to 6-acetylneomorphine, which yields on acetylation diacetylneomorphine, or on deacetylation, neomorphine, a new isomer of morphine. By hydrogenation of 6-acetylneomorphine, followed by hydrolysis, dihydromorphine is obtained; this confirms the nature of the isomerism.

BETHESDA 14, MD.

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