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REACTIONS OF DIHYDROCODEINONE WITH HYDRAZINE AND WITH ETHYL MERCAPTAN

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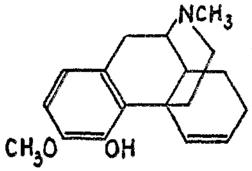
The effect upon physiological action which results from replacement of the alcoholic hydroxyl group of the morphine series by hydrogen is of theoretical and practical interest (1). The best-known derivative of this type is dihydrodesoxymorphine-D ("Desomorphine"). The enhanced analgesic action of this drug is offset in such degree by brevity of action and increased euphoric properties that medical use in this country was deemed inadvisable. There has nevertheless been some demand for experimental quantities of Desomorphine from pharmacologists and enzymologists, and a method of preparation simpler than those existing (2) would be welcome. Since Desomorphine can be obtained in nearly quantitative yield by demethylation of dihydrodesoxycodeine-D, the production of the latter compound from dihydrocodeinone (*ex* thebaine) was undertaken, and this paper summarizes our experience in applying the Wolff-Kishner reduction and the Raney nickel desulfurization to this purpose. Neither of these reactions led to Desomorphine methyl ether.[2]



I

The Wolff-Kishner reduction, Huang-Minlon modification, of dihydrocodeinone proceeded with unexpected ease at 120–130°, and was complete in less than two hours. The product appeared to be a mixture of phenolic dihydrodesoxycodeines, resembling the so-called dihydrodesoxycodeine-A, which Small and Lutz (3) showed to be a mixture of isomers B and C (Δ^6 and Δ^5). Assuming this to be so, the laborious separation of these by crystallization (3) was not attempted, and the main constituent, dihydrodesoxycodeine-C (I), was isolated directly by chromatography on alumina. Its identity was demonstrated by catalytic reduction (1 mole H_2) to tetrahydrodesoxycodeine, and by degradation to the well-characterized des-N-methyldihydrodesoxycodeine-C.

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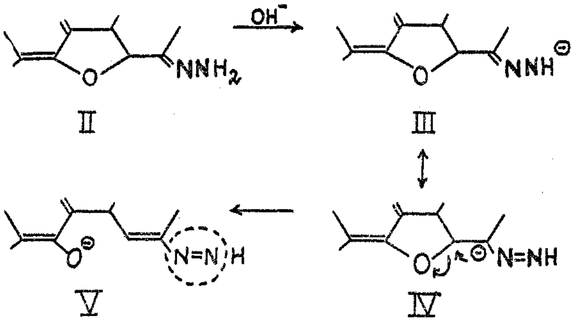
[1] Public Health Service, Federal Security Agency.

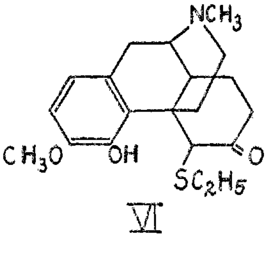
[2] Addition to proof, Oct. 10, 1952. While this work was in progress, the paper of Rapoport and Bonner, *J. Am. Chem. Soc.*, **73**, 2872 (1951) appeared, which makes dihydrodesoxycodeine-D reasonably accessible through detosylation of codeine 6-tosyl ester, and hydrogenation of the resulting Δ^7-desoxycodeine. We find that dihydrodesoxycodeine-D also is obtained directly in satisfactory yield by detosylation of dihydrocodeine 6-tosyl ester (resin, *perchlorate* m.p. 127–130°, found: S, 5.5; *acid tartrate monohydrate* m.p. 130–150° gas, found: C, 57.9; H, 5.9 anhyd.; H_2O, 2.5).

The failure of the reaction to proceed in the normal way may well be attributed to the proximity of the ether linkage at C-5 to the unsaturated group at C-6, which in numerous examples in the morphine group facilitates scission of the furan ring. The Kishner reduction or its modifications, where a hydroxyl group is located on a carbon adjacent to the carbonyl function, is known to result often in unsaturated compounds (4). It is apparent, that in dihydrocodeinone (hydrazone) the ether linkage is equivalent to an adjacent alcoholic group, and after scission appears as the 4-hydroxyl in the unsaturated end-product. A possible (5) reaction mechanism is indicated in part formulas II–V.

A second procedure which would be expected to result in the desired transformation is the Raney nickel reduction of dihydrocodeinone diethylmercaptole. The reaction of dihydrocodeinone with ethyl mercaptan, however, failed to involve the carbonyl group; according to the conditions, it took two courses, or probably two phases of a single process. If the alkaloid in concentrated hydrochloric acid (towards which it is stable) was in contact with ethyl mercaptan for one hour, the crystalline hydrochloride of dihydrothebainone was deposited.



If, on the other hand, the reaction time was limited to two minutes, an oily product could be separated. When this was warmed with dilute (2.5 *N*) hydrochloric acid, a new crystalline compound resulted, in which the 4,5-oxide ring had been opened, the 6-carbonyl retained, and a C_2H_5S— group introduced. This derivative we represent as in formula VI, in which the thioethyl group is provisionally assigned the 5-position as most reasonable. Compound VI is undoubtedly an intermediate in the sequence which results in dihydrothebainone, for it reacts with additional C_2H_5SH in concentrated HCl to give the sulfur-free ketone.



VI

The nature of VI was further demonstrated by oxime formation, by its reduction to the corresponding alcohol with lithium aluminum hydride, and by its transformation to dihydrothebainone by Raney nickel desulfurization. An attempt to prove the C-5 location of the thioethyl group by furan ring-closure analogous to that of 1,5-dibromothebainone was unsuccessful.

The thioethyl compound VI is being examined for analgesic activity by Dr. N. B. Eddy of this Institute.

EXPERIMENTAL

Melting points were taken in a Hershberg-type melting point apparatus without further correction. Some melting points taken on the Koffler hot-stage differed widely from values reported heretofore.

Dihydrodesoxycodeine-C by the Huang-Minlon procedure. Dihydrocodeinone (30 g.) was suspended in 200 ml. of diethylene glycol, to which was added 20 ml. of 85% hydrazine hydrate. Upon warming, solution was rapidly effected. After 30 min., 35 g. of 87% KOH pellets was added. On further warming, nitrogen evolution commenced at 87° and proceeded at a suitable rate at 117°. After 1 liter of gas had been liberated the temperature was raised to 130° until a total of about 2 liters had been evolved (calc'd *ca.* 2.5 liters). This required about 1 hour. After a further 40 minutes at this temperature, the reaction mixture was poured on ice, ether added, and the mixture stirred. A crystalline solid formed, m.p. 90–120°, yield 16 g. A further 5.5 g. was obtained by chloroform extraction of the mother liquors. The mother liquors gave a feeble test for alkaloidal material (Mayer's reagent).

The crystalline product gave positive tests for phenolic hydroxyl (diazotized sulfanilic acid, and $FeCl_3$) and showed the characteristic behavior with alkali which is peculiar to many of the 4-phenolic compounds of the codeine series (6). Recrystallization of the base from aqueous acetone gave material having $[\alpha]_D^{20}$ +4.0° (abs. alc., *c*, 0.6). The hydrochloride showed $[\alpha]_D^{20}$ −1.1° (H_2O, *c*, 5.3). Purification of the base through dilute hydrochloric acid and sodium hydroxide gave a product of m.p. 96–110°. The *hydrochloride* showed m.p. 158–159°.

The product was obtained in a purified state by chromatography from benzene onto Al_2O_3. The material eluted with benzene-chloroform (80:20) had m.p. 115–116° after one recrystallization, and showed $[\alpha]_D^{20}$ +5.2° (alcohol, *c*, 1.2). Dihydrodesoxycodeine-C is reported to have the m.p. 109–111°, $[\alpha]_D^{24}$ +5.6°; the hydrochloride sinters at 157–163°, melts at 241–242°, $[\alpha]_D^{27}$ +11.2° (3, 7).

The structure of this product was confirmed by conversion of the crude base to the methiodide, and degradation of this derivative to des-N-methyldihydrodesoxycodeine-C. The crude material (4.4 g.) gave 5.3 g. of *methiodide* which darkened at 230° and melted with decomposition at 241–243°; $[\alpha]_D^{20}$ +15.3° (H_2O, *c*, 1.3). Lit. (3, 7) m.p. 245–246°; $[\alpha]_D^{21.5}$ +15.4°.

The methiodide (1.25 g.) in 15 ml. of warm water was shaken with 22.6 ml. of 0.13 *N* thallous hydroxide, filtered, and the filtrate evaporated in a vacuum desiccator. The resultant solid was sublimed at 160° and 1 μ. Crystallization of the sublimate from a mixture of methanol, ethanol, and acetone gave needles of m.p. 178–179° and $[\alpha]_D^{20}$ −11° (abs. $CHCl_3$, *c*, 0.5). Lit. (3) m.p. 175–176°; $[\alpha]_D^{26}$ −13.8°.

Further confirmation of structure was obtained by reducing the original product to tetrahydrodesoxycodeine. When 2.5 g. was reduced in 25 ml. of methanol with 0.1 g. of PtO_2 catalyst, the material absorbed 213 ml. of H_2 in 1 hour, when the uptake ceased completely. The product was sublimed at 100° and 1 μ. The m.p. was 124.6–125.4°. When seeded with authentic allotropic tetrahydrodesoxycodeine of m.p. 158°, the m.p. was 158–158.5°; $[\alpha]_D^{20}$ −72.3° (benzene, *c*, 1.8). Lit. (8) m.p. 123–124° and 157–158°; $[\alpha]_D^{18}$ −72.0 and −72.3°.

Anal. Calc'd for $C_{18}H_{25}NO_2$, M.w. 287.39: C, 75.22; H, 8.77; N, 4.87.
Found: C, 75.38; H, 9.00; N, 4.93.

The action of ethyl mercaptan on dihydrocodeinone. (a) *Formation of dihydrothebainone.*

Dihydrocodeinone (15 g.) was suspended in 50 ml. of ethyl mercaptan (E.K., technical grade), cooled in an ice-bath, and slowly acidified with conc'd HCl until the vigorous reaction had subsided. At this point the balance of 50 ml. of conc'd HCl was added at one time and the mixture was stirred in a stoppered flask for 1 hour. This was shaken with ether, and three layers were formed; the middle one crystallized rapidly when stirred with alcohol-ether, giving 10.8 g. of a crystalline hydrochloride. From the other fractions a total of 2.2 g. of hydrochloride and 0.5 g. of base was obtained.

The hydrochloride was recrystallized from methanol-ether. The m.p. was 215-300°. This dihydrothebainone hydrochloride retained a small amount of methanol, removable only by intensive drying. It had $[\alpha]_D^{20}$ −52.2° (H_2O, *c*, 1.0); lit., $[\alpha]_D^{20}$ −50.7°.

Anal. Calc'd for $C_{18}H_{23}NO_3 \cdot HCl$, M.w. 337.83: C, 63.99; H, 7.16.

Found: C, 63.76; H, 7.10.

The base liberated from the hydrochloride melted at 127-135°, and could not be purified easily by crystallization, as has been previously observed.[3] However, the perchlorate proved to be very suitable for this purpose. When 15 g. of authentic dihydrothebainone was dissolved in 150 ml. of hot alcohol, cooled, and rapidly treated with 5.4 ml. of 60% perchloric acid, and the mixture chilled, 12.9 g. of crystalline perchlorate was obtained, which had m.p. 238-239°, $[\alpha]_D^{20}$ −45.5° (H_2O, *c*, 1.0).

Anal. Calc'd for $C_{18}H_{24}ClNO_7$, M.w. 401.84: C, 53.80; H, 6.02.

Found: C, 53.89; H, 6.20.

When our reaction product was similarly treated, an identical perchlorate was obtained; m.p. 238.5-239.5°; $[\alpha]_D^{20}$ −45.5° (H_2O, *c*, 1.0).

Anal. Found: C, 54.15; H, 5.96.

The base, liberated from the perchlorate had m.p. 139-143°. The rotation of a sample of base not purified through the perchlorate, which showed m.p. 139-146°, was $[\alpha]_D^{20}$ −70.7° (alc., *c*, 1.0). Lit. m.p. 138-143°; $[\alpha]_D^{18}$ −72.5° (9).

(b) *Formation of ethylthiodihydrothebainone* (VI). Dihydrocodeinone (10 g.) was suspended in 30 ml. of ethyl mercaptan and acidified with 6 ml. of conc'd HCl as in part (a), and the reaction continued for only two minutes. After evaporation to dryness at the water pump, the residue was warmed on the steam-bath for 30 min. with 2.5 *N* HCl. Basification with aqueous K_2CO_3 gave a crystalline solid, 6.0 g., m.p. 159-164°. Two recrystallizations from aqueous alcohol gave 5 g. of VI, m.p. 169-171.5°; $[\alpha]_D^{20}$ +3.7° (abs. alc., *c*, 1.0). It was sublimed, and recrystallized from aqueous alcohol, m.p. 170.5-171.5°; soluble in dilute NaOH, green ferric chloride test.

Anal. Calc'd for $C_{20}H_{27}NO_3S$, M.w. 361.49: C, 66.45; H, 7.53; N, 3.88; S, 8.87.

Found: C, 66.46; H, 7.63; N, 3.91; S, 7.64.

With this compound the usual sodium fusion test for sulfur was not satisfactory, and the quantitative analysis could not be improved.

Refluxing VI with hydroxylamine hydrochloride in alcohol for 10 min. gave VI oxime hydrochloride, m.p. 215-217°; $[\alpha]_D^{20}$ +5.2° (H_2O, *c*, 1.0). The oxime hydrochloride was very hygroscopic, and was dried at 100° for 5 hours prior to analysis.

Anal. Calc'd for $C_{20}H_{29}ClN_2O_3S$, M.w. 412.97: C, 58.16; H, 7.08; S, 7.76.

Found: C, 57.83; H, 6.78; S, 7.85.

The *oxime base* had m.p. 253-254° and $[\alpha]_D^{20}$ +2.8° (10% acetic acid, *c*, 0.5).

Anal. Calc'd for $C_{20}H_{28}N_2O_3S$, M.w. 376.50: C, 63.80; H, 7.50; S, 8.52.

Found: C, 63.65; H, 7.34; S, 8.38.

Lithium aluminum hydride reduction of VI. 5(?)-Ethylthiodihydrothebainol. One centimole of VI in ether was reduced with 0.01 mole of $LiAlH_4$ at room temperature for 15 min.

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[3] In the purification by repeated crystallization from alcohol of two kilograms of dihydrothebainone (*ex* thebaine, by hydrogenation) it was found by one of us (L. F. S., 1937) that the best fractions sintered at 137°, melted at 143-144°, evolved gas at 151°. The varying melting points in the literature testify to this difficulty. Schöpf and Winterhalder [*Ann.*, **452**, 232 (1927)] used the oxime for characterization.

At the end of this time the Michler's ketone test was positive. After decomposing with ice, the product was extracted with chloroform. The resultant carbinol weighed 3.5 g. It was recrystallized from acetone, m.p. 180–182°. The product gave a good ferric chloride test for a phenol, and was easily soluble in dilute NaOH; $[\alpha]_D^{20}$ −68° (95% alc., *c*, 1.0).

Anal. Calc'd for $C_{20}H_{29}NO_3S$, M.w. 363.50: C, 66.08; H, 8.04; S, 8.82.
Found: C, 65.98; H, 8.12; S, 8.71.

The perchlorate was prepared by adding aqueous perchloric acid to a solution of the base in aqueous HCl. After recrystallization from aqueous alcohol, the material crystallized as diamond-shaped plates, sintering at 142–144°, gas evolution at 165°. The salt was extremely hygroscopic and for analysis, was dried at 80° *in vacuo*; $[\alpha]_D^{20}$ −41.9° (alc., *c*, 1.3).

Anal. Calc'd for $C_{20}H_{30}ClNO_7S$, M.w. 463.97: C, 51.77; H, 6.52; S, 6.91.
Found: C, 51.79; H, 6.80; S, 6.53.

Raney nickel desulfurization of VI. Two grams of VI in about 125 ml. of ethanol was refluxed with a large excess of Raney nickel for 4 hours, using a magnetic stirrer to reduce bumping. The resultant dihydrothebainone was converted to the perchlorate, yield 1.4 g., m.p. 236–237°, $[\alpha]_D^{20}$ −45.7° (H_2O, *c*, 1.0). The dihydrothebainone base liberated from the perchlorate had m.p. 135–136°, and after recrystallization from acetone and then alcohol, had m.p. 135–138° and $[\alpha]_D^{20}$ −74° (alc., *c*, 1.0).

Treatment of VI with KOH. One gram of VI in 25 ml. of ethanol and 1 g. of solid KOH were refluxed together on the steam-bath for several hours. The product proved to be unaltered VI, having m.p. 173.2–173.4° and $[\alpha]_D^{20}$ +3° (abs. alc., *c*, 1.0).

Reduction of VI by ethyl mercaptan. When a mixture of 150 mg. of VI, 0.5 ml. of C_2H_5SH, and 1 ml. of conc'd hydrochloric acid was stirred for 1 hour, and evaporated at water-pump vacuum, a gum was obtained, which could be crystallized by the addition of ethanol.

A sample of the base obtained from this material was crystallized by evaporating an ether solution, and proved to be dihydrothebainone; m.p. 140–145°, authentic material m.p. 139–144°, mixture m.p. 138–143°. The *perchlorate*, from alcohol, had m.p. 238–239°.

Acknowledgment. For the microanalyses, we are indebted to W. C. Alford, Mary Jean Barnett, Paula M. Parisius, and Evelyn Peake, of the Analytical Laboratory of these Institutes.

SUMMARY

Dihydrocodeinone reacts with hydrazine in the Wolff-Kishner reaction to give mainly dihydrodesoxycodeine-C.

Dihydrocodeinone with ethyl mercaptan forms initially a phenolic thioethyl ketone, which apparently reacts with excess mercaptan to yield dihydrothebainone.

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