[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Oxidation of Acetyldihydrocodeine: N-Formyldihydronorcodeine

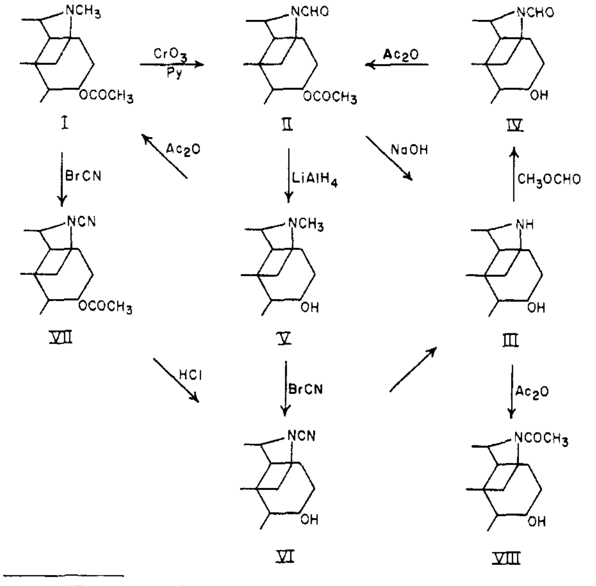
T. D. PERRINE AND LYNDON F. SMALL

Received September 26, 1955

The oxidation of 6-acetyldihydrocodeine with chromic anhydride in pyridine converts the N-methyl compound to a non basic N-formyl derivative. The interconversion with the dihydronorcodeine series is demonstrated.

The oxidation of codeine or dihydrocodeine with chromic acid under specific conditions leads to the corresponding 10-hydroxy derivatives,[1] whose structures were recently proved by Rapoport and Stevenson.[2] Although Rapoport and Stevenson improved the yield of these elusive substances, the preparation of the 10-hydroxycodeine types in quantity remains a tedious task.

In an attempt to find a better route to 10-hydroxydihydrocodeine, the action of chromic anhydride in pyridine (Poos, *et al.*)[3] on 6-acetyldihydrocodeine was investigated. We were unable to isolate any 10-hydroxylated material from this reaction; the only homogeneous product was a non-basic, nitrogen-containing crystalline substance (10-30% yield) which proved to be N-formyl-6-acetyldihydronorcodeine (II). This appears to be the first such direct oxidation of the N-methyl group of the morphine series, and suggests an analogous intermediate step in the transformation of codeine-N-oxide to norcodeine with potassium chromate.[4]



Proof of structure of the new N-formyl derivative (II) was obtained both by synthesis and by partial degradation. The known[5] dihydronorcodeine (III), with methyl formate, gave N-formyldihydronorcodeine (IV), which was acetylated smoothly to yield II, identical in all respects with the material from the oxidation. The formamide (II) shows in the infrared spectrum a strong C=O peak at 1740 cm^{-1}, and an amide peak at 1656 cm^{-1}. There is no hydroxyl peak in the 3584 cm^{-1} region, but a rather broad band at about 3400 cm^{-1}.

Simultaneous reduction of the two acyl groups of N-formyl-6-acetyldihydronorcodeine with lithium aluminum hydride gave dihydrocodeine (V), and alkaline hydrolysis alone resulted in dihydronorcodeine (III).

The dihydronorcodeine required for the synthesis of II was prepared both from 6-acetyldihydrocodeine (I), and from dihydrocodeine (V) itself; whereas von Braun observed that it was necessary to protect or inactivate the 6-hydroxyl group of codeine in the reaction with cyanogen bromide, this is not necessary with dihydrocodeine. The N-cyanodihydronorcodeine (VI) specimens obtained by the alternative methods were identical, and showed m.p. 232.5-234°, in contrast to m.p. 213-214° previously reported.[5] The infrared spectrum showed a hydroxyl peak at 3584 cm^{-1}, and for the N-cyano group a very strong sharp peak at 2200 cm^{-1}.

Treatment of dihydronorcodeine (III) with one mole of acetic anhydride in pyridine gave N-acetyldihydronorcodeine (VIII) (negligible acetylation of the hydroxyl group), which had an amide peak at 1626 cm^{-1} and a hydroxyl peak at 3571 cm^{-1} in the infrared.

Acknowledgment. The microanalytical and optical data are from the Institute's analytical laboratory under the direction of Dr. W. C. Alford.

EXPERIMENTAL

All melting points were taken on the Koffler block, and infrared spectra were determined in absolute chloroform.

N-Formyl-6-acetyldihydronorcodeine (II). *a. By oxidation of 6-acetyldihydrocodeine* (I). A solution of 3.5 g. of I in 250 ml. of anhydrous pyridine with 2.0 g. of CrO_3 was stirred for 24 hours at room temperature. After filtration, 250 ml. of anhydrous ether was added, the precipitate was removed, and the filtrate was concentrated to dryness under diminished pressure. The residue was dissolved in chloroform, the solution extracted with dilute HCl, and the acid solution

---

(1) Knorr and Schneider, *Ber.*, **39**, 1414 (1906).

(2) Rapoport and Stevenson, *J. Am. Chem. Soc.*, **76**, 1796 (1954); see also Rapoport and Masamune, *J. Am. Chem. Soc.*, **77**, 4330 (1955).

(3) Poos, Arth, Beyler, and Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953); Holloway, Cohen, and Westheimer, *J. Am. Chem. Soc.*, **73**, 66 (1951).

(4) Diels and Fischer, *Ber.*, **47**, 2043 (1914); **49**, 1721 (1916); Scheuer, Kimoto, and Ohinata, *J. Am. Chem. Soc.*, **75**, 3029 (1953).

(5) von Braun, *Ber.*, **47**, 2312 (1914).

extracted twice with chloroform. From the combined chloroform was obtained 0.3 g. of crude II (in one run, not duplicated, using 6.0 g. of CrO_3, the yield was 1.0 g., pure). This was purified by high-vacuum sublimation (180°) and crystallization from alcohol, then acetone; m.p. 217–218°, $[\alpha]^{20}_{D}$ −212° (U.S.P. $CHCl_3$, *c*, 1.0).

Anal. Calc'd for $C_{20}H_{23}NO_5$ (357.39): C, 67.2; H, 6.49. Found: C, 67.3; H, 6.63.

b. From dihydronorcodeine (III). A suspension of 1.0 g. of dihydronorcodeine[5] in a large excess of methyl formate was boiled under reflux for 16 hours, the solvent was evaporated, and the residue was recrystallized from ethanol, yield nearly quantitative. After sublimation at 200°, 10^{-4} mm., the N-formyldihydronorcodeine showed m.p. 256–257°, $[\alpha]^{20}_{D}$ −190° (U.S.P. $CHCl_3$, *c*, 1.0).

Anal. Calc'd for $C_{18}H_{21}NO_4$ (315.36): C, 68.6; H, 6.71; N, 4.43. Found: C, 68.8; H, 6.75; N, 4.35.

Acetylation was accomplished by refluxing with 10 parts of acetic anhydride for 5 min. N-Formyl-6-acetyldihydronorcodeine crystallized on cooling, and was purified from acetone; m.p. 217–218°, $[\alpha]^{20}_{D}$ −212° (U.S.P. $CHCl_3$, *c*, 1.0). This did not depress the m.p. of a sample prepared by method "*a*," and the IR spectra were identical.

Anal. Found: C, 67.5; H, 6.50.

Reduction of N-formyl-6-acetyldihydronorcodeine (II). To a solution of II in tetrahydrofuran was added an excess of solid lithium aluminum hydride. After one hour the mixture was treated with water, and the ether-soluble material was sublimed at 80°, 10^{-4} mm., and recrystallized from ether. The m.p. and mixture m.p. with authentic dihydrocodeine was 110–112° (lit. m.p. 112–113°); the bitartrate trihydrate had the m.p. 189–193°, authentic material 186–192°.

Hydrolysis of II by refluxing with 2.5 *N* NaOH for one hour gave a basic product of m.p. 198–201°; for authentic dihydronorcodeine (III), m.p. 201–201.5°.

N-Cyanodihydronorcodeine (VI) *and N-cyano-6-acetyldihydronorcodeine* (VII). Reaction of cyanogen bromide with dihydrocodeine, by the method of von Braun[5] gave N-cyanodihydronorcodeine (VI) of m.p. 234–236° (cap. tube m.p. corr. 231–232° with darkening). The parallel reaction with acetyldihydrocodeine (I) gave N-cyano-6-acetyldihydronorcodeine (VII) of m.p. 232–233°; in mixture these melted at 190–200°. Hydrolysis of the acetyl group of VII gave the hydroxy compound VI above, no depression in mixture m.p. N-Cyanodihydronorcodeine (VI) was purified by crystallization from ethanol and vacuum sublimation, and showed $[\alpha]^{20}_{D}$ −176° (U.S.P. $CHCl_3$, *c*, 1.1). The yield of VI m.p. 230–233° from V was 73%.

Anal. Calc'd for $C_{18}H_{20}N_2O_3$ (312.36): C, 69.2; H, 6.45; N, 8.97. Found: C, 69.0; H, 6.57; N, 9.14.

Acetylation of dihydronorcodeine (III). A suspension of 0.5 g. of III in 8 ml. of dry pyridine with 0.2 ml. of acetic anhydride stood for two hours, was poured onto ice, and separated into basic (<0.1 g.) and non-basic material. The latter, N-acetyldihydronorcodeine (VIII) was crystallized from ethanol and sublimed at 190°, 10^{-4} mm.; m.p. 197–198°, $[\alpha]^{20}_{D}$ −214° (U.S.P. $CHCl_3$, *c*, 1.0).

Anal. Calc'd for $C_{19}H_{23}NO_4$ (329.38): C, 69.3; H, 7.04; N, 4.25. Found: C, 69.4; H, 6.97; N, 4.35.

BETHESDA 14, MARYLAND