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THE MANNICH REACTION WITH DIHYDROCODEINONE

HENRY RAPOPORT[1] AND LYNDON SMALL

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The outstanding pharmacological advantages (1) of methyldihydromorphinone (Metopon) (2) over other drugs in the morphine series has stimulated interest in a more practical synthesis of this compound and in nuclear substituted morphine derivatives generally (3). As a promising method for possibly accomplishing both these objectives, the Mannich reaction with dihydro ketones in the codeine series was selected for investigation. If the reaction proceeded normally, dialkylaminomethyl ketones, a new type of morphine derivative, should result, and these might then be converted to the methyl ketones.

When dihydrocodeinone (I) was subjected to the Mannich reaction with dimethylamine hydrochloride and formaldehyde according to the modification of Fry (4), reaction took place as evidenced by the inability to recover any starting material; the crystalline product (about 40% yield) seemed to be a mixture, which could apparently be separated by laborious fractionation from methanol into a low-melting (174°) and a high-melting (247°) portion. These are shown below to be dimorphic forms of the same base.

If condensation had taken place at the reactive 1-position as well as with the expected α-hydrogen in the 7-position, the resulting complexity of the reaction product might explain its resistance to purification. Hence, the reaction was next studied with a compound in which the 1-position was blocked.

From 1-bromodihydrocodeinone (II) (5), dimethylamine hydrochloride, and formaldehyde, a crystalline product was isolated in 90% yield. However, this was not the expected dimethylaminomethyl ketone, since the substitution of diethylamine for dimethylamine gave the same product. The failure of this compound to sublime indicated it might be dimolecular, and analysis and molecular weight determinations strongly supported the assignment of a methylenebis-(1-bromodihydrocodeinone) structure. Juncture through the aromatic ring was made improbable by the recovery of dihydrodesoxycodeine-D (V) (6) unchanged under the conditions of the reaction, and therefore 7,7′-methylenebis-(1-bromodihydrocodeinone)[2] (III) was designated as the structure of the reaction product.

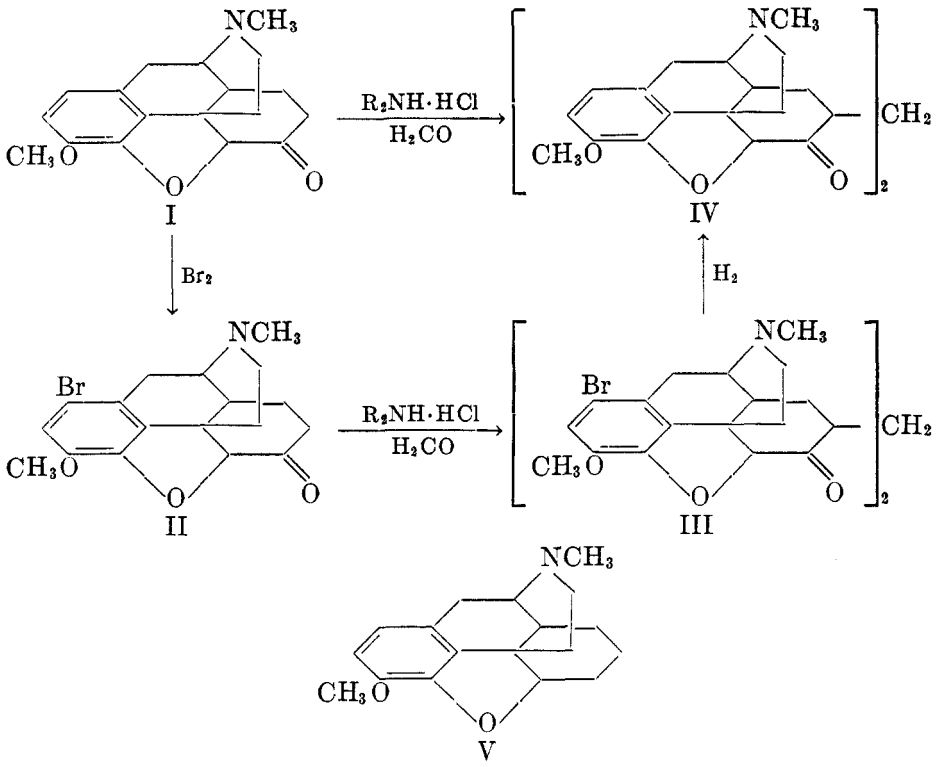
The formation in high yield of a methylenebis compound by the above reaction instead of the expected Mannich base was investigated further by replacing the dimethylamine with trimethylamine. No reaction took place in the presence of the tertiary amine, indicating that the complex formation between amine

[1] National Research Fellow in Chemistry, 1945–1946, at the National Institute of Health, when this work started. Present address, Department of Chemistry, University of California, Berkeley, California.

[2] That the structure might be 5,5′- or 5,7′- is recognized, but the 7,7′-linkage was selected as being the most probable because of its much less hindered nature.

and formaldehyde, which occurred with the secondary amine but not with the tertiary, was a necessary condition for reaction.

Debromination of (III) by catalytic hydrogenation using a palladous chloride-gum arabic catalyst (5) proceeded slowly to give a 76% yield of the des-bromo compound, 7,7′-methylenebisdihydrocodeinone. This des-bromo compound should be identical with the reaction product from dihydrocodeinone, since the unreactivity of dihydrodesoxycodeine-D seems to eliminate the 1-position as a possible site of reaction.



Hence, the condensation with dihydrocodeinone was re-examined, and by using the des-bromo compound prepared by hydrogenolysis as seed, a 55% yield of 7,7′-methylenebisdihydrocodeinone (IV) was obtained. It crystallized in dimorphic forms, m.p. 174–175° and 247–248°, either of which was obtainable directly from acetone solution. The high-melting form could also be obtained by slowly heating the low-melting form above its melting point or by heating it at 150° in a vacuum. Both forms and the compound prepared by reductive debromination of the bromo analog were identical as shown by specific rotations and mixed melting points.

The methylenebis structure of (IV) was further substantiated by analysis, molecular weight determinations, and formation of a monosemicarbazone. A dihydrochloride and dimethiodide were prepared, and reaction took place with

hydroxylamine but the oxime could not be isolated pure. Attempted demethylation to the morphine analog gave only resinous products.

Thus a new type of morphine derivative has been synthesized which may be considered as an analog of methyldihydrocodeinone. Other dimolecular morphine derivatives are known, but they result from either dimolecular oxidation (7) or reduction (8), and nothing is known of the structure of the reported dicodeylmethane (9).

EXPERIMENTAL

All melting points are corrected, and all above 200° were taken in evacuated tubes; rotations are in 95% alcohol unless otherwise specified. Microanalyses were performed by C. W. Koch of the Department of Chemistry, University of California.

7,7′-Methylenebis-(1-bromodihydrocodeinone) (III). A mixture of 1.8 g. (0.06 mole) of paraformaldehyde, 4.8 g. (0.059 mole) of dimethylamine hydrochloride, 25 ml. of benzene, 15 ml. of nitrobenzene, and 0.05 ml. of concentrated hydrochloric acid was placed in a two-necked flask fitted with a mechanical stirrer and reflux condenser (protected from moisture with a calcium chloride tube). After stirring and refluxing (bath temp. 110°) for 30 min. during which most of the paraformaldehyde went into solution, the sublimed paraformaldehyde was scraped from the condenser (in the shorter neck of the flask) back into the reaction mixture, and 20 g. (0.053 mole) of 1-bromodihydrocodeinone (II) (1) was added. Stirring and refluxing (bath temp. 120–125°) were continued for 1.5 hours with a water-trap present during the last hour (total water collected, 0.8 ml.), and then the solution was poured into 250 ml. of 2% acetic acid. The organic layer was separated, extracted with two 50-ml. portions of 2% acetic acid, and the combined aqueous extracts, after washing with ether, were basified with concentrated ammonia and extracted thoroughly with four 100-ml. portions of ethyl acetate. The residue after evaporation under reduced pressure of the combined, dried ethyl acetate extracts was digested with 250 ml. of ethanol and on cooling gave 11.7 g. of crystals, m.p. 244–250°. Concentration of the mother liquor to 75 ml. yielded another 4.6 g., m.p. 240–250°, and an additional 2.1 g. of material, m.p. 215–225°, was obtained by further concentration to 50 ml.; total, 18.4 g. of crude, 90%. It is insoluble in ether and methanol, slightly soluble in ethanol and acetone, and very easily soluble in dioxane and benzene. It does not sublime up to 200°/0.05 mm. and was best purified by dissolving in excess acetone, concentrating the solution until crystals appeared, and then cooling. In this way, 75% of the crude product was obtained as material melting from 272–274°. Repeated crystallization from acetone raised the m.p. to 274–275°, $[\alpha]_D^{20}$ −287° (dioxane, c = 0.90).

Anal. Calc'd for $C_{37}H_{40}Br_2N_2O_6$: C, 57.82; H, 5.25; N, 3.65; M.W., 768.
Found: C, 57.90; H, 5.37; N, 3.54; M.W., 747 (cryoscopic in benzene).

The *dihydrochloride* was prepared with 0.75 *N* hydrochloric acid from which it also was recrystallized. It is extremely soluble in water and abs. ethanol, and final purification was accomplished by washing the crystals with a small amount of cold abs. ethanol followed by a mixture of abs. ethanol-ether (1:1) and then abs. ether. The thoroughly dried material was very hygroscopic and absorbed three moles of water when exposed to the atmosphere; the hydrate had m.p. 271-273°, $[\alpha]_D^{20}$ −243° (alcohol, c = 1.07).

Anal. Calc'd for $C_{37}H_{42}Br_2Cl_2N_2O_6 + 3H_2O$: C, 49.62; H, 5.40; H_2O, 6.04.
Found: C, 49.94; H, 5.26; H_2O, 6.67.

When 1-bromodihydrocodeinone hydrochloride was substituted for the free base in the above condensation, it was necessary to double the total volume of solvent and increase the nitrobenzene-benzene ratio to 1:1 in order to maintain stirring, as a gummy solid separated toward the end of the reaction. All the other conditions were kept the same, and a 61% yield of 7,7′-methylenebis-(1-bromodihydrocodeinone) resulted.

The same methylenebis compound was obtained in 48% yield when diethylamine hydro-

chloride was substituted for dimethylamine hydrochloride in the above reaction with 1-bromodihydrocodeinone. However, when trimethylamine hydrochloride was used, no reaction appeared to occur. The paraformaldehyde remained completely undissolved after the initial 30-min. reflux period, and sublimation at 150°/0.3 mm. of the residue after evaporation of the ethyl acetate gave 81% of unchanged starting material as crystalline sublimate. From the small amount of slightly brown residue no 7,7'-methylenebis-(1-bromodihydrocodeinone) could be isolated.

Attempted condensation with dihydrodesoxycodeine-D (V). Using the procedure given above, a condensation was carried out with 3.0 g. (0.0105 mole) of dihydrodesoxycodeine-D (6). The residue after evaporation of the ethyl acetate was sublimed at 95°/0.2 mm. and 2.7 g., 90%, of the starting material was recovered as crystalline sublimate, m.p. 104–106°.

Hydrogenolysis of 7,7'-methylenebis-(1-bromodihydrocodeinone). Hydrogenolysis of 1.0 g. (0.0013 mole) of 7,7'-methylenebis-(1-bromodihydrocodeinone) in 25 ml. of 2 *N* acetic acid with 1.5 g. of sodium acetate, 1 ml. of 1% gum arabic solution, and 3 ml. of a 1% palladous chloride solution proceeded slowly and ceased completely after fifteen hours, with the absorption of 2.3 moles of hydrogen. The solution was warmed on the steam-bath for 10 min. after the addition of decolorizing carbon and 25 ml. of water, and filtration gave a clear filtrate which was basified with concentrated ammonia. The resulting precipitate, after copious washing, was free of halogen as evidenced by a negative Beilstein test, and crystallization from acetone gave 0.6 g. (76%) of the des-bromo compound, 7,7'-methylenebisdihydrocodeinone (IV). It melted from 169–174° and on slow, continued heating above its melting point completely resolidified by 200° and melted sharply at 246–247°, $[\alpha]_D^{20}$ −322° (dioxane, c = 0.94). Conversion to the high-melting form could also be accomplished by heating at 150° for 10 hours in a vacuum.

7,7'-Methylenebisdihydrocodeinone (IV). The condensation was carried out as described above for the bromo analog, using 2.8 g. (0.092 mole) of paraformaldehyde, 7.5 g. (0.092 mole) of dimethylamine hydrochloride, 0.05 ml. of concentrated hydrochloric acid, 50 ml. of benzene, 25 ml. of nitrobenzene, and 25 g. (0.084 mole) of dihydrocodeinone (I); 1.6 ml. of water was collected. The residue after evaporation of the ethyl acetate was dissolved in 75 ml. of acetone and seeded with the crystals obtained by hydrogenolysis of the bromo analog. Cooling gave 10 g. of crystalline material, m.p. 165–168°, and concentration of the mother liquor to 25 ml. resulted in an additional 4 g., m.p. 160–165°, total, 14 g., 55%. Seeding with either the low-melting form or the high-melting form of the des-bromo compound gave crystals of only the low-melting form. By heating the low-melting form at 150° for 10 hours in a vacuum or by concentrating the acetone solution until considerable solid had separated and then cooling slowly, the high-melting form, m.p. 247–248°, could be obtained. A pure sample of the low-melting form was prepared by several crystallizations from acetone and melted at 174–175°. It showed no loss in weight when heated at 150° in a vacuum, had $[\alpha]_D^{29}$ −314° (dioxane, c = 0.943), and did not depress the m.p. of material melting at 247–248°. Pure high-melting crystals were obtained by several crystallizations from acetone as described above, m.p. 247–248°, $[\alpha]_D^{20}$ −318° (dioxane, c = 1.064); admixture with material from the hydrogenolysis of the bromo analog caused no depression in m.p. It does not sublime up to 250°/0.1 mm.

Anal. Calc'd for $C_{37}H_{42}N_2O_6$: C, 72.76; H, 6.93; N, 4.59; M.W., 610; Neut. Equiv., 305.
Found: C, 72.99; H, 6.76; N, 4.67; M.W., 581 (cryoscopic in benzene); Neut. Equiv., 314.

The *dihydrochloride*, prepared with 3 *N* hydrochloric acid, was recrystallized from 1 *N* hydrochloric acid, and excess acid was removed by washing with a small portion of cold abs. ethanol, a mixture of abs. ethanol-ether (1:1), and then repeated with abs. ether. After drying in a vacuum at 100° it melted at 278–280° with decomp. and on exposure to air avidly absorbed 5 moles of water; the hydrate had $[\alpha]_D^{20}$ −252° (alcohol, c = 0.96).

Anal. Calc'd for $C_{37}H_{44}Cl_2N_2O_6 + 5H_2O$: C, 57.43; H, 7.03.
Found: C, 57.46; H, 6.91.

The *dimethiodide* was prepared in and purified from methanol. After thorough drying, it absorbed 2 moles of water on exposure to the air, m.p. 270–272° with decomp., $[\alpha]_D^{20}$ −177° (75% alcohol, c = 0.92).

Anal. Calc'd for $C_{39}H_{48}I_2N_2O_6 + 2H_2O$: C, 50.33; H, 5.63; H_2O, 3.86.
Found: C, 49.82; H, 5.47; H_2O, 4.28.

The *monosemicarbazone* was prepared by refluxing 0.75 g. of 7,7′-methylenebisdihydrocodeinone, 2.0 g. of semicarbazide hydrochloride, and 1 ml. of pyridine in 25 ml. of methanol for one hour. After standing overnight, the solution was evaporated under reduced pressure and the residue taken up in 50 ml. of water. Basifying with concentrated ammonia gave a precipitate which was recrystallized by dissolving in ethanol and adding water until the warm solution became cloudy. Cooling gave crystals, m.p. 218–220° with preliminary softening, $[\alpha]_D^{20}$ −383° (alcohol, c = 0.512).

Anal. Calc'd for $C_{38}H_{45}N_5O_6$: C, 68.34; H, 6.79; N, 10.49.
Found: C, 67.81; H, 6.76; N, 9.83.

SUMMARY

The Mannich reaction with dihydrocodeinone and 1-bromodihydrocodeinone is found to yield 7,7′-methylenebis compounds instead of the usual dialkylaminomethyl derivatives.

BETHESDA, MD.
BERKELEY, CALIFORNIA

REFERENCES

(1) SMALL, EDDY, MOSETTIG, AND HIMMELSBACH, "Studies on Drug Addiction," Suppl. 138 Public Health Reports (1938); HIMMELSBACH, *J. Pharmacol.*, **67**, 239 (1939). Announcement, *J. Am. Med. Assoc.*, **134**, 291 (1947).
(2) SMALL, FITCH, AND SMITH, *J. Am. Chem. Soc.*, **58**, 1457 (1936); SMALL, TURNBULL, AND FITCH, *J. Org. Chem.*, **3**, 204 (1938).
(3) SMALL AND RAPOPORT, *J. Org. Chem.*, **12**, 284 (1947).
(4) FRY, *J. Org. Chem.*, **10**, 259 (1945).
(5) SCHÖPF AND PFEIFER, *Ann.*, **483**, 157 (1930).
(6) SMALL AND MORRIS, *J. Am. Chem. Soc.*, **55**, 2874 (1933).
(7) SMALL AND LUTZ, "Chemistry of the Opium Alkaloids", Suppl. 103 Public Health Reports, p. 170; SMALL AND FARIS, *J. Am. Chem. Soc.*, **56**, 1930 (1934).
(8) MOSETTIG, COHEN, AND SMALL, *J. Am. Chem. Soc.*, **54**, 793 (1932); GOTO AND OGAWA, *Ann.*, **511**, 202 (1934).
(9) German Patent 89,963 (1896); *Frdl.*, **4**, 1246 (1894–1897).