[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ENDO PRODUCTS, INC.]

Derivatives of Morphine. I. 14-Hydroxydihydromorphinone

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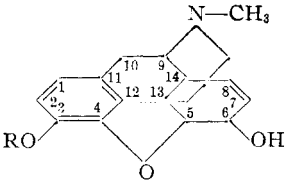
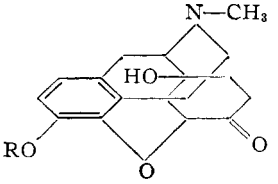
14-Hydroxydihydrocodeinone with concentrated hydrobromic acid yields 14-hydroxydihydromorphinone, an analgesic considerably more potent than morphine.

It is well known that of the compounds of the morphine series, those having a free phenolic hydroxyl in position 3 (*e.g.*, morphine itself, I) are much stronger analgesics than their ethers (*e.g.* codeine, II), which in general show only moderate pain-relieving action.

Among the compounds of the latter type, 14-hydroxydihydrocodeinone[2] (III) is generally considered one of the most active analgesics, with an effect considerably exceeding that of II.



I, R = H
II, R = CH_3



III, R = CH_3–
IV, R = H–

On the basis of those facts, the phenolic compound, 14-hydroxydihydromorphinone (IV), corresponding to III, could be expected to be an exceptionally potent analgesic. This compound does not appear in the chemical literature.

It has been found that IV can be obtained by short action of boiling aqueous hydrobromic acid on III. Prepared in this way, the new compound forms colorless crystals which decompose at 248–249°. The elementary analysis is in good agreement with formula IV, as are several color reactions: blue color with ferric chloride in aqueous medium, no reaction in ethanol (compound I and many related compounds show the same behavior); pink color with *m*-dinitrobenzene and alkali (presence of the group $-CO-CH_2-$).

For final proof of identity, IV was methylated with diazomethane back to III, which was identified by comparison of the free base, its hydrochloride and the oxime with authentic samples, establishing conclusively that during the treatment of III with hydrobromic acid no changes in the molecule beyond the desired demethylation take place.

Pharmacology.—In tests on animals,[3] IV (Numorphan) showed the anticipated high analgesic potency, being about 12–15 times as active as I. Preliminary results of clinical tests likewise seem to indicate a strong, protracted pain-relieving effect, both parenterally and *per os*.

Experimental

14-Hydroxydihydromorphinone.—Thirty grams of 14-hydroxy-dihydrocodeinone (III) was rapidly introduced into 300 ml. of concentrated aqueous hydrobromic acid which had been preheated to about 90°. The stirred mixture was quickly heated to 110–120° and maintained at this temperature for 20 minutes. III dissolved rapidly and the originally yellow solution turned dark brown.

Ice was added, and the *p*H of the liquid was brought to 10–11 by dropwise addition of strong alkali, keeping the temperature below about 10°. Unchanged III was removed by several extractions with chloroform; about 10–20% of it may be recovered.

The aqueous phase was chilled, made acid to congo red with dilute hydrochloric acid, and treated with charcoal. The light orange filtrate was adjusted to a *p*H of about 8.5 by dropwise addition of aqueous ammonia and extracted with 6–8 portions of chloroform, separating the layers by centrifugation because of the appearance of a small amount of solid material.

The combined chloroform extracts were dried with sodium sulfate, treated with charcoal, and evaporated *in vacuo*. The last traces of chloroform were removed by adding benzene and distilling; yield of yellowish crude material about 19 g. (60%). This impure IV was refluxed briefly with 40 ml. of benzene[4] and allowed to stand overnight. Collection yielded about 10 g. (35%) purified base.[5] Several recrystallizations from boiling ethanol, ethyl acetate or benzene gave pure IV as colorless crystals which melt to a black liquid at 248–249°[5,6] after preliminary darkening. The compound is soluble in chloroform and boiling acetone, moderately in boiling ethanol, sparingly soluble in benzene, and readily soluble in aqueous alkali.

In aqueous suspension, IV yields a beautiful blue color with ferric chloride; in ethanol, merely the yellow color of the reagent is shown. Selenium oxychloride in concentrated sulfuric acid gives a green, *m*-dinitrobenzene and alkali a pink color with IV.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.75; H, 6.36. Found: C, 67.99, 67.76; H, 6.14, 6.16.[7]

IV forms a well-crystallized, water-insoluble Reineckate; it does not yield an insoluble perchlorate (difference from III).

The hydrochloride of IV, prepared by dissolving the base in dilute hydrochloric acid (1:1) and adding excess ethanol, is well crystallized and non-hygroscopic.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot HCl \cdot H_2O$: N, 3.94; Cl, 9.97. For a dihydrate: N, 3.75; Cl, 9.49. Found: N, 3.77; Cl, 9.90.

Methylation of IV to III.—To a solution of 200 mg. of IV in 60 ml. of ether containing 1 ml. of ethanol was added excess ethereal diazomethane. The mixture was kept at room temperature overnight. Dilute acetic acid was added next, the layers were separated and the ether phase was extracted several more times with dilute acetic acid. The combined aqueous layers were treated with charcoal and made alkaline with sodium hydroxide; III crystallized out after a few seconds; m.p. 217–220°, the mixed m.p. with an authentic sample of m.p. 218–221° was 218–221°. Like authentic III, the methylated substance formed a water-insoluble, crystalline perchlorate. The hydrochloride, obtained from an alcoholic solution with ethanolic hydrochloric acid, melts with decomposition at 264–266°; the mixed m.p. with an authentic sample of m.p. 267–268° was 266.5–267.5°.

The remainder of the methylation product was converted

(1) The New York Botanical Garden, New York 58, N. Y.

(2) M. Freund and E. Speyer, *J. prakt. Chem.*, [2] **94**, 135 (1916).

(3) H. Blumberg, S. Carson and E. Stein, *Federation Proc.*, **13**, 451 (1954).

(4) This treatment with benzene is necessary in order to remove a contaminant which prevents successful recrystallization of IV. This by-product has not yet been obtained pure; its $FeCl_3$ reaction (purple in alcoholic medium, changing to green with excess reagent) resembles that of dihydrothebainone and other 4-phenols of this series.

(5) Subsequent work by Dr. Nathan Weiner of these laboratories has resulted in markedly improved yields (private communication).

(6) Melting points are not corrected.

(7) Micro-analyses by Schwarzkopf Laboratories, Woodside, N. Y.

to the oxime, which was found to melt in part around 95°; on further heating the sample resolidified and remelted at 194°.

The oxime base of III is mentioned in the literature[2] but no details are given. A sample, prepared from authentic III and recrystallized from dilute ethanol, melted in part around 95°, resolidified and remelted at 197°. Its mixture with the oxime of the methylation product of IV melted at 195–196°.

Anal. Calcd. for $C_{18}H_{22}N_2O_4$: N, 8.48. For a monohydrate: N, 8.04. Found: (sample dried *in vacuo* at 100°): N, 8.08.

For further proof of identity, the infrared spectra, in KBr discs, of the methylation product of IV, and of the oxime derived from it, were taken[8] and compared with those of authentic samples of III and its oxime. Complete agreement was found.

(8) We are indebted to Dr. S. Lieberman, Columbia University College of Physicians and Surgeons, N. Y., for permission to use the Perkin Elmer 21 spectrophotometer.

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Piptadenia Alkaloids. Indole Bases of *P. peregrina* (L.) Benth. and Related Species

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Four indole bases have been found to occur in the seeds and pods of *P. peregrina* (L.) Benth. and *P. macrocarpa* Benth. The pods contain N,N-dimethyltryptamine, and the seeds contain bufotenine, bufotenine oxide and N,N-dimethyltryptamine oxide. In addition, a 5-hydroxyindole base of unknown structure was found in *P. macrocarpa* seeds. The identification of these compounds was accomplished by isolation through paper chromatography, and comparison with authentic samples involving R_f data, ultraviolet spectra and fluorescence analysis. The synthesis of these two oxides, hitherto unknown as components of plant or animal metabolism, is described.

One of the most interesting customs of certain Indian tribes of South America and the Caribbean is the use of a ceremonial snuff inhaled through a bifurcated tube fitting the nose. The use of this snuff during the late fifteenth century was described by Ramon Pane, and a number of later writers have also described its preparation and use.[1,2] All accounts stress the power of the snuff to produce a kind of intoxication during which visions were reputed to occur; excessive doses apparently induced a violent temporary derangement. Seeds of *Piptadenia peregrina* (L.) Benth. and possibly *P. macrocarpa* Benth. were reportedly used for the preparation of the snuff, and the isolation of bufotenine from *P. peregrina* seeds of Puerto Rican origin was described recently.[3]

Further work on the indole bases of *Piptadenia* species has now been carried out. Because of current interest in the effects of 5-hydroxyindoles on the central nervous system, it was hoped that some direct means could be found to establish a connection between the suggested source of the snuff, *Piptadenia* seeds, and authentic snuff. Fortunately, the Smithsonian Institution collection includes under Cat. No. 387781 a Piaroa snuff box of relatively recent origin (1949); the box was found to contain a few milligrams of snuff, and this was used for comparison with "synthetic" laboratory snuff samples prepared in a way that corresponded as closely as possible to the descriptions of Humboldt and Spruce.[2,4] Using paper chromatography in a propanol–ammonia system, with Ehrlich's reagent as a spray, one indole area of major intensity and four additional lighter areas were found for the authentic snuff. With laboratory snuff from *peregrina* seeds of Puerto Rican origin, the area of major intensity was duplicated (bufotenine), and two additional areas were also identical in R_f value, in color of the sprayed area, and in relative intensity of the color. Two faint areas present for the South American snuff were not observed for the laboratory samples. This evidence indicates that the origin of the authentic snuff was undoubtedly *Piptadenia* seeds, although the species could not be identified with certainty.

Earlier tests on leaves, bark and seeds of *P. peregrina* indicated that organic bases were present only in the seeds. These observations were extended through examination of the seeds and seed pods of *P. peregrina*, *P. macrocarpa* and *P. paniculata* from several areas (Brazil, Florida, Puerto Rico). With the exception of *paniculata*, all seed samples gave very strong alkaloid tests, while the pods gave tests of varying strength (Table I). Preliminary experiments indicated that the indole bases, including bufotenine, were readily extractable with alcohol or with a tetrahydrofuran–chloroform–ammonia mixture and could be separated by paper chromatography for purposes of identification. A combined seed–seed pod sample of *P. macrocarpa* from Florida was chosen for detailed examination.

TABLE I

PRECIPITATION TESTS FOR ALKALOIDS

Species	Source	Seeds	Pods
P. peregrina (L.) Benth.	Puerto Rico, 1954	+++	+
P. peregrina	Puerto Rico, 1955	+++	+++
P. peregrina	Brazil, 1955	+++	+++
P. macrocarpa Benth.	Brazil, 1955	+++	+++
P. macrocarpa	Florida, 1955	+++	+
P. paniculata Benth.	Brazil, 1955	+	[a]

[a] Not received.

(1) The distribution of modern tribes following this custom is shown by J. E. Cooper in "Handbook of the South American Indian," Bureau of American Ethnology, Bulletin 143, U. S. Government Printing Office, Washington, D. C., 1949, Vol. 5, pp. 536–539.

(2) Summaries of several early accounts are in Safford, *J. Washington Acad. Sci.*, **6**, 547 (1916). Spruce's description of snuff preparation ("Notes of a Botanist on the Amazon and Andes," Ed. by A. R. Wallace, the Macmillan Co., Ltd., London, 1908, Vol. II, pp. 426–430) differs from that of Humboldt in the omission of calcined calcium carbonate.

(3) V. L. Stromberg, THIS JOURNAL, **76**, 1707 (1954).

(4) We are indebted to Dr. Herbert W. Krieger, Curator, Division of Ethnology, Smithsonian Institution, for advice and help in securing the authentic snuff sample.