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

Structures Related to Morphine. X.[1] A Position Isomer of (±)-3-Hydroxy-*N*-methylmorphinan (Racemorphan)

EVERETTE L. MAY

Received January 9, 1958

A position isomer (with respect to nitrogen attachment) of (±)-3-hydroxy-*N*-methylmorphinan (Vc), namely 1,2,3,9,-10,10a-hexahydro-6-hydroxy-11-methyl-1,4a(4*H*)-iminoethanophenanthrene (VIIc), has been synthesized. The intermediate ketophenanthrene (VIII) was formed directly from the dinitrile III with refluxing 30% hydrochloric acid. The analgesic potency of VIIc was almost twice that of the deoxy analog (VIIa) but less than 2% of the potency of Vc.

The synthesis of 1,2,3,9,10,10a-hexahydro-11-methyl-1,4a (4*H*)-iminoethanophenanthrene (VIIa) was disclosed in an earlier report.[2] Although VIIa differs structurally from *N*-methylmorphinan (Va)[3] only at the position of closure of the nitrogen ring, it is nevertheless considerably less effective than Va in raising the pain threshold in mice. It has been demonstrated that appropriate substitution of a phenolic hydroxyl (i.e. *meta* to the quaternary carbon) into such moderately active compounds as Va[4,5] and certain benzmorphans[2,6] and phenylmorphans[7] invariably increases analgesic potency and reduces acute toxicity. In order to determine the effect of similar hydroxyl substitution in a compound of a low order of potency, yet one possessing the generally recognized constitutional requirements necessary for the mediation of morphine-like analgesia, the 6-hydroxy derivative (VIIc) of VIIa has been synthesized.

The sequence of reactions used in the synthesis of VIIc was essentially the same as that employed for the deoxy compound (VIIa). The Knoevenagel reaction of 5-(*m*-methoxyphenyl)-2-methyl-9-oxomorphan (I) and malononitrile proceeded normally to give the unsaturated dinitrile (II) in 84% yield. Hydrogenation (platinum oxide) of II was not chemically selective; optimal hydrogen absorption appeared to be 1.1 molecular equivalents and gave a 46% yield of the stereochemically pure, saturated dinitrile (III). However, in contrast to experience in this laboratory with the deoxy series[2] where the dinitrile was hydrolyzed and decarboxylated to the corresponding acetic acid derivative, III was cyclized in 35% yield to the ketophenanthrene (VIII) by refluxing 25–30% hydrochloric acid. The relative ease with which this cyclization[8] takes place may of course be ascribed to the influence of the favorably located, electron-donating, methoxyl group. In addition to VIII a small amount of crystalline phenolic material was isolated. Provisionally it has been assigned the structure IV on the basis of its infrared spectrum (carbonyl absorption at 6.11 μ comparable to that of *p*-hydroxyacetophenone),[9] its ultraviolet spectral pattern, and its elemental analysis. The remainder of the material (intractable) from this experiment was soluble in aqueous sodium hydroxide and gave a rather nondescript infrared diagram showing hydroxyl but little or no carboxyl absorption. Wolff-Kishner reduction of VIII produced VIIb which was converted to the phenol (VIIc) with boiling 48% hydrobromic acid.

Alkali treatment of the methiodide of VIIb and hydrogenation of the methine resulting gave 4a-(2-dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,-10a-octahydrophenanthrene (VI) identical with the product obtained similarly from (±)-3-methoxy-*N*-methylmorphinan (Vb).[4] As one would predict, more vigorous conditions had to be used to effect the alkaline cleavage of the methiodide of VIIb than were necessary for the methiodide of Vb. On the reasonable assumption that the hydrogen of the tertiary carbon (C_{10a}) is not involved in the Hofmann elimination of VIIb, rings C and B

(1) Paper IX, N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

(2) E. L. May and J. G. Murphy, *J. Org. Chem.*, **19**, 618 (1954). The name heteromorphinan has been suggested for this ring system by Dr. Nathan B. Eddy, Chief, section on analgesics of this institute. Thus VIIc would be 3-hydroxy-*N*-methylheteromorphinan in analogy with the naming of V.

(3) R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948).

(4) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

(5) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949).

(6) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

(7) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955).

(8) Presumably III first undergoes cyclization to a hydrogenated phenanthrene β-iminonitrile [*cf.* C. K. Bradsher and D. J. Beavers, *J. Org. Chem.*, **21**, 1067 (1956)] which then hydrolyzes and suffers loss of carbon dioxide.

(9) A. H. Soloway and S. L. Friess, *J. Am. Chem. Soc.*, **73**, 5000 (1951). There was also a sharp, strong band for IV at 2.89 μ. Infrared analysis of the material resulting from treatment of pure VIII with refluxing 48% hydrobromic acid for a few minutes indicated that it was composed of a mixture of VIII and IV, the former in predominance. If refluxing was continued for 20–30 min., extensive decomposition occurred.

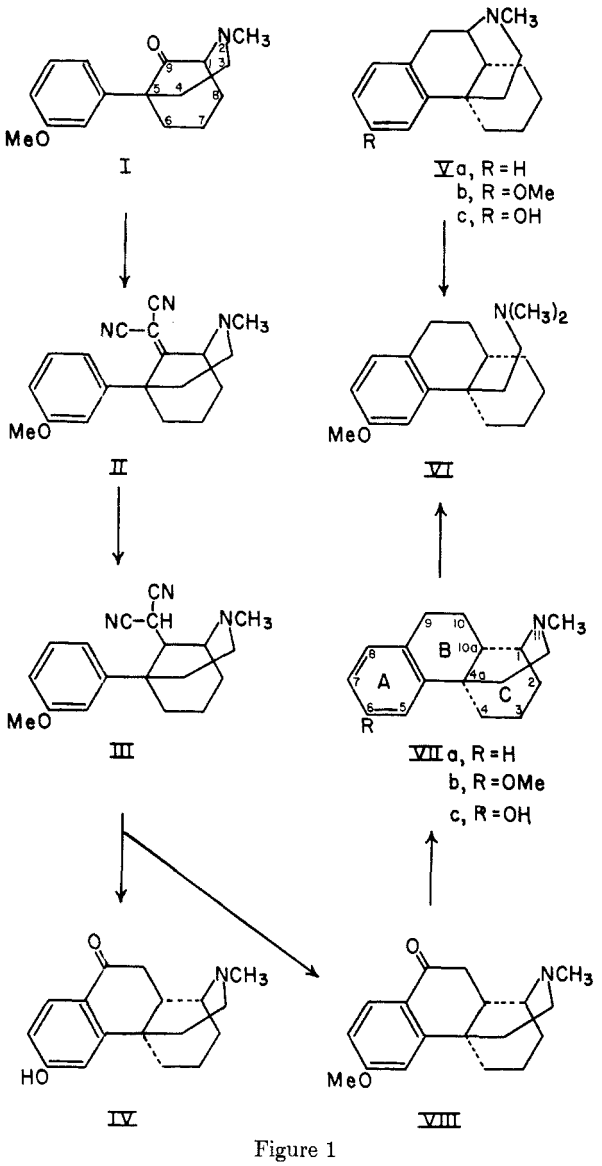


Figure 1

may be designated as cis-fused[2,10] as in the morphinans (V).[4]

The analgesic potency of VIIc was less than twice that of the parent deoxy compound (VIIa) and only 2% of that of the isomeric racemorphan (Vc) as determined in mice. Thus *m*-hydroxylation of VIIa, a compound of relatively low effectiveness, has resulted in a much smaller increase in activity than has been noted earlier for similar substitution in analogous compounds of moderate potency.[1,4,5,7,11]

EXPERIMENTAL

Microanalyses are from the institutes' service analytical laboratory under the direction of Dr. William C. Alford. Melting points were taken in a Hershberg apparatus with total-immersion thermometers. Infrared and ultraviolet spectral data were supplied by Mr. William Jones and Mrs. Ann Wright, respectively, both of this institute.

9-Dicyanomethylene-2-methyl-5-(m-methoxyphenyl)morphan (II) *hydrochloride.* The hydrochloride of I (4.0 g.)[7] was converted to the base (dilute, aqueous ammonia-ether). This base, 1.2 g. of malononitrile, 0.3 g. of ammonium acetate, 0.6 ml. of acetic acid, and 8 ml. of benzene were refluxed vigorously for 1 hr. while collecting the azeotropically distilled water. The solution was diluted to 100 ml. with ether and filtered through Super Cel. Acidification of the filtrate with hydrogen chloride gave a hygroscopic solid which was collected on a sintered glass filter and triturated with 10–12 ml. of warm acetone. Cooling overnight at −5° and filtration gave 3.9 g. (84%) of II hydrochloride, m.p. 200–210°; needles from acetone (after addition of a little ether), m.p. 208–212° (dec.).

Anal. Calcd. for $C_{19}H_{22}ClN_3O$: C, 66.36; H, 6.45. Found: C, 66.47; H, 6.69.

9-(Dicyanomethyl)-2-methyl-5-(m-methoxyphenyl)morphan (III) *hydrochloride.* A mixture of 3.9 g. of II hydrochloride, 0.3 g. of platinum oxide, and 100 ml. of methanol absorbed 1.1 molecular equivalents of hydrogen (at atmospheric pressure) during *ca.* 2 hr., when the absorption rate was fairly constant at 0.75 ml./minute. The reaction was interrupted, and the mixture was treated with a little Norit and filtered through Super Cel. Concentration of the filtrate to 7–8 ml. (water-pump vacuum), seeding, and cooling at −5° for 2–3 hours gave 1.8 g. (46%) of III hydrochloride, m.p. 244–247°. A recrystallization from methanol by addition of a little ether gave analytically pure, oblong plates, m.p. 246–248° (dec.).

Anal. Calcd. for $C_{19}H_{24}ClN_3O$: C, 65.96; H, 6.99. Found: C, 65.53; H, 6.91.

1,2,3,9,10,10a-Hexahydro-6-methoxy-11-methyl-9-oxo-1,4a-(4H)-iminoethanophenanthrene (VIII) *hydrochloride.* The hydrochloride of III (1.8 g.), 17 ml. of concentrated HCl, and 4 ml. of water were refluxed for 16 hr., the solution was evaporated to dryness (water pump), and the residue digested with boiling 1:1 alcohol-acetone. Filtration gave 0.47 g. (84%) of ammonium chloride. The filtrate was evaporated to dryness and the residue partitioned between ether and excess 10% sodium hydroxide. Distillation of the dried ethereal layer gave 0.9 g. of a viscous liquid which, in 5 ml. of acetone was acidified to Congo Red with dry HCl. After 1.5 hr. at −5°, 0.6 g. (35%) of VIII hydrochloride, m.p. 255–260°, was obtained. It was recrystallized to constant melting point with absolute ethanol–ether; long plates, m.p. 261–263°, λ_{max}^{Nujol} 5.96 μ.

Anal.[12] Calcd. for $C_{18}H_{24}ClNO_2$: C, 67.18; H, 7.52; Cl, 11.02. Found: C, 67.54; H, 7.78; Cl, 11.37.

Concentration of the filtrate and washings from the 0.6 g. of VIII hydrochloride gave 0.11 g. of principally needles, m.p. 190–220°. Several recrystallizations from absolute ethanol–acetone gave fine needles, m.p. 191–198°, λ_{max}^{Nujol} 2.89 and 6.11 μ (the latter identical to that reported for *p*-hydroxyacetophenone), λ_{max}^{EtOH} 217, 260, 336 mμ (ϵ 22,000, 13,000, 5,800). On the basis of these data, its solubility in aqueous sodium hydroxide, and the following analytical values the structure (IV) is assigned (*cf.* also footnote 9).

Anal. Calcd. for $C_{17}H_{22}ClNO_2 \cdot {}^1/_2H_2O$: C, 64.42; H, 7.33; N, 4.53. Found: C, 64.05; H, 7.29; N, 4.66.

After drying at 110° the sample gave the following values:

Anal. Calcd. for $C_{17}H_{22}ClNO_2$: C, 66.33; H, 7.21. Found: C, 65.81; H, 7.52.

The 10% sodium hydroxide layer above gave intractable material which showed little or no carboxyl absorption in the infrared

1,2,3,9,10,10a-Hexahydro-6-methoxy-11-methyl-1,4a(4H)-iminoethanophenanthrene (VIIb). The hydrochloride of VIII (0.6 g.), 0.5 g. of potassium hydroxide, 0.5 ml. of 95% hydrazine, and 5 ml. of triethylene glycol were kept at 170–

(10) It follows that addition of hydrogen to II affords III with the H of position 9 *cis* to the —CH_2CH_2N bridge.

(11) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

(12) After drying to constant weight (loss 2%) at 110° in high vacuum.

180° for 16 hr. and at 200° for 10 min. The cooled solution was treated with water and ether. The dried ether layer was evaporated to give 0.5 g. (98%) of VIIb, m.p. 85–90°; plates from methanol-water, m.p. 93–94°.

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.66; H, 9.29 Found: C, 79.45; H, 9.02.

The methiodide crystallized from methanol in prisms of m.p. 265–267° (froth).

Anal. Calcd. for $C_{19}H_{28}INO$: C, 55.21; H, 6.83. Found: C, 54.99; H, 6.62.

The hydrochloride crystallized from alcohol-ether in needles which appear to be the hemihydrate.

Anal. Calcd. for $C_{18}H_{26}ClNO \cdot {}^1/_2H_2O$: C, 68.21; H, 8.59. Found: C, 68.02; H, 8.81.

1,2,3,9,10,10a-Hexahydro-6-hydroxy-1-methyl-1,4a(4H)-iminoethanophenanthrene (VIIc). A mixture of 0.4 g. of VIIb and 3 ml. of 48% hydrobromic acid was refluxed for 0.5 hr. and evaporated to dryness *in vacuo*. The residue, digested with 3–5 ml. of absolute alcohol and cooled to 5°, gave 0.4 g. (83%) of VIIc hydrobromide (m.p. 268–272°) which was converted to the base with aqueous ammonium hydroxide; prisms from methanol, m.p. 246–248° (froth).

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.34; H, 9.01. Found: C, 79.48; H, 9.00.

The *hydrobromide*[13] crystallized from 95% ethanol in small prisms (m.p. 150–155°, froth) which apparently contain one molecular equivalent of solvate ethanol.

Anal. Calcd. for $C_{17}H_{24}NO + C_2H_5OH$: C, 59.37; H, 7.87; Br, 20.80; C_2H_5OH, 11.98. Found: C, 58.75; H, 7.70; Br, 21.45; C_2H_5OH (determined as ethoxyl), 11.73.

4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VI) *picrate*. (*a*) *From* Vb. (±)-3-Methoxy-*N*-methylmorphinan (Vb) hydrobromide[5] (0.2 g.) was converted to Vb (aqueous ammonium hydroxide–ether) which in turn gave 0.15 g. of the methiodide (methyl iodide–methanol-ether). This methiodide and 5 ml. of 10% sodium hydroxide were refluxed 1–2 hr. and the resultant base (after drying in ether) was hydrogenated in methanol (5 mg. of platinum oxide) during 10 min. The filtered solution was evaporated to dryness *in vacuo*, and the residue was treated with saturated alcoholic picric acid to give 0.15 g. (79%) of the picrate of m.p. 158–159°. A recrystallization from alcohol did not alter the melting point.

Anal. Calcd. for $C_{25}H_{32}N_4O_8$: C, 58.13; H, 6.25. Found: C, 57.77, 57.91; H, 6.13, 5.95.

(*b*) *From* VIIb. The methiodide of VIIb (0.09 g.), 0.4 g. of potassium hydroxide, 4 ml. of water, and 1 ml. of triethylene glycol were kept at 135–140° (bath temperature)[14] for 3 hr. and treated with water and ether. The residue from the dried ether layer was distilled at 0.5 mm. (bath temperature 150°). The distillate was hydrogenated as described in the previous experiment. The product gave 35 mg. (31%) of picrate, m.p. 145–150°. Careful recrystallization from alcohol yielded 25 mg. of picrate, m.p. 156–157.5°, indistinguishable in crystal form, melting phenomena, and infrared spectrum, from that prepared from Vb.

Acknowledgment. I am indebted to Mr. J. Harrison Ager for valuable assistance in the chemical work and to Dr. Nathan B. Eddy, Chief, section on analgesics, for the pharmacological results.

BETHESDA, MD.

(13) This material was quantitatively convertible to VIIc.

(14) Unlike Vb methiodide, this methiodide (of VIIb) was unaffected by boiling 10% sodium hydroxide.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

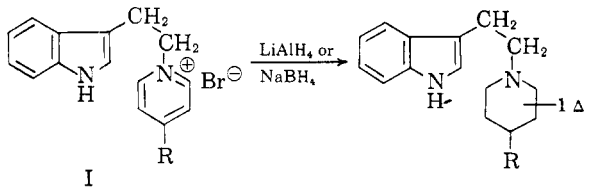
Alstonia Alkaloids. IX. Synthesis of Alstonilinol and Analogs by Reductive Ring Closure[1]

ROBERT C. ELDERFIELD AND BALTHASAR A. FISCHER

Received March 21, 1958

Tetrahydroalstonilinol has been synthesized by reductive ring closure of 2-[β-(6-methoxy-3-indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide. Dehydrogenation of tetrahydroalstonilinol gave alstonilinol.

In a preceding paper the action of lithium aluminum hydride and sodium borohydride upon a series of β-(3-indolylethyl)-1-pyridinium bromides (I) was reported.[2] It was shown that, although two double bonds in the pyridine ring were reduced, no ring closure to a tetracyclic β-carboline resulted. In the present paper we present the results of a study of the action of the two hydrides on β-(3-indolylethyl)-2-isoquinolinium bromides which led to a total synthesis of alstonilinol (XXII). This interesting ring closure to a pentacyclic β-carboline was first described by Robinson and Potts[3] and a preliminary note dealing with our experiences has already appeared.[4]



I

Inasmuch as the ultimate objective was a synthesis of alstoniline itself which carries a carbomethoxyl group in the 16 position of the parent yohimbane carbon skeleton (disregarding unsatu-

(1) The work here reported was done in part under Research Grant H-1733 from the National Heart Institute and in part under Research Grant CY-2961 from the National Cancer Institute.

(2) R. C. Elderfield, B. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

(3) Sir Robert Robinson and K. T. Potts, *J. Chem. Soc.*, 2675 (1955). *cf.* B. Belleau, *Chem. & Ind. (London)*, 229 (1955).

(4) R. C. Elderfield and B. Fischer, *J. Org. Chem.*, **23**, 332 (1958).