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

Structures Related to Morphine. VI.[1] N-Phenylethyl Derivatives of Some Phenyl- and Benz-morphans

EVERETTE L. MAY

Received March 19, 1956

The conversion of 5-phenyl-2-methylmorphan (I-a), the *m*-methoxy derivative (I-b), and 2,5-dimethyl-6:7-benzmorphan (V) to the corresponding N-(2-phenylethyl) compounds II-a, II-b, and VI is described. Phenylethylation of the secondary amine intermediates was achieved in 80% over-all yield by phenylacetylation and lithium aluminum hydride reduction of the resulting amides. The N-phenylethyl analogs II-a, III, and VI were two to three times less effective than the respective N-methyl counterparts in producing analgesia in mice.

Although the substitution of other radicals for methyl on the nitrogen in such analgesics as morphine and meperidine does not always markedly reduce potency, it has been the consensus that optimal analgesic behaviour is exhibited by these and similar structures when the heterocyclic nitrogen is linked to methyl.[2] Recently, however, it was revealed that 4-carbethoxy-4-phenyl-1-(2-phenylethyl)piperidine,[3] and 3-hydroxy-N-(2-phenylethyl)morphinan[4] were far more effective than the parent N-methyl compounds meperidine and racemorphan. These surprising results have prompted the synthesis of 5-(*m*-hydroxyphenyl)-2-(2-phenylethyl)morphan (III), its deoxy analog (II-a), and 5-methyl-2-(2-phenylethyl)-6:7-benzmorphan (VI) for comparison of their analgesic activity with that of the N-methyl counterparts IV,[5] I-a,[6] and V[7] respectively.

Reaction of I-a, I-b, and V with cyanogen bromide by the method of von Braun[8] as modified by Grüssner[9] yielded the corresponding N-cyano compounds which, without purification, were hydrolyzed-decarboxylated to the secondary amines (*nor*-compounds) with dilute hydrochloric acid. From 10–20% of the starting N-methyl compounds could always be recovered as the hydrobromide after cyanogen bromide treatment.

Reaction of the *nor*-compounds with phenylacetyl chloride gave phenylacetamides which were easily reduced to the phenylethyl derivatives II-a, II-b, and VI with lithium aluminum hydride. This facile 2-step procedure gave 80% over-all yields, while one attempt at a direct alkylation using 2-phenylethyl bromide produced a difficulty separable mixture. Boiling 48% hydrobromic acid effectively demethylated II-b to III.

Tested in mice, compounds II-a, III, and VI were found to be half to a third as active as the N-methyl analogs I-a, IV, and V respectively, contrary to results obtained with meperidine and racemorphan types.[3,4,10]

EXPERIMENTAL

Melting points were taken by capillary with calibrated, total immersion thermometers. Microanalyses are from the Institute's service analytical laboratory under the direction of Dr. William C. Alford.

2-(m-Methoxyphenyl)morphan hydrobromide. To 1.2 g. of cyanogen bromide in 7 ml. of dry chloroform was added (stirring) 2.4 g. of I-b[5] in 10 ml. of chloroform during 45 minutes. The solution was refluxed for 3 hours and evaporated to dryness *in vacuo*. The residue was dissolved in ethanol, and the solution was refluxed briefly and again evaporated to dryness. From 10 ml. of ethyl acetate the residue deposited 0.5 g. of I-b hydrobromide,[5] m.p. 158–162°. The filtrate was freed of ethyl acetate *in vacuo*. The residue and 45 ml. of 6% HCl were refluxed overnight, cooled to 0°, basified with 10% KOH, and the liberated oil was dried in ether. Addition of 32% HBr-acetic acid gave, after keeping overnight at 0°, a semisolid from which the ether was poured. After being washed with ether by decantation this semisolid was triturated with ethyl acetate containing a little acetone to give 1.3 g. of hydrobromide, m.p. 127–130°. The filtrate contained *ca.* 0.3 g. more (total yield 67% based on recovered I-b) as shown by evaporation to dryness and conversion of the residue to II-b as described below. The secondary amine hydrobromide crystallized from acetone-ether in rods of m.p. 129–131°.

Anal. Calc'd for $C_{15}H_{22}BrNO$: C, 57.7; H, 7.1. Found: C, 57.7; H, 7.2.

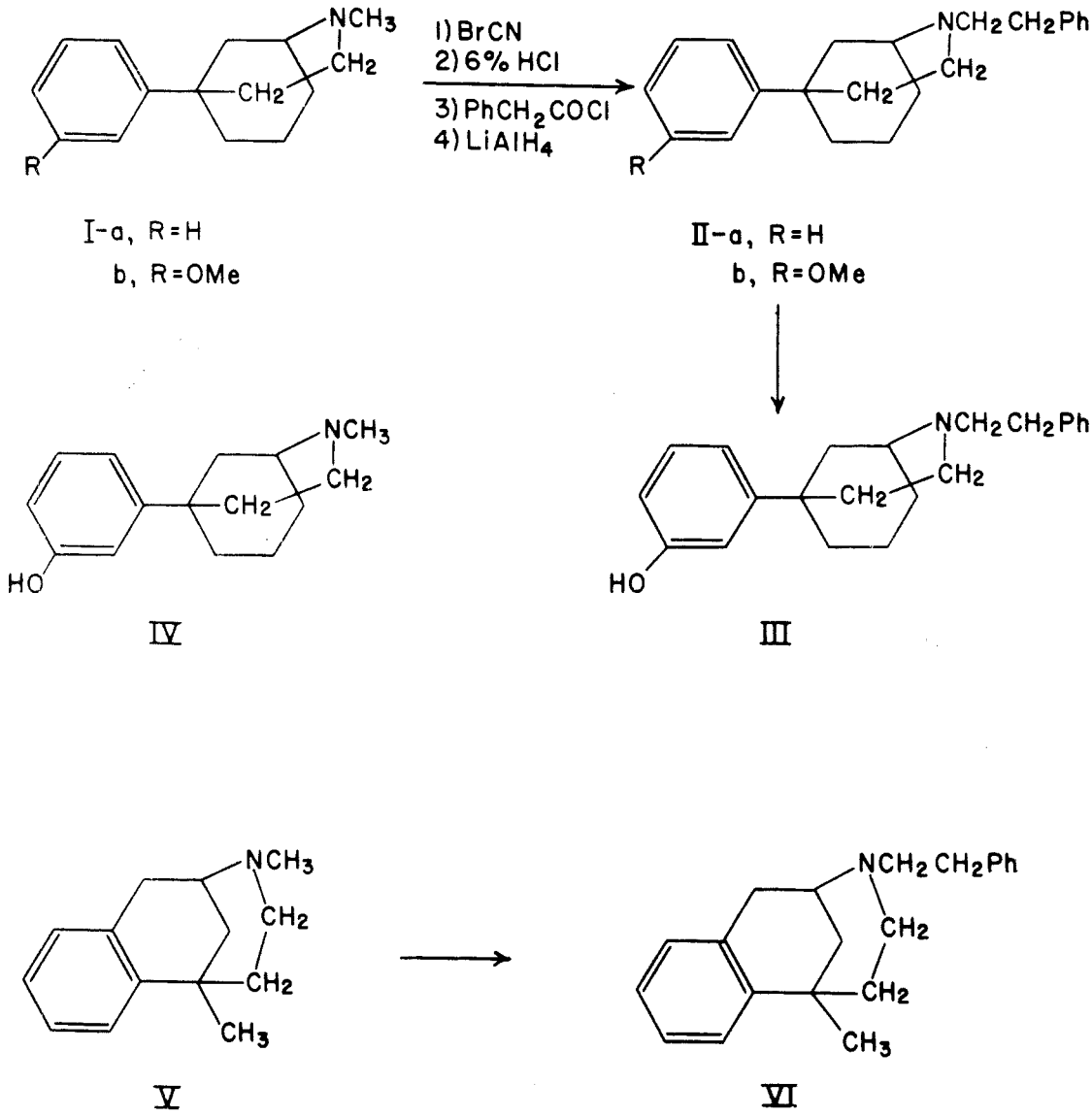
The *picrate*, stout, yellow prisms from alcohol, melted at 162–165°.

Anal. Calc'd for $C_{21}H_{24}N_4O_8$: C, 54.8; H, 5.3. Found: C, 54.6; H, 5.5.

5-(m-Methoxyphenyl)-2-(2-phenylethyl)morphan (II-b) *hydrobromide.* Phenylacetyl chloride (1.0 ml.) was added during 3–5 minutes to a stirred mixture of 1.0 g. of the above

(1) Previous paper, May, *J. Org. Chem.*, **21**, 223 (1956).
(2) Braenden, Eddy, and Halbach, *Bull. World Health Organization*, **13**, 937 (1955).
(3) Perrine and Eddy, *J. Org. Chem.*, **21**, 125 (1956).
(4) Eddy, N. B., Personal communication.
(5) May and Murphy, *J. Org. Chem.*, **20**, 1197 (1955).
(6) May and Murphy, *J. Org. Chem.*, **19**, 618 (1954).
(7) May and Murphy, *J. Org. Chem.*, **20**, 257 (1955).
(8) von Braun, Kruber, and Aust, *Ber.*, **47**, 2312 (1914).
(9) Personal communication from Dr. Grüssner, F. Hoffmann-La Roche & Co., Basle, Switzerland.
(10) Added in proof. Recently, Weijlard, Orahovats, Sullivan, Purdue, Heath, and Pfister, *J. Am. Chem. Soc.*, **78**, 2342 (1956) have reported striking effects in both the morphine and meperidine series with various N-(2-phenylethyl) derivatives.

Fig. 1



hydrobromide, 1.5 g. of K_2CO_3, 5 ml. of water, and 15 ml. of methanol. The mixture was stirred for an hour, diluted with 3 volumes of water, and extracted with ether. The ether extracts were washed with dilute HCl, then dilute NaOH, dried, and evaporated to dryness to give 1.5 g. of a sirup which, in 20 ml. of dry ether was treated gradually with 20 ml. of 1.4 *M* ethereal lithium aluminum hydride. The mixture was refluxed overnight and treated carefully (stirring) with 10–15 ml. of water. The ether was decanted from residual hydroxides which were washed thrice. Drying and acidification (32% HBr-AcOH) of the combined ethereal portions gave 1.1 g. (83%) of II-b hydrobromide; leaflets from acetone, m.p. 209–211°.

Anal. Calc'd for $C_{23}H_{30}BrNO$: C, 66.3; H, 7.3. Found: C, 66.4; H, 7.3.

5-(m-Hydroxyphenyl)-2-(2-phenylethyl)morphan (III) *hydrobromide.* Refluxing 1.1 g. of II-b hydrobromide and 7 ml. of 48% HBr for 30 minutes, evaporating to dryness *in vacuo*, and triturating the residue with absolute alcohol containing a little acetone gave 0.9 g. (82%) of III hydrobromide, m.p. 260–270°. It was dissolved in 75 ml. of boiling methanol. The solution was filtered, concentrated to 20–25 ml., and kept at 0° overnight to give 0.8 g. of small prisms, m.p. 274–277.5°.

Anal. Calc'd for $C_{22}H_{28}BrNO$: C, 65.7; H, 7.0. Found: C, 65.8; H, 6.9.

5-Phenyl-2-(2-phenylethyl)morphan (II-a) *hydrobromide.* To a stirred solution of 0.5 g. of cyanogen bromide in 3 ml. of chloroform was added during one hour 0.9 g. of I-a[8] in 5 ml. of chloroform. The solution was refluxed for 3 hours and evaporated to dryness *in vacuo*. The residue and a little alcohol were refluxed briefly, and the solution was evaporated to dryness. The residual sirup and 20 ml. of 6% HCl were refluxed together overnight to give an almost clear solution which was shaken with ether. Basification of the aqueous layer with 10% NaOH liberated an oil which was dried in ether and brought to reaction with phenylacetyl chloride as described in the preparation of II-b above. The resultant amide (1.3 g.) was reduced with 15 ml. of 1.4 *M* lithium aluminum hydride (see above) to give 0.8 g. (53% based on used I-a) of II-a hydrobromide, m.p. 248–260°. For purification it was dissolved in boiling 95% alcohol,

filtered, and the filtrate was concentrated to 10–15 ml. and kept at 0° overnight; glittering plates, m.p. 264–267° after shrinking from 250°. Inserted in a bath preheated to 255°, melting was instantaneous and complete.

Anal. Calc'd for $C_{22}H_{28}BrN$: C, 68.4; H, 7.3. Found: C, 68.5; H, 7.4.

The *picrate* crystallized from acetone-alcohol in yellow cubes of m.p. 184–186°.

Anal. Calc'd for $C_{28}H_{30}N_4O_7$: C, 62.9; H, 5.7. Found: C, 63.1; H, 5.6.

From the acid washings after phenylacetylation, 0.2 g. of I-a[6] was recovered as the hydrochloride.

5-Methyl-2-(2-phenylethyl)-6:7-benzmorphan (VI) *hydrochloride.* Essentially as described in the preparation of II-a, 1.6 g. of V[7] yielded 1.1 g. of VI hydrochloride (dry HCl acidification of the ethereal solution of VI) with recovery of 0.2 g. of V as the hydrochloride after the phenylacetylation reaction; yield based on used V 50%. The VI hydrochloride crystallized from absolute alcohol, on addition of a few drops of ether to the hot solution, in flakes, m.p. 278–280° (dec.).

Anal. Calc'd for $C_{21}H_{26}ClN$: C, 76.9; H, 8.0. Found: C, 77.3; H, 7.9.

The *picrate* crystallized from alcohol containing a little picric acid to prevent hydrolysis, in yellow crusts, m.p. 142–146°.

Anal. Calc'd for $C_{27}H_{28}N_4O_7$: C, 62.3; H, 5.4. Found: C, 62.1; H, 5.3.

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