Structures Related to Morphine. XXII.[1] A Benzomorphan Congener of Meperidine

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The synthesis of 5-carbethoxy-2-methyl-6,7-benzomorphan (VIII), in essence a hybrid of the benzomorphan and meperidine classes of analgesics, has been accomplished in eight steps from phenylacetonitrile. The intermediate acid VII has also been converted to the dimethyl amide XII, which was reduced to the diamine XIII.

The azabicyclo structure 2,5-dimethyl-6,7-benzomorphan (IX)[2] which displays about half the analgesic potency of meperidine (X) in mice may be looked upon as a relative of X, in which there is methyl rather than carbethoxy at C-4 of X and with the phenyl substituent at the same position, linked *ortho* to C-2 by a methylene group. In general, meperidine and analogs, particularly those containing large N-functions, have shown marked ability to suppress morphine abstinence in monkeys while the benzomorphans (irrespective of the N-substituent) are rated low in this property.[3] However, meperidine types have elicited less addiction liability in man than would have been predicted from the monkey-substitution tests, and the opposite type of quantitative discrepancy in the two mammalian species is known to occur with phenazocine,[4] the only benzomorphan so studied in man[5] to date.[6] We wish to report the synthesis of 5-carbethoxy-

(1) Paper XXI, S. Saito and E. L. May, *J. Org. Chem.*, **27**, in press (1962).

(2) E. L. May and J. G. Murphy, *ibid.*, **20**, 257 (1955).

(3) M. H. Seevers, G. Deneau and D. A. McCarthy, personal communications and Minutes of the Meetings of the Committee on Drug Addiction and Narcotics, National Research Council, 1959–1961 inclusive.

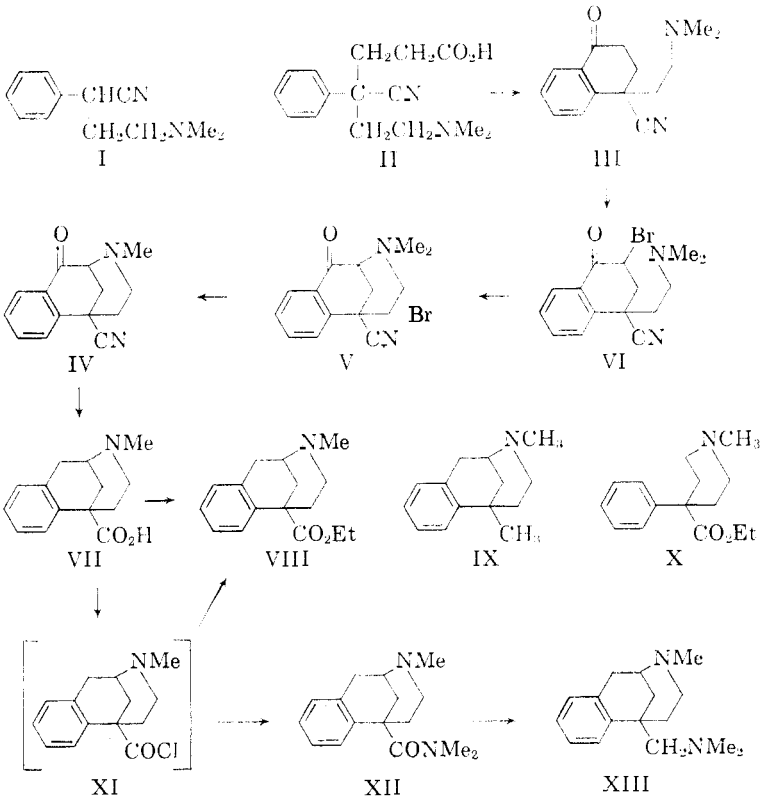
(4) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959). Phenazocine is (±)5,9-dimethyl-2′-hydroxy-2-phenethyl-6,7-benzomorphan.

(5) Addendum 3 to the Minutes of the 20th Meeting (1959) of the Committee on Drug Addiction and Narcotics of the National Research Council.

(6) It should be pointed out that these species differences are chiefly quantitative and not qualitative and appear to arise with strong analgesics having a substituent other than methyl on the nitrogen, e.g., H, phenethyl, phenacyl, etc. Thus the addiction potential of morphine, codeine, meperidine, members of the methadone series, and (±)-3-hydroxy-N-methylmorphinan (racemorphan), all containing an N-methyl substituent, can be fairly reliably predicted from the data obtained in monkey suppression tests. Several recently prepared N-methyl-6,7-benzomorphans, ranging in potency from heroin to codeine show little or no abstinence-suppressing capacity in monkeys.

2-methyl-6,7-benzomorphan (VIII), a hybrid of meperidine and 2,5-dimethyl-6,7-benzomorphan.

The starting material in this synthesis, α-(2-dimethylaminoethyl)-phenylacetonitrile (I)[7] was condensed with methyl acrylate to give (after ester hydrolysis) the caproic acid derivative II. Friedel and Crafts cyclization of the acid chloride of II afforded the α-tetralone derivative (III). Bromination of III and internal quaternization of the resultant bromo ketone (VI) yielded the 2-azabicyclo bromide (V) which in boiling 1-nonanol lost methyl bromide to give the base (IV). Wolff–Kishner conditions (Huang-Minlon modification) achieved simultaneously, hydrogenolysis of the carbonyl group and hydrolysis of the cyano group; the resultant amino acid (VII) was



(7) C. E. Kwartler and P. Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946).

isolated as the hydrochloride salt. Conversion of VII to the desired VIII could be brought about either by direct esterification (ethanolic hydrogen chloride) or by refluxing the acid chloride (XI) with ethanol. Treatment of XI with excess dimethylamine yielded the amide (XII), lithium aluminum hydride reduction of which afforded the diamine (XIII) characterized as the dihydrobromide and dipicrate.

The analgesic activity of VIII (ED_{50} 10.0 mg./kg.) as determined by the procedure of Eddy and Leimbach,[8] is comparable to that of meperidine (ED_{50} 9.9 mg./kg.) by the subcutaneous route of administration. The amide XII is about half as potent (ED_{50} 18.1 mg./kg.), while the corresponding amine (XIII) is substantially inactive. The abstinence-suppressing capacity of VIII is being determined.

Experimental

Melting points (corrected) were taken in a capillary. Microanalyses are by the Analytical Services Unit of this Institute, Harold McCann, director, and infrared spectra (Perkin–Elmer Model 20) by H. K. Miller and Ann Wright, also of this Institute.

4-Cyano-6-dimethylamino-4-phenylhexanoic Acid (II).—To 73 g. of I[7] in 150 ml. of benzene was added 3.5 g. of sodium methoxide (stirring). After 1 hr. 33.5 g. of methyl acrylate in 20 ml. of benzene was added during 25 min., the temperature being kept at 25–30°. Stirring was continued overnight. The mixture was poured into 200 ml. of water and extracted with ether. Drying and evaporation of the extracts left 95.5 g. of red viscous oil (crude ester) which was added to 28 g. of potassium hydroxide in 140 ml. of methanol and 28 ml. of water. The temperature rose to 40°. The mixture was stirred for 5–6 hr., treated with 100 ml. of water and washed with ether. The aqueous layer was treated with 100 ml. of concd. hydrochloric acid and concentrated *in vacuo* at a bath temperature of 60° until the hydrochloride of II separated. It was filtered and washed with a little cold water; yield 75.5 g. (66%), m.p. 194–197°, λ_{max}^{Nujol} 4.45^{w}, 5.76 μ.

Anal. Calcd. for $C_{15}H_{21}ClN_2O_2$: C, 60.70; H, 7.11. Found: C, 60.48; H, 7.29.

4-Cyano-3,4-dihydro-4-(2-dimethylaminoethyl)-1(2H)-naphthalenone (III) Hydrobromide.—Thionyl chloride (25 g.), 25 g. of II hydrochloride and 1 drop of pyridine were kept at 60–65° for 30 min. Excess reagent was evaporated at the aspirator. The residual, red crystals were pulverized, washed with heptane, then stirred vigorously in 250 ml. of heptane while adding 32 g. of aluminum chloride. There was gentle refluxing. After stirring was no longer possible, solvent was decanted from the gummy residue which was dissolved in water. The aqueous solution was washed with ether, made basic with concd. ammonium hydroxide and extracted with ether. Evaporation of the dried extracts and evaporative distillation of the residue at 170–190° (bath temperature) (0.1 mm.) gave

(8) N. B. Eddy and D. Leimbach, *J. Pharmacol Exptl. Therap.*, **107**, 385 (1953).

15.7 g. of crude III which, in acetone, was acidified with 30% hydrogen bromide in acetic acid. The resultant hydrobromide was washed with acetone, then ethanol; yield 19 g. (70%), m.p. 216–218°, cubes from methanol, m.p. 218–220°, λ_{max}^{Nujol} 4.46 5.90, 6.26 μ.

Anal. Calcd. for $C_{15}H_{19}BrN_2O$: C, 55.73; H, 5.92; N, 8.67. Found: C, 55.44; H, 5.94; N, 8.38.

2-Bromo-4-cyano-3,4-dihydro-4-(2-dimethylaminoethyl)-1(2H)-naphthalenone (VI) Hydrobromide.—To a gently refluxing solution of 19 g. of III hydrobromide in 100 ml. of acetic acid was added during 15 min., 9.5 g. of bromine in 45 ml. of acetic acid. After refluxing for an additional 15 min., and cooling under a stream of nitrogen, 400 ml. of ether was added gradually. The separated oil crystallized on cooling at 5° overnight. Filtration and washing the crystals with acetone gave 24.5 g. (98%) of VI hydrobromide, m.p. 190–192° dec.; plates from ethanol λ_{max}^{Nujol} 4.48, 5.80, 6.26 μ.

Anal. Calcd. for $C_{15}H_{18}Br_2N_2O$: C, 44.80; H, 4.51; N, 6.97. Found: C, 45.03; H, 4.70; N, 6.83.

5-Cyano-2-methyl-8-oxo-6,7-benzomorphan Methobromide (V).—To a well-stirred suspension of 24.5 g. of VI hydrobromide and 80 ml. of water was added dropwise 9 ml. of concd. ammonium hydroxide (cooling). After stirring for 1 hr. and cooling at 5° overnight the crystals which had begun separating after a few min. were filtered and washed with acetone–ether; yield 12.2 g., m.p. 233–235°. Evaporation of the filtrate to dryness and recrystallization of the residue from 90% ethanol gave 5.8 g. more of V, making the total yield 91%. The analytical sample (from 90% ethanol) melted at 237–239° dec.; λ_{max}^{Nujol} 4.45, 5.9, 6.23 μ.

Anal. Calcd. for $C_{15}H_{17}BrN_2O$: C, 56.08; H, 5.32. Found: C, 56.16; H, 5.54.

5-Cyano-2-methyl-8-oxo-6,7-benzomorphan (IV).—A suspension of 100 ml. of 1-nonanol and 21 g. of V was immersed in a bath preheated to 240°. After refluxing for 15 min., and cooling under nitrogen, the solution was diluted with ether and extracted three times with 2% hydrochloric acid. The extracts were washed with ether and made alkaline with concd. ammonium hydroxide. The resultant precipitate was shaken into ether. Drying and evaporation of the ether left 14 g. (91%) of IV, yellow needles from petroleum ether (60–70°), m.p. 102–103.5°; λ_{max}^{Nujol} 4.47, 5.93, 6.24 μ.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.23; N, 12.36. Found: C, 74.60; H, 6.44; N, 12.16.

5-Carboxy-2-methyl-6,7-benzomorphan (VII) Hydrobromide.—Potassium hydroxide (3 g.), 3 g. of IV, 3 ml. of 95% hydrazine and 30 ml. of diethylene glycol were heated under reflux at a bath temperature of 190–210° for 1 hr. The condenser was removed and the heating continued for another hr. Finally the mixture was refluxed for 4 hr. The solvent was evaporated *in vacuo* as completely as possible at a bath temperature of 170-180°. To the cooled residue was added 20 ml. of concd. hydrochloric acid and the mixture again evaporated to dryness *in vacuo*. Ethanol (100 ml.) was added to the residue; inorganic material was filtered. Evaporation of the filtrate to dryness, addition of 100 ml. of ethyl acetate and overnight cooling at −5° gave 2.1 g. (59%) of VII hydrochloride, m.p. 272–274° dec. A small sample was converted to the hydrobromide by heating with excess 48% hydrobromic acid and evaporation to thorough dryness *in vacuo*.

The hydrobromide (from ethanol) melted at 281–282° dec.; λ_{max}^{Nujol} 5.75 μ.

Anal. Calcd. for $C_{14}H_{18}BrNO_2$: C, 53.85; H, 5.81. Found: C, 53.63; H, 6.00.

5-Carbethoxy-2-methyl-6,7-benzomorphan (VIII) Hydrochloride. (a) By Direct Esterification.—Ethanol (25 ml.) and 0.35 g. of VII hydrochloride were saturated with hydrogen chloride and refluxed for 5 hr. The solvent was evaporated and the residue dissolved in water. Addition of concd. ammonium hydroxide liberated an oily base which was dried in ether. The residue left from ether distillation was distilled at 130–140° (0.3 mm.) to give 0.2 g. (60%) of VIII which was converted to the hydrochloride (hydrogen chloride gas) in ethyl acetate containing a trace of water. It crystallized from ethanol–ethyl acetate as the monohydrate in flakes of m.p. 124-126°, λ_{max}^{Nujol} 2.86, 2.91, 5.77 μ.

Anal. Calcd. for $C_{16}H_{22}ClNO_2 \cdot H_2O$: C, 61.25; H, 7.71; Cl, 11.30. Found: C, 61.24; H, 8.08; Cl, 11.18.

(b) Via the Acid Chloride XI.—Thionyl chloride (10 ml.) and 1 g. of VII hydrochloride were refluxed for 1 hr. Excess reagent was evaporated *in vacuo* leaving brown oily XI to which was added carefully 10 ml. of ethanol. The mixture was refluxed for 1 hr. As described above 0.6 g. (62%) of oily VIII was obtained. Its hydrochloride was identical with that prepared by the direct esterification of VIII.

5-Carbodimethylamino-2-methyl-6,7-benzomorphan (XII).—To crude XI prepared from 3 g. of VII hydrochloride was added gradually (cooling) 20 ml. of dimethylamine (cooled in Dry-ice-acetone). The mixture was stirred for 1 hr. without cooling and then excess dimethylamine was evaporated. The residue was dissolved in 3% hydrochloric acid, and the solution was washed with ether. Concentrated ammonium hydroxide was added and the liberated base dried in ethyl acetate. Distillation of the ethyl acetate and the residue (bath temperature 220–240° 0.5 mm.) gave 1.6 g. (55%) of XII which gradually crystallized; m.p. 95–97°. The hydrochloride crystallized from methanol, apparently as the hemihydrate, in prisms of m.p. 205–207°, λ_{max}^{Nujol} 2.9, 2.97, 6.12 μ.

Anal. Calcd. for $C_{16}H_{23}ClN_2O \cdot 0.5\,H_2O$: C, 63.25; H, 7.96; N, 9.22. Found: C, 63.59; H, 7.87; N, 9.55.

5-Dimethylaminomethyl-2-methyl-6,7-benzomorphan (XIII) Dihydrobromide.—A mixture of 0.8 g. of XII, 0.3 g. of lithium aluminum hydride and 60 ml. of tetrahydrofuran was refluxed overnight, decomposed carefully with water, and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue dried in ether. Evaporation of the ether and distillation of the residue at 180–200° (bath temperature) (0.3 mm.) gave 0.5 g. (66%) of XIII whose dihydrobromide crystallized from methanol–acetone in plates, m.p. 258–260° dec. The infrared spectrum (Nujol) showed transparency in the 5.0–6.5 μ region.

Anal. Calcd. for $C_{16}H_{26}Br_2N_2$: C, 47.31; H, 6.45; Br, 39.35; N, 6.90. Found: C, 47.63; H, 6.63; Br, 39.05; N, 6.92.

The dipicrate crystallized from acetone in plates, m.p. 202–204°.

Anal. Calcd. for $C_{28}H_{30}N_8O_{14}$: C, 47.86; H, 4.30; N, 15.95. Found: C, 47.90; H, 4.25; N, 15.87.