moval of the catalyst and the addition of benzene to the filtrate. The material that separated consisted of colorless, fine needles that were so hygroscopic that no significant analytical data for boron and nitrogen could be obtained; m.p. 48–50°, ν^{KBr} 3125 cm.$^{-1}$ (NH_3^+), 1661 cm.$^{-1}$ (amino acid band-I), 1626 cm.$^{-1}$ (amide carbonyl), 1558 cm.$^{-1}$ (CO_2^-), 1543 cm.$^{-1}$ (amide-II band), 1493 cm.$^{-1}$ (amino acid band-II), triptych pattern 1200-950 cm.$^{-1}$ The material gave positive tests for boron and for an amino acid (ninhydrin).

ST. LOUIS, MO.

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

Structures Related to Morphine. XIV.[1] 2′-Hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan, the 9-Demethyl Analog of NIH 7519 (Phenazocine) from 3,4-Dihydro-7-methoxy-2(1H)naphthalenone

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3,4-Dihydro-7-methoxy-2(1H)naphthalenone has been converted to 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (V), an interesting intermediate for the synthesis of neuropharmacologic agents. Pyrolysis of V gives a mixture of the base VII and the α,β-unsaturated ketone (VI). Compound VII, readily convertible to the 9-demethyl analog (VIII) of phenazocine (XI) is characterized by its avidity for water or alcohol with simultaneous disappearance of infrared carbonyl absorption in the presence of acids. The *N*-phenethyl compound (VIII) is an effective analgesic in mice.

As reported previously,[2] 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (XI) is a promising agent for the relief of human pain. Of interest, therefore, was the 9-demethyl analog (VIII) of XI, despite the fact that the related 2′-hydroxy-2,5-dimethyl-6,7-benzomorphan (IX)[3] is only one third as effective in mice as the 9-methyl homolog (XII),[3,4] the corresponding relative of XI.

The most feasible route to VIII appeared to be *via* the *N*-methyl compound IX which hitherto has been prepared either from γ-picoline methiodide in low yield[3] or from phenylacetonitrile in a lengthy sequence.[3,5] Still another possible approach to IX would involve the intermediate bicyclic ketone methobromide (V) which was needed for other investigations as well. The synthesis of V from 3,4-dihydro-7-methoxy-2-(1H)naphthalenone (I) as shown in Fig. 1 was achieved without particular difficulty.

Methylation of I by the method of Stork[6] gave the 1-methyl compound (II) in 80% yield. Dimethylaminoethylation (sodamide, benzene) of II and bromination of the hydrobromide salt of the resultant III yielded IV hydrobromide which, when neutralized with ammonia, cyclized rapidly

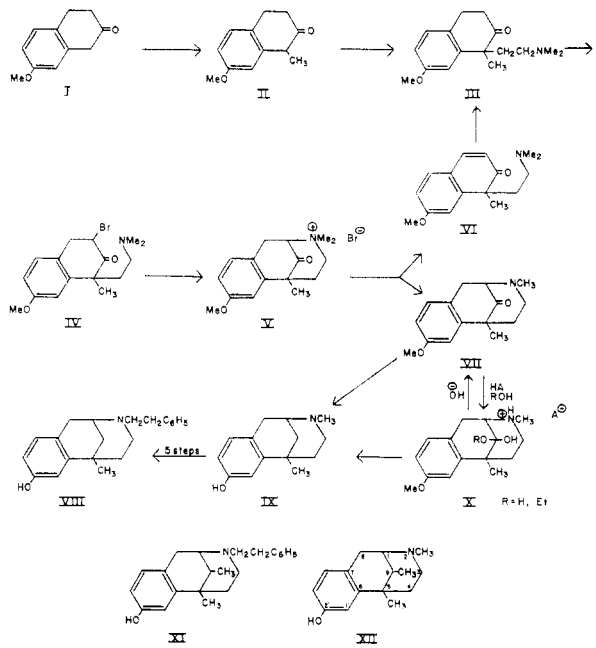

Fig. 1. Synthesis of 2′-hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan, VIII

to the quaternary compound V. Pyrolysis of V by dry distillation in a high vacuum led principally to tar, the only identifiable product being the α,β-unsaturated ketone VI. However, if the pyrolysis were effected in boiling 1-octanol a 40% yield of the desired base VII could be obtained along with about 15% of VI. The use of either boiling 1-heptanol or 1-hexanol reversed this ratio, giving about 40% of VI and never more than 20% of VII. Hydrogenation of VI (palladium–barium sulfate), the ultraviolet and infrared absorption curves of which were consistent with the structure

(1) Paper XIII, J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960).

(2) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

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

(4) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(5) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).

(6) G. Stork, R. Terrell, and J. Smuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

shown, afforded III. Wolff-Kishner reduction of VII, followed by *O*-demethylation of the product, gave IX. The latter was converted to VII in a five-step process as described previously[2] for similar compounds.

Noteworthy was the disappearance of carbonyl absorption when VII (λ_{max}^{smear} 5.76 μ) in the presence of water or alcohol was converted to a salt. The hydrochloride, hydrobromide, perchlorate, and picrate salts showed no carbonyl absorption in the infrared but always absorbed in the 3 μ region.[7] Elemental analysis of these salts indicated the presence of the elements of water or alcohol depending upon which was present in the salt preparation. Treatment of the salts with ammonium hydroxide instantaneously regenerated VII with its characteristic carbonyl (5.76 μ) absorption. These facts permit the assignment of formula X for salts of VII, although an ethyleneimmonium structure (containing solvate water or alcohol) resulting from carbonyl-amine proton interaction[8] may be another possibility.

The *N*-phenethyl compound VIII, ED_{50} 0.48 mg./kg. (mice, subcutaneous injection)[9] is twenty times as potent as the *N*-methyl parent (IX),[3] four times as potent as morphine but only about half as effective as phenazocine (XI).[2] The α,β-unsaturated ketone (VI) was analgesically inert.

EXPERIMENTAL

Melting points were taken in a capillary (total immersion thermometers). Microanalyses are by Paula Parisius, Byron Baer, Evelyn Peake, Elizabeth Fath, and W. C. Alford of the institute's service analytical laboratory.

3,4-Dihydro-7-methoxy-1-methyl-2(1H)naphthalenone (II) *semicarbazone.* To 23.4 g. of I[10] and 25 ml. of benzene was added during 5–10 min. (stirring, nitrogen atmosphere) 14 ml. of pyrrolidine. The mixture was refluxed for 45 min. (2.6 ml. of water distilled azeotropically) cooled, and added to 32 ml. of methyl iodide (stirring) so as to cause gentle refluxing. After an additional reflux period of 3–4 hr. 200 ml. of water was added and refluxing was resumed. After 30 min. the benzene layer was shaken with a saturated solution of sodium bisulfite, then dried and evaporated at the water pump. Distillation of the residue gave 19.6 g. of II, b.p. 110–115°/0.3–0.4 mm., n_D^{20} 1.5544. A small sample was converted to the semicarbazone (semicarbazide·hydrochloride, sodium acetate, alcohol-water) in nearly quantitative yield; plates from 90% ethanol, m.p. 198–200°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93. Found: C, 63.14; H, 6.73.

3,4-Dihydro-7-methoxy-1-methyl-1-(2-dimethylaminoethyl)-2(1H)naphthalenone (III) *hydrobromide.* To 5 g. of sodamide in 60 ml. of dry, refluxing benzene (stirring) was added as rapidly as possible 24 g. of II in 60 ml. of dry benzene. After 1 hr. of refluxing 15 g. of 2-chloro-*N,N*-dimethylethylamine in 100 ml. of benzene was added during 1–2 hr. Refluxing and stirring were continued overnight. The benzene was washed twice with water and these washings extracted with ether. The combined ether and benzene extracts were shaken thrice with excess 10% hydrochloric acid. These extracts were made alkaline (ammonium hydroxide) and extracted with ether. The dried (sodium sulfate) extracts were evaporated at the water pump leaving a residue which was distilled at 0.3 mm. (bath temperature 170–180°) through a very short path giving 22.5 g. of crude III. This in 150 ml. of dry ether was acidified with about 22 ml. of 30% hydrobromic acid in acetic acid to give an oil which rapidly crystallized. After decantation (or filtration) the precipitate was slurried with 25 ml. of warm acetone. After keeping at −5° overnight the yield of III hydrobromide was 26.5 g., m.p. 183–188°. It crystallized from acetone in small plates, m.p. 187–190°, λ_{max}^{nujol} 5.83 μ.

Anal. Calcd. for $C_{16}H_{24}BrNO_2$: C, 56.15; H, 7.07; Br, 23.35. Found: C, 55.88; H, 7.09; Br, 23.57.

3-Bromo-3,4-dihydro-7-methoxy-1-methyl-1-(2-dimethylaminoethyl)-2(1H)naphthalenone (IV) *hydrobromide.* To a stirred refluxing solution of III hydrobromide in 200 ml. of acetic acid was added during 15–25 min. 12 g. (4 ml.) of bromine in 25 ml. of acetic acid. The solution was cooled under a stream of nitrogen and diluted with 300 ml. of ligroin (b.p. 30–60°) and 100 ml. of ether. After thorough cooling at −5°, solvents were decanted through a suction filter and the semisolid residue was stirred with 35 ml. of acetone to the disappearance of all lumps. After cooling overnight at −15°, filtering, and washing the precipitate with cold 2:1 acetone-ether, the yield of IV hydrobromide, m.p. 151–154° dec. was 21 g.[11]; needles from acetone, m.p. 157–158° dec.

Anal. Calcd. for $C_{16}H_{23}Br_2NO_2$: C, 45.63; H, 5.53. Found: C, 45.61; H, 5.83.

2'-Methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (V). Finely divided IV hydrobromide (21 g.), 100 ml. of cold water, 100 ml. of ether, and 6 ml. of concd. ammonium hydroxide were shaken vigorously in a separatory funnel until all but a few small lumps had disappeared. The ethereal layer was transferred quickly to a 250-ml. round bottom flask. The aqueous layer was extracted twice with 25-ml. portions of ether. The combined ethereal extracts were evaporated to dryness at the water pump. The residue and 25 ml. of methanol were warmed to complete crystallization and kept at −5° overnight to give 12.3 g. of V, m.p. 199–203°. The filtrate was evaporated to dryness and the residue was extracted thrice with ether.[12] Crystallization of the residue from 5 ml. of methanol gave an additional 1.0 g. of V. It crystallized from absolute alcohol in feathery crystals, m.p. 204–206°, λ_{max}^{nujol} 5.75 μ.

Anal. Calcd. for $C_{16}H_{22}BrNO_2$: C, 56.48; H, 6.52. Found: C, 56.31; H, 6.36.

The *methiodide* prepared by aqueous potassium iodide

(7) With the demethoxy compound[5] corresponding to VII, it was possible, by using dry ether–hydrogen chloride, to obtain a hydrochloride salt showing strong carbonyl absorption at 5.74 μ (in nujol). This was not achieved with VII and usually not with the demethoxy compound.

(8) For a leading reference *cf.* M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 151 (1960).

(9) Test results are from N. B. Eddy, Chief, Section on Analgesics, and staff, by a method reported previously; N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

(10) B. W. Horrom and H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 721 (1950); G. B. Diamond and M. D. Soffer, *J. Am. Chem. Soc.*, **74**, 4126 (1952).

(11) Careful addition of ether to the warmed filtrate followed by prolonged cooling (−5°) gave 5.0 g. more of IV hydrobromide. If the intermediate V were desired, the filtrate from the 21 g. of IV hydrobromide was evaporated to dryness and the sirupy residue (10 g.) was cyclized to 3.5 g. of V as described for the 21 g. of IV hydrobromide.

(12) Evaporation of the ether extracts to dryness gave a residue which, in 10 ml. of acetone, was acidified to Congo Red giving from 2–5% of the α,β-unsaturated ketone (VI) as the hydrochloride. Excess ammonium hydroxide or higher cyclization temperatures increased the yield of VI which was identified as described elsewhere in this paper. We are indebted to Hiroshi Kugita, visiting scientist from Osaka, Japan, for this observation.

treatment of V crystallized from 95% ethanol in ellipsoids, m.p. 199–201°, λ_{max}^{nujol} 5.71 μ.

Anal. Calcd. for $C_{16}H_{22}INO_2$: C, 49.62; H, 5.73. Found: C, 49.49; H, 5.96.

Pyrolysis of V *to* VI *and* VII. A mixture of 3.0 g. of V and 13 ml. of 1-octanol[13] was immersed in a bath preheated to 210°, stirred, and refluxed until solution was complete (10–12 min.). After cooling under nitrogen, ether was added. The mixture was extracted thrice with excess 5% hydrochloric acid. Addition of ammonium hydroxide to the combined extracts gave an oil which was dried in ether. Evaporation of the ether and evaporative distillation of the residue at 150–175° (bath temperature)/0.3 mm. gave 1.5 g. of oil. This was dissolved in 10 ml. of acetone, and the solution was filtered from a little solid and acidified to a *p*H of 6–6.5 with hydrogen chloride. After cooling to −15° for 1 hr., 0.25 g. of *7-methoxy-1-methyl-1-(2-dimethylaminoethyl)-2(1H)naphthalenone* (VI) hydrochloride, m.p. 203–206°, was obtained; prisms from alcohol-ether, m.p. 206–208°, λ_{max}^{nujol} 6.01 μ, $\lambda_{max}^{C_2H_5OH}$ 340 mμ (ϵ 26,400).

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 64.98; H, 7.51; Cl, 11.98. Found: C, 64.66; H, 7.69; Cl, 11.73.

The combined filtrate and acetone-ether washings from the 0.25 g. of VI hydrochloride above were acidified to Congo Red and kept at −15° overnight giving 1.0 g. of the *hydrochloride* (X. R = H, A = Cl) of VII, m.p. 125–128°. It crystallized from alcohol-ether in slim rods, m.p. 130–132°, λ_{max}^{nujol} 2.96, 3.11 μ (no carbonyl absorption).

Anal. Calcd. for $C_{15}H_{21}NO_3 \cdot HCl \cdot H_2O$.[14] C, 56.68; H, 7.61. active H(5), 1.57. Found: C, 56.52; H, 7.61; active H, 1.59.

Treatment of the hydrochloride (X. R = H, A = Cl) with ammonium hydroxide and extraction with ether gave, after evaporative distillation at 0.2 mm. (bath temperature 150°), 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan (VII), λ_{max}^{smear} 5.76 μ. It gradually becomes discolored on standing.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.02; H, 7.79.

The *hydrobromide* (X. R = H, A = Br) of VII crystallized from acetone in cubes, m.p. 132–134°, λ_{max}^{nujol} 3.1 μ (no carbonyl absorption).

Anal. Calcd. for $C_{15}H_{21}NO_3 \cdot HBr \cdot {}^1/_2H_2O$: C, 50.99; H, 6.56. Found: C, 50.91; H, 6.70.

The *picrate* prepared from VII with alcoholic picric acid crystallized from alcohol acetone in yellow prisms, m.p. 155–157° (gas evolution), λ_{max}^{nujol} 3.1 μ (weak) with no carbonyl absorption. It may be formulated as X (R = C_2H_5, A^- = picrate anion).

Anal. Calcd. for $C_{23}H_{28}N_4O_{10}$: C, 53.07; H, 5.42. Found: C, 53.39; H, 5.57.

Preparation and recrystallization of the picrate from aqueous acetone gave yellow plates, m.p. 120–122°, λ_{max}^{nujol} 2.96 (broad, medium) and no carbonyl absorption. This X (R = H, A^- = picrate anion) is a hemihydrate.

Anal. Calcd. for $C_{21}H_{24}N_4O_{10} \cdot {}^1/_2H_2O$: C, 50.30; H, 5.05; H_2O, 5.40. Found: C, 50.57; H, 5.05; loss in wt. (105–110°), 6.73.

The dried sample showed no absorption in the 3 μ region and relatively weak absorption at 5.74 μ.

Anal. Calcd. for $C_{21}H_{22}N_4O_9$: C, 53.16; H, 4.68. Found: C, 53.62; H, 4.80.

(13) The use of 1-hexanol or 1-heptanol gave 40% of VI and 15% of VII; pyrolysis by dry distillation gave a little VI, no VII, and principally tar.

(14) Evidently X (R = H, A = Cl) is a monohydrate. The hydrate water was indeterminate by loss in weight. All salts (X) prepared of VII could be reconverted to VII with aqueous ammonia. The perchlorate prepared in alcohol absorbed (nujol) at 2.85 and 3.19 μ (no carbonyl band) and melted at 117–121°. Analysis indicated the presence of 1 mole of ethanol. Thus it is formulated as X (R = C_2H_5, A = ClO_4).

Conversion of VI *to* III. A mixture of 1.0 g. of VI hydrochloride, 0.3 g. of 5% palladium-barium sulfate, and 10 ml. of absolute ethanol absorbed 1.1 molar equivalents of hydrogen during 0.5–1 hr. The filtered solution was evaporated to dryness at the water pump. The residue (III hydrochloride) crystallized from 5 ml. of acetone in a yield of 0.75 g.; rods from ethanol-ether, m.p. 165–168°, λ_{max} 5.82 μ.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 64.53; H, 8.12. Found: C, 64.52; H, 8.26.

This hydrochloride was converted to the hydrobromide salt which melted at 187–190° alone or in mixture with the III hydrobromide prepared directly from II. The infrared spectra of the two were identical.

2′-Hydroxy-2,5-dimethyl-6,7-benzomorphan (IX). Two grams of X (R = H, A = Cl) or 2 g. of crude VII, 2 g. of potassium hydroxide, 2 ml. of 95% hydrazine, and 15 ml. of triethylene glycol were kept at 170–175° for 4–5 hr., cooled, and treated with water. Two ether extractions and drying and evaporation of the extracts gave 1.4 g. of sirup. This and 10 ml. of 48% hydrobromic acid were heated under reflux for 20 min. The cooled solution was made alkaline with ammonium hydroxide and extracted thrice with chloroform. The dried (sodium sulfate) chloroform extracts were evaporated at the water pump. The residue crystallized from 5 ml. of acetone to give 1.0 g. (65% based on X, R = H, A = Cl) of IX, m.p. 209–214° which proved to be identical with that described previously.[3]

2′-Hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan (VIII) *hydrobromide.* Methylation of 1.0 g. of IX with ethereal diazomethane containing a little methanol gave 0.9 g. of evaporatively distilled (bath temperature 150–175°, pressure 0.3 mm.) methyl ether. This in 6 ml. of chloroform was added during 45 min. (stirring) to 0.5 g. of cyanogen bromide in 5 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness at the water pump. The residue and 18 ml. of 6% hydrochloric acid were refluxed for 3 hr. cooled, made alkaline with ammonium hydroxide, and extracted with chloroform. The dried chloroform extracts, on evaporation to dryness *in vacuo*, gave 0.7 g. of sirup. This base, 15 ml. of methanol, 5 ml. of water, and 0.8 g. of potassium carbonate were treated (stirring) with 0.8 ml. of phenylacetyl chloride during 5–10 min. The mixture was diluted to 100 ml. with water, extracted with ether, and the ether extracts washed with dilute hydrochloric acid. Evaporation of the dried (sodium sulfate) ether extracts to thorough dryness gave 1.1 g. of crude phenylacetamide derivative which was treated slowly with 15 ml. of 1.3*M* ethereal lithium aluminum hydride (stirring). The mixture was refluxed for 10–15 hr., decomposed with 5 ml. of water, and the ether decanted and dried over sodium sulfate. Acidification of the ether with 33% hydrobromic-acetic acid, decantation, and trituration of the oil with a little acetone gave 0.4 g. of hydrobromide of the methyl ether of VIII, m.p. 376–278°. This material, 4 ml. of 48% hydrobromic acid, and 2 ml. of 33% hydrobromic-acetic acid were refluxed and stirred vigorously for 30 min. and evaporated to dryness at the water pump. A little absolute ethanol was added to the residue and the evaporation repeated. The residue was then decolorized (Norit) in boiling alcohol and the filtrate again evaporated to dryness Trituration of the residue with acetone gave 0.3 g. of VIII hydrobromide, m.p. 220–225°. It crystallized from acetone in blades, m.p. 237–238°.

Anal.[15] Calcd. for $C_{21}H_{26}BrNO$: C, 64.94; H, 6.75. Found: C, 65.00; H, 6.73.

The *base* (VIII) melted at 155.5–156.5°, prisms from methanol-water.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20. Found: C, 82.08; H, 8.38.

BETHESDA 14, MD.

(15) After drying (water pump) for 60 hr. at 60–65°.