# Structures Related to Morphine. XXIX.[1] Further Experiments on the Stereo-Controlled Reduction of 9-Methylene-6,7-benzomorphans

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The stereochemistry of addition of alkyl–metallo reagents and platinum-catalyzed hydrogen to 9-oxo-6,7-benzomorphans,[3] and of similarly catalyzed hydrogen to 9-methylene-6,7-benzomorphans[1,4] appears to depend largely on the electrical environment produced by the proximate nitrogen. Additional experiments of this kind have now been carried out with 2-methyl-9-oxo-5-propyl-6,7-benzomorphan methobromide (II) and 2-methyl-9-methylene-5-propyl-6,7-benzomorphan (IV), not only to determine the effect of a bulkier group at C-5, but also to develop alternative syntheses for potentially useful analgetics.

Methobromide II was prepared from 3,4-dihydro-2-(1H)-naphthalenone (β-tetralone, I) as described before for various analogs.[1,3a,3d,5] Its reaction with methylmagnesium iodide was stereochemically identical (albeit somewhat slower) with that observed with lower 5-alkyl homologs.[3a,b,d] The resulting methylcarbinol (III) was isolated (80% yield) as the methiodide which, after dry distillation gave III with hydroxyl oriented toward nitrogen (equatorial for the hydroaromatic ring, α-series) as indicated by an infrared maximum at 3445 cm.$^{-1}$ (OH–N bonding).[3] As before[3] no β-isomer could be detected.

Treatment of III with thionyl chloride gave an oily mixture which, upon column chromatography, afforded a 15% yield of IV, isolated as the monohydrated hydrochloride. Platinum oxide hydrogenation of this hydrochloride (whose infrared characteristics helped identify it) in alcohol produced, nearly quantitatively, α-2,9-dimethyl-5-propyl-6,7-benzomorphan (V) as described for another series.[1,4] This stereochemistry of addition of hydrogen could be only partially reversed in excess hydrochloric acid to give a 1:1.5 mixture of V and the β-isomer VI, respectively.[6]

Methiodide rate studies served to distinguish isomers V and VI, the former being quaternized five times more rapidly than the latter.[1,7] Furthermore, the synthesis of these two compounds from 3-methyl-4-propylpyridine and the conversion of V to the known α-2,9-dimethyl-2′-hydroxy-2-methyl-5-propyl-6,7-benzomorphan[1] will be reported later.

(1) Paper XXVIII: C. F. Chignell, J. H. Ager, and E. L. May, *J. Med. Chem.*, **8**, 235 (1965).

(2) Visiting Associate from the Chelsea School of Pharmacy, London, England.

(3) (a) E. L. May, H. Kugita, and J. H. Ager, *J. Org. Chem.*, **26**, 1621 (1961); (b) E. L. May and H. Kugita, *ibid.*, **26**, 188 (1961); (c) H. Kugita and E. L. May, *ibid.*, **26**, 1954 (1961); (d) S. Saito and E. L. May, *ibid.*, **26**, 4536 (1961).

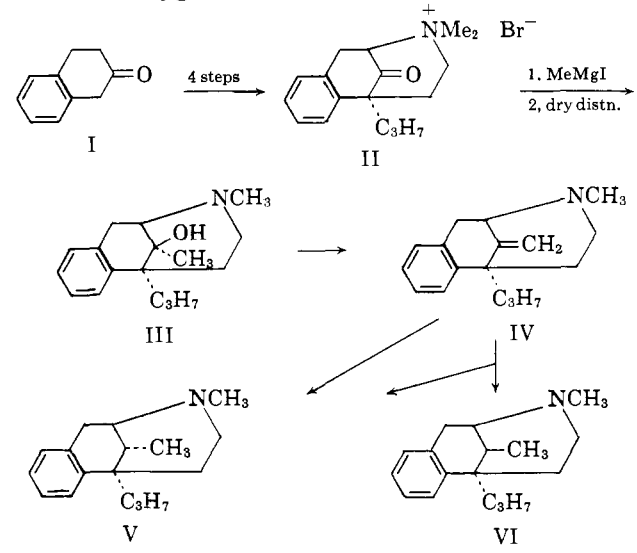
(4) S. Saito and E. L. May, *ibid.*, **27**, 1087 (1962).

(5) J. G. Murphy, J. H. Ager, and E. L. May, *ibid.*, **25**, 1386 (1960).

(6) In the 2′-methoxy-5,9-dimethyl series[3] a 70% yield of β (to the practical exclusion of α) was obtained, but in the 2′-methoxy-9-methyl-5-propyl series[1] a 1:1 mixture of α and β was formed. The additional bulk of the 5-substituent probably accounts for the partial loss in stereoselectivity and helps overcome the electrical effects of the neighboring nitrogen.

(7) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

Compounds IV–VI were tested for analgetic activity by the mouse hot-plate method.[8] The 9-methylene compound IV, the first benzomorphan of its kind to be tested for analgetic activity, was fairly active ($ED_{50}$ 5.2 mg./kg.) falling between morphine and codeine. The β-isomer VI was similarly effective ($ED_{50}$ 4.8) and the α-compound V was codeine-like ($ED_{50}$ 11.5). This is surprisingly good activity for compounds of this type devoid of oxygen.




## Experimental

Melting points (capillary) are corrected. Microanalyses are by the Microanalytical section of this institute, W. C. Alford, Chief.

**3,4-Dihydro-1-propyl-2(1H)-naphthalenenone.**—Pyrrolidine (37.8 g.) was added dropwise (stirring, nitrogen atmosphere) to 67.9 g. of I[9] in 200 ml. of benzene. The solution was refluxed for 1 hr. (7.5 ml. of water distilled azeotropically) and cooled to 25°. Propyl iodide (217 g.) was added in one lot. After refluxing for 20 hr., 250 ml. of water was added, and the mixture refluxed for an additional 9 hr. The aqueous layer was separated and shaken with two 200-ml. portions of benzene, and the combined benzene solutions were dried ($Na_2SO_4$). The material left from evaporation of solvent distilled at 105–110° (0.2–0.5 mm.), $n^{24}D$ 1.5445, yield 73 g.

*Anal.* Calcd. for $C_{13}H_{16}O$: C, 82.9; H, 8.6. Found: C, 83.0; H, 8.7.

**3,4-Dihydro-1-(2-dimethylaminoethyl)-1-propyl-2(1H)-naphthalenone Hydrobromide.**—The above oil (73 g.) in 120 ml. of benzene was added dropwise during 1.5 hr. to 15 g. of sodamide in 120 ml. of refluxing benzene (stirring). After refluxing for a further 3 hr., 46 g. of 2-chloro-N,N-dimethylethylamine in 300 ml. of benzene was added dropwise during 3 hr., and the mixture was refluxed and stirred for 18 hr. The cooled benzene solution was washed with water and the washings were extracted with three 100-ml. portions of ether. The combined ether extracts and benzene were shaken with three 150-ml. portions of 10% HCl; the aqueous extracts were made basic with concentrated $NH_4OH$ and extracted with ether. The dried ($Na_2SO_4$) extracts were evaporated to give 69 g. of base, m.p. 123–124° (0.25–0.4 mm.). This in 500 ml. of ether was acidified with 30% HBr in acetic acid to give an oil which, after trituration in acetone and storage overnight at −5°, gave 84 g. of hydrobromide, m.p. 157.5–158°; prisms from ethanol–ether.

*Anal.* Calcd. for $C_{17}H_{26}BrNO$: C, 60.0; H, 7.7; N, 4.1. Found: C, 59.3; H, 7.9; N, 4.2.

**3-Bromo-3,4-dihydro-1-(2-dimethylaminoethyl)-1-propyl-2-(1H)-naphthalenone Hydrobromide.**—Bromine (2.4 g.) in 25 ml. of acetic acid was added dropwise during 15 min. to a stirred,

(8) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). We are indebted to Mrs. Louise Atwell for performing these tests and to Mrs. Wendy Ness for statistical analysis of the data. Both are in the section on Medicinal Chemistry, National Institutes of Health.

(9) J. H. Burckhalter and J. R. Campbell, *J. Org. Chem.*, **26**, 4232 (1961); also available from the Aldrich Chemical Co.

refluxing solution of 5 g. of the above hydrobromide in 25 ml. of acetic acid. The solution was allowed to cool to room temperature under a stream of nitrogen and diluted with 350 ml. of ether. The precipitated oil solidified after storage overnight at −5°; the yield of hydrobromide was 3.9 g., m.p. 147–148°. By evaporating the filtrate and crystallizing the residue from ethanol–ether, a further 1.5 g. was obtained as feathery plates from methanol–acetone, m.p. 157–158°.

*Anal.* Calcd. for $C_{17}H_{23}Br_2NO$: C, 48.7; H, 6.0; Br, 38.3. Found: C, 48.8; H, 5.9; Br, 38.1.

**2-Methyl-9-oxo-5-propyl-6,7-benzomorphan Methobromide (II).**—The above, finely divided bromo ketone hydrobromide (2.0 g.), 18 ml. of water, and 7 ml. of concentrated $NH_4OH$ were shaken vigorously with three 50-ml. portions of ether, and the extracts were separated quickly. The combined ethereal solutions were evaporated at the water pump; the residue was crystallized from ethanol–ether to give 1.0 g. of II, m.p. 175–176°; feathery plates, m.p. 191–192° (sinters 186°), from methanol–acetone.

*Anal.* Calcd. for $C_{17}H_{24}BrNO$: C, 59.8; H, 7.2; N, 4.2. Found: C, 60.1; H, 7.0; N, 4.2.

**α-2,9-Dimethyl-9-hydroxy-5-propyl-6,7-benzomorphan (III) Methiodide.**—To a stirred suspension of 11.7 g. of II in 100 ml. of dry ether was added dropwise, 100 ml. of methylmagnesium iodide (from 24.5 g. of methyl iodide and 4.2 g. of magnesium). The mixture was stirred and refluxed for 48 hr., then poured onto a mixture of 50 g. of ice, 15 g. of potassium iodide, and 25 ml. of concentrated HCl. The solid which separated (while stirring for 2 hr.) was filtered, washed with ether, and recrystallized from methanol–acetone; yield of III methiodide, m.p. 200–202°, 10 g. The analytical sample (from methanol–acetone) melted at 223–224°.

*Anal.* Calcd. for $C_{18}H_{28}INO$: C, 54.0; H, 7.0; N, 3.5. Found: C, 54.6; H, 7.1; N, 3.7.

The **base III** was obtained in a yield of 1.9 g. by dry distillation (0.6 mm., bath temperature 210°) of 3.0 g. of III methiodide; prisms from ligroin (60–80°), m.p. 94.5–95.5°, $\nu_{max}^{CCl_4}$ 3445 cm.$^{-1}$ (OH–N bonding).[1,2]

*Anal.* Calcd. for $C_{17}H_{25}NO$: C, 78.7; H, 9.7; N, 5.4. Found: C, 78.4; H, 9.5; N, 5.4.

The **hydrochloride** of III crystallized from ethanol–ether as prisms, m.p. 221–222°.

*Anal.* Calcd. for $C_{17}H_{26}ClNO$: C, 69.1; H, 8.9; N, 4.8. Found: C, 69.0; H, 8.9; N, 5.0.

**2-Methyl-9-methylene-5-propyl-6,7-benzomorphan (IV) Hydrochloride.**—Thionyl chloride (60 ml.), 1 ml. of pyridine, and 10 g. of III were kept at 40° for 2 hr. (stirring). Solvents were removed at the water pump. To the residue was added ice and concentrated $NH_4OH$ in excess. Drying ($Na_2SO_4$) of the liberated bases in three 100-ml. portions of ether gave 6.1 g. of an oil which, in ligroin (66–75°), was placed on an alumina column (Woelm grade III, neutral, 150 g.) and eluted with benzene–ligroin (66–75°). The fractions eluted by 10–55% benzene were combined to give 3.5 g. of crude IV, $\lambda_{max}^{nujol}$ 6.05 and 10.6 μ (=$CH_2$). The hydrochloride, prepared in acetone by addition of dry HCl and ether, crystallized as the monohydrate; yield 1.6 g.; m.p. 180–182°; $\lambda_{max}^{Nujol}$ 2.80, 2.95 ($H_2O$), and 6.05, 10.6 μ (=$CH_2$).

*Anal.* Calcd. for $C_{17}H_{24}ClN \cdot H_2O$: C, 68.9; H, 9.0; Cl, 12.0; N, 4.7. Found: C, 68.4; H, 9.0; Cl, 11.9; N, 4.5.

The molecule showed 2.6 active hydrogens based on a molecular weight of 295.8.

**α-2,9-Dimethyl-5-propyl-6,7-benzomorphan (V) Hydrochloride.**—The hydrochloride of IV (0.32 g.), 25 ml. of ethanol, and 0.15 g. of platinum oxide absorbed the calculated amount of hydrogen during 30 min. The residue from filtration and evaporation of the filtrate to dryness crystallized from acetone–ether in a yield of 0.27 g., m.p. 194° (sinters 176°). The analytical sample melted at 199–200°.

*Anal.* Calcd. for $C_{17}H_{26}ClN$: C, 72.9; H, 9.4; N, 5.0. Found: C, 72.8; H, 9.3; N, 5.0.

**β-Isomer (VI) Hydrochloride.**—The hydrochloride of IV (1.1 g.), 20 ml. of concentrated hydrochloric acid, 0.5 g. of platinum oxide, and 10 ml. of ethanol absorbed 1 molar equiv. of hydrogen during 2.5 hr. Filtration, evaporation to dryness *in vacuo*, addition of excess $NH_4OH$, and extraction with ether gave a mixture of V and VI (1:1.5) which was successfully separated by preparative, thin layer chromatography (silica gel G; ethanol, dioxane, benzene, concentrated $NH_4OH$, 5:40:50:5) in 85% recovery. The crude β-isomer (VI) in acetone was acidified with dry HCl. Addition of ether to turbidity and storage at −5° overnight gave a solid which was recrystallized from acetone–ether; yield 0.4 g., m.p. 248–249°.

*Anal.* Calcd. for $C_{17}H_{26}ClN$: C, 72.9; H, 9.4; N, 5.0. Found: C, 72.8; N, 9.3; N, 5.0.

**Stereochemistry of V and VI.**—By a method described before,[3] compound V was shown to form the methiodide five times more rapidly than did VI. Thus the 9-methyl substituent of V is oriented away from nitrogen (axial for the hydroaromatic ring). The β-structure[7] can therefore be assigned to VI.

## Synthesis of 17-Acetoxy-6-chloro-21-fluoropregna-4,6-diene-3,20-dione, a Highly Active Oral Progestin

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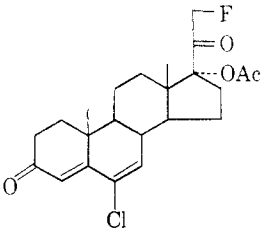
Among the groups which afford enhanced progestational activity when introduced into progesterone-type molecules are the 21-fluoro[1] and the $\Delta^6$-6-chloro[2] functions. We wish to report here the synthesis of I, a highly active progestational agent resulting from the introduction of both of these functions into 17-acetoxyprogesterone.

Compound I was prepared by established procedures from 17-acetoxy-21-fluoroprogesterone[3] by 6-dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone,[4] and 6α,7α-epoxidation with monoperphthalic acid,[5] followed by treatment with HCl[6] to effect oxide ring opening and concomitant dehydration.




I

When assayed for progestational activity by the oral Clauberg procedure[7] compound I had a relative potency approximately 300 times that of 17-acetoxyprogesterone. Thus, introduction of the 21-fluoro group into 17α-acetoxy-6-chloropregna-4,6-diene-3,20-dione moderately enhances the activity of the latter compound, which we find to have a potency of 190 relative to 17-acetoxyprogesterone.

### Experimental

**General.**—Melting points were taken on a Mel-Temp apparatus in open capillary tubes and are corrected. Optical rotations

(1) P. Tamhankar, R. J. Peace, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956).

(2) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *ibid.*, **81**, 3485 (1959).

(3) C. G. Bergstrom, P. B. Sollman, R. T. Nicholson, and R. M. Dodson, *ibid.*, **82**, 2322 (1960).

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(5) A. L. Nussbaum, G. Brabazon, T. L. Popper, and E. P. Oliveto, *J. Am. Chem. Soc.*, **80**, 2722 (1958).

(6) L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi, and H. J. Ringold, *ibid.*, **82**, 1230 (1960).

(7) Clauberg assays were carried out under the supervision of Dr. E. Shipley of the Endocrine Labs, Madison, Wis., according to the McPhail modification [M. K. McPhail, *J. Physiol.* (London), **83**, 145 (1934)].