The **hydrochloride** was prepared in a yield of 47.3 g. (68%), m.p. 247–248°; ultraviolet analysis in 0.1 *N* HCl showed $\lambda_{max}$ 267 mμ ($E^{1\,cm}_{1\%}$ 5.91), 260.5 (8.97), 256 (9.98), 250.5 (7.39).

*Anal.* Calcd. for $C_{12}H_{18}ClN$: C, 68.07; H, 8.58; N, 6.62. Found: C, 68.14; H, 8.62; N, 6.64.

The base was treated with phenyl isothiocyanate to yield 1-phenyl-3-(1-phenylcyclohexyl)-2-thiourea, m.p. 168–169° (lit.[7] m.p. 156°).

*Anal.* Calcd. for $C_{19}H_{22}N_2S$: C, 73.50; H, 7.14. Found: C, 73.61; H, 7.29.

In addition, 1-phenylcyclohexylamine formed an acetate salt melting at 144–145° (lit.[7] m.p. 155°).

**B. From 1-Phenylcyclohexene.**—To a mixture of 1-phenylcyclohexene (15.8 g., 0.1 mole), 50 ml. of dibutyl ether, and NaCN (12.2 g., 0.25 mole) at 40° was added in 1 hr. 30 ml. of $H_2SO_4$. After stirring for an additional hour, the reaction mixture was poured into water and extracted with ether. The ether and dibutyl ether were distilled *in vacuo*, 30 ml. of HCl was added to the residue, and the mixture refluxed for 3 hr. The aqueous layer was separated, made alkaline with NaOH, and then extracted with ether.

The **hydrochloride** was prepared by adding a solution of HCl in 2-propanol, and the cloudy solution was evaporated to dryness. To the residue was added 20 ml. of acetone, and the crude product was recrystallized twice from methanol and ether to give needles, m.p. 247–248°. A mixture melting point of this hydrochloride with that prepared from 1-phenylcyclohexanecarboxamide showed no depression. The infrared spectra (KBr disk) were identical.

**1-Phenylcyclohexyl Isocyanate.**—In a separate preparation from 43.8 g. of 1-phenylcyclohexanecarboxamide, the intermediate 1-phenylcyclohexyl isocyanate was isolated by evaporation of the ether extracts. After separation of 4.7 g. of colorless crystalline material, presumably the urea, a yellow oil was obtained. This was distilled through a Vigreux column *in vacuo* to give 27.5 g. (63.5%) of colorless oil, b.p. 101–102° (0.25–0.40 mm.), $n^{27}D$ 1.5341; the ultraviolet spectrum in absolute ethanol had $\lambda_{max}$ 263 mμ ($E^{1\,cm}_{1\%}$ 8.6), 257 (11.8), 252 (10.4), and 247 (8.1).

*Anal.* Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.72; H, 7.51.

**Type IIc Compounds (Method G). 1-(*m*-Tolyl)-N-benzylcyclohexylamine.**—To a solution of *m*-tolyllithium [from *m*-bromotoluene (171 g., 1.0 mole), lithium (14 g., 2.0 g.-atoms), and 500 ml. of anhydrous diethyl ether] was added a solution of N-benzylcyclohexylideneamine [(187 g., 1.0 mole) prepared by refluxing a solution of benzylamine and cyclohexanone in toluene with a water trap] in 500 ml. of anhydrous diethyl ether over a period of 1 hr. at reflux. The reaction mixture was heated at reflux for an additional 3 hr.

After cooling in an ice bath, the reaction mixture was hydrolyzed with 300 ml. of water. The organic layer was separated and the aqueous layer was extracted with 100 ml. of benzene. The combined organic layers, after drying, were distilled to remove solvent, and the residue was distilled *in vacuo*. After removal of a forerun of N-benzylcyclohexylidineamine, there was obtained 72.5 g. of 1-(*m*-tolyl)-N-benzylcyclohexylamine (26% yield), $n^{28}D$ 1.5687, b.p. 137–140° (75 μ); the ultraviolet spectrum in 0.1 *N* HCl showed $\lambda_{max}$ 286 mμ ($E^{1\,cm}_{1\%}$ 45.2), 274 (45.8), 267 (47.2), and 257 (50.4).

*Anal.* Calcd. for $C_{20}H_{25}N$: C, 85.96; H, 9.02; N, 5.01. Found: C, 85.76; H, 9.34; N, 5.13.

The **hydrochloride** was prepared using 2-propanolic hydrogen chloride, m.p. 221–222°.

*Anal.* Calcd. for $C_{20}H_{26}ClN$: C, 76.04; H, 8.30; Cl, 11.23. Found: C, 76.18; H, 8.33; Cl, 11.32.

**1-(*m*-Tolyl)cyclohexylamine.**—1-(*m*-Tolyl)-N-benzylcyclohexylamine (30 g.) was reduced catalytically in glacial acetic acid using 20% palladium on carbon at an initial pressure of 3.5 kg./cm.² (50 p.s.i.). After removal of the catalyst, the filtrate was concentrated *in vacuo* to give a viscous liquid. On standing, this material crystallized. Recrystallization from 2-propanol and ether gave 8.0 g. of 1-(*m*-tolyl)cyclohexylamine acetate. Further recrystallization from 2-propanol gave colorless needles, m.p. 126–128°; the ultraviolet spectrum in 0.1 *N* HCl showed $\lambda_{max}$ 272 mμ ($E^{1\,cm}_{1\%}$ 17.4), 265 (19.6).

*Anal.* Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.63. Found: C, 71.89; H, 9.37; N, 5.56.

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# Structures Related to Morphine. XXVIII.[1] Alternative Syntheses of α- and β-2,9-Dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan

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α- and β-2,9-dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphans (VI and V, respectively) have been synthesized from either 7-methoxy-β-tetralone or 3-methyl-4-propylpyridine and degraded to 7-methoxy-2-methyl-1-propylnaphthalene. Certain reactions in these sequences can be stereo regulated, some to only a limited extent. The rate of methiodide formation and infrared absorption data have served to distinguish V and VI. Both isomers (particularly V) are potent analgetics.

In a "summary" paper[3] on 6,7-benzomorphans, the α-2,9-dimethyl-2′-hydroxy-5-propyl analog (VI) was included but only limited chemical and pharmacological data were then available. The present report is concerned with the synthesis of VI and the β-diastereoisomer (V) by two different routes (some of the reactions being stereo regulatable) along with analgetic (mice) and addiction (monkey) data.

When 1,3-dimethyl-2-(*p*-methoxybenzyl)-4-propyl-1,2,5,6-tetrahydropyridine (IV), prepared from 1,3-dimethyl-4-propylpyridinium iodide by a method described previously[3,4] for homologous series, was cyclized with 48% hydrobromic acid at 140–150° or with 85% phosphoric acid at 180°, a 40–50% yield of α-benzomorphan (VI) was obtained. However, contrary to previous experience,[3] no crystalline β-base (V) or salts

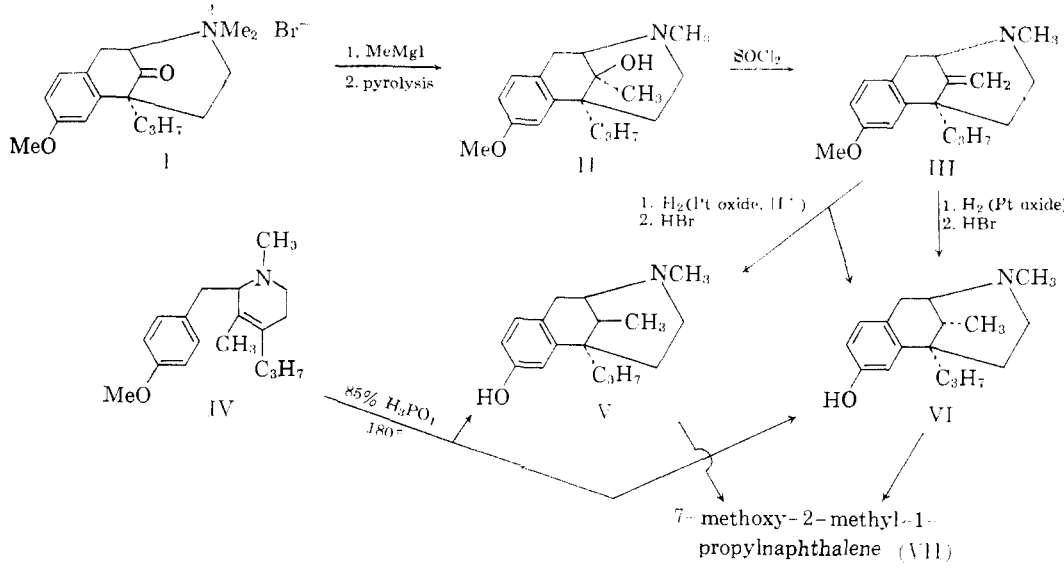
(1) Paper XXVII: A. E. Jacobson and E. L. May, *J. Med. Chem.*, **7**, 409 (1964).

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

(3) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

(4) E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

SCHEME I




thereof could be obtained from the mother liquors which consisted of three or four products as determined by thin layer chromatographic analysis. Consequently, we resorted to an alternative sequence[5] devised for the preparation of either $\alpha$- or $\beta$-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (one to the exclusion of the other) dependent upon stereochemical control of addition of hydrogen at one stage.

Stork propylation[6] of 3,4-dihydro-7-methoxy-2(1*H*)-naphthalenone followed by dimethylaminoethylation, bromination, and cyclization in the usual manner[7] afforded 2′-methoxy-2-methyl-9-oxo-5-propyl-6,7-benzomorphan methobromide (I) without complications. Addition of methylmagnesium iodide to I likewise proceeded normally[8] to give, after dry distillation of the isolated methiodide of II, the $\alpha$-methylcarbinol (II) whose infrared absorption (in carbon tetrachloride) at 3440 cm.$^{-1}$ showed clearly that the hydroxyl was intramolecularly bonded to nitrogen, therefore oriented toward nitrogen (in equatorial conformation for the hydroaromatic ring).[8]

Thionyl chloride treatment of II gave a mixture of products which could be separated by careful column chromatography into three isomeric fractions (about 30% yield of each), one of which proved to be the desired 9-methylene compound (III). In the 5,9-dimethyl series a 70% yield of 9-methylene derivative had been obtained.[5] Hydrogenation of III in alcohol with platinum oxide gave a quantitative yield of homogeneous material which, after O-demethylation, yielded a product that was identical with the $\alpha$-benzomorphan (VI) prepared from 3-methyl-4-propylpyridine (see Scheme I). When the hydrogenation was conducted in aqueous, alcoholic hydrochloric acid, the stereochemistry of addition was only partially reversed; O-demethylation of the resultant mixture and separation of the phenolic bases gave approximately equal parts of VI and the $\beta$-isomer.[9]

Hofmann degradation of the methyl ethers of V and VI and palladium–charcoal aromatization of the resulting open nitrogen compounds gave, in each case, 8–10% yields of 7-methoxy-2-methyl-1-propylnaphthalene (isolated as the picrate) proving their diastereoisomeric relationship at C-9. Infrared data,[10a] rate of quaternization by methyl iodide (10:1 favoring VI),[10b] and analgetic evaluation[3] distinguish the $\alpha$- and $\beta$-isomers. On seeding the mother liquors of VI obtained from IV with the V hydrobromide prepared from III, a 5–10% yield of V hydrobromide crystallized.

The subcutaneous analgetic activity of II, V, and VI (all racemates) was determined in mice (hot plate method).[3] Compound II was codeine-like, and $\alpha$-isomer VI ($ED_{50}$ 2.9 mg./kg.)[3] was comparable to morphine ($ED_{50}$ 2.1 mg./kg.). The $\beta$-isomer V ($ED_{50}$ 0.12 mg./kg.) is the second most potent compound of the benzomorphan series.[3] Its oral activity was also relatively high ($ED_{50}$ 4 mg./kg.). Thus, V and VI (total number of carbons in the positions 5 and 9 equal to 4) are comparable to the $\alpha$- and $\beta$-diethyl relatives.[3] The acute toxicity (mice, subcutaneous administration) of V is comparatively low ($LD_{50}$ *ca.* 250 mg./kg.) so that its therapeutic index (2500) is very favorable.

Regarding drug dependence, the $\alpha$-isomer (VI), like other members of the $\alpha$-series and the 5-(mono-) alkyl derivatives,[3] has little or no capacity to suppress withdrawal symptoms in monkeys stabilized on 3 mg./kg. of morphine, at doses of 2–16 mg./kg.; the 16-mg. dose caused convulsions. However, at 4 mg./kg. (about 30 times the mouse analgetic dose) nearly complete suppression was observed with the $\beta$-compound (V).[11] Thus it is apparent that, while definite separation of analgetic activity (in mice) and abstinence-suppressant efficacy (in monkeys) has been demonstrated for the highly potent $\beta$-benzomorphans, a much more favor-

(5) S. Saito and E. L. May, *J. Org. Chem.*, **27**, 1087 (1962).

(6) G. Stork, A. Brizzolara, H. Landesman, J. Szmiszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(7) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

(8) E. L. May and H. Kugita, *ibid.*, **26**, 188 (1961); S. Saito and E. L. May, *ibid.*, **26**, 4536 (1961).

(9) In the 5-methyl-9-methylene series,[5] a 70% yield of $\beta$-isomer and no $\alpha$-isomer was obtained. The additional bulk of the 5-propyl radical in III probably accounts for this partial loss of stereoselectivity, hitherto thought to be regulated principally by the electrical environment of the neighboring nitrogen.[8]

(10) (a) S. E. Fullerton, J. H. Ager, and E. L. May, *J. Org. Chem.*, **27**, 2554 (1962); (b) S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).

(11) G. A. Deneau, University of Michigan, personal communication; see also ref. 3.

able (in fact nearly complete) divorcement of these two parameters is seen with the α- and 5-alkylbenzomorphans,[3] analgetically comparable to morphine.

## Experimental

Melting points, taken in a capillary, are corrected. Microanalyses are by Paula Parisius, Evelyn Peake, Alice Wong, and Byron Baer of this laboratory.

**1,3-Dimethyl-4-propylpyridinium Iodide.**—A mixture of 39 ml. (36 g.) of 3-methyl-4-propylpyridine, 34 ml. of methyl iodide, and 50 ml. of acetone were kept at room temperature (occasional ice cooling) for 2–3 hr., diluted with 20 ml. of ethyl acetate, and cooled to −15°; the yield of iodide was 62.7 g. (85%), m.p. 113–114° (from acetone–ethyl acetate).

*Anal.* Calcd. for $C_{10}H_{16}IN$: C, 43.3; H, 5.8. Found: C, 43.1; H, 5.6.

**1,3-Dimethyl-1-(*p*-methoxybenzyl)-4-propyl-1,2,5,6-tetrahydropyridinium Chloride.**—To 62.7 g. of the above iodide, 343 ml. of 1 *N* sodium hydroxide and 115 ml. of methanol was added (stirring) 11.0 g. of sodium borohydride. The temperature rose to 55–60° where it was maintained for 90 min. The mixture was diluted with cold water and extracted three times with ether. The combined extracts were washed once with water, dried ($Na_2SO_4$), and evaporated at the water pump, leaving 35 g. of crude base which was treated with 36.0 g. of *p*-methoxybenzyl chloride in 50 ml. of acetone (exothermic reaction). After cooling to room temperature then to −15° (2 hr.), 52.3 g. (68%) of white solid, m.p. 138–141° (after drying at 50°, vacuum oven), separated; thin prisms from acetone, m.p. 139–141°.

*Anal.* Calcd. for $C_{18}H_{28}ClNO$: C, 69.8; H, 9.11. Found: C, 69.6; H, 9.4.

**1,3-Dimethyl-2-(*p*-methoxybenzyl)-4-propyl-1,2,5,6-tetrahydropyridine (IV) Picrate.**—To 52.3 g. of the above chloride was added (stirring) as rapidly as possible, 262 ml. of 2.0 *M* ethereal phenyllithium. The mixture was stirred for 2 hr. after the initial vigorous ebullition had ceased and was poured into ice water. The ethereal layer was extracted three times with excess 10% hydrochloric acid, the combined extracts were made alkaline with aqueous ammonia, and the liberated base was dried in ether. Evaporation of the ether left 45 g. of liquid which in 100 ml. of acetone was treated with 45.0 g. of picric acid to give 51.2 g. (44%) of the picrate of IV; yellow rods from acetone, m.p. 114–115°.

*Anal.* Calcd. for $C_{24}H_{30}N_4O_8$: C, 57.4; H, 6.0; N, 11.2. Found: C, 57.3; H, 5.8; N, 11.1.

**3,4-Dihydro-7-methoxy-1-propyl-2(1H)-naphthalenone Semicarbazone.**—Pyrrolidine (18.4 g.) was added dropwise (stirring, nitrogen atmosphere) to 33.2 g. of 3,4-dihydro-7-methoxy-2-(1H)-naphthalenone[12] in 150 ml. of benzene. The mixture was refluxed for 1 hr. (3 ml. of water distilling azeotropically), cooled, and treated with 141 g. of propyl iodide in one lot. After refluxing for 21 hr., 150 ml. of water was added, and the mixture was stirred and refluxed for another 12 hr. The aqueous layer was separated and shaken with two 150-ml. portions of benzene, and the benzene was dried ($Na_2So_4$). Solvent was removed at the water pump and the residue was distilled to give 33.0 g. of 3,4-dihydro-7-methoxy-1-propyl-2(1H)-naphthalenone, b.p. 122–126° (0.1 mm.), $n^{20}D$ 1.5433. A small sample was converted to the semicarbazone (semicarbazide hydrochloride, sodium acetate, ethanol–water); small prisms from methanol, m.p. 134–135°.

*Anal.* Calcd. for $C_{15}H_{21}N_3O_2$: C, 65.4; H, 7.7; N, 15.3. Found: C, 65.2; H, 7.5; N, 15.2.

**3,4-Dihydro-1-(2-dimethylaminoethyl)-7-methoxy-1-propyl-2(1H)-naphthalenone Hydrobromide.**—3,4-Dihydro-7-methoxy-1-propyl-2(1H)-naphthalenone (33 g.) in 60 ml. of benzene was added dropwise during 40 min. to a stirred, refluxing suspension of 5.7 g. of sodamide in 60 ml. of benzene. After 2 hr. of refluxing, 17 g. of 2-chloro-N,N-dimethylethylamine in 150 ml. of benzene was added dropwise during 3 hr.; the mixture was refluxed and stirred for a further 16 hr. The benzene was washed with two 100-ml. portions of water and extracted three times with excess 10% HCl. The combined acid extracts were made basic with concentrated ammonium hydroxide and extracted with four 200-ml. portions of ether to give, after drying and distillation of ether, an oil, b.p. 123–128° (0.03–0.07 mm.). The distillate (23 g.) in 250 ml. of ether was acidified with 30% hydrogen bromide in acetic acid to give, after storage at −5° overnight, 30 g. of hydrobromide, m.p. 171–178°; small prisms from acetone, m.p. 188–189°, $\lambda_{max}^{Nujol}$ 5.85 μ.

*Anal.* Calcd. for $C_{18}H_{28}BrNO_2$: C, 58.4; H, 7.6; N, 3.78. Found: C, 59.4; H, 7.6; N, 3.6.

**3-Bromo-3,4-dihydro-1-(2-dimethylaminoethyl)-7-methoxy-1-propyl-2(1H)-naphthalenone Hydrobromide.**—Bromine (12.6 g.) in 150 ml. of acetic acid was added dropwise (stirring) during 40 min. to a refluxing solution of 29 g. of the above hydrobromide in 150 ml. of acetic acid. The solution was allowed to cool to room temperature under a stream of nitrogen, then diluted with 2 l. of ether. The oil which precipitated solidified on storage overnight at −5°; yield 20 g. of hydrobromide, m.p. 152–154°. Evaporation of the filtrate to dryness and crystallization of the residue from ethanol–ether gave an additional 5.8 g.; small prisms from methanol–acetone, m.p. 160–161°.

*Anal.* Calcd. for $C_{18}H_{27}Br_2NO_2$: C, 48.1; H, 6.1; Br, 35.7; N, 3.1. Found: C, 48.4; H, 6.0; Br, 35.2; N, 3.0.

**2′-Methoxy-2-methyl-9-oxo-5-propyl-6,7-benzomorphan Methobromide (I).**—Finely divided 3-bromo-3,4-dihydro-1-(2-dimethylaminoethyl)-7-methoxy-1-propyl-2(1H)-naphthalenone hydrobromide (10.2 g.), 90 ml. of water, and 35 ml. of concentrated ammonium hydroxide were shaken vigorously with three 50-ml. portions of ether, and the layers separated quickly. The combined ethereal extracts were evaporated at the water pump, and the residue was crystallized from acetone–ether; yield of I, m.p. 178–180°, 6.6 g. The analytical sample melted at 188–189°, feathery plates.

*Anal.* Calcd. for $C_{18}H_{26}BrNO_2$: C, 58.7; H, 7.1; N, 3.8. Found: C, 58.6; H, 6.9; N, 3.6.

**α-2,9-Dimethyl-9-hydroxy-2′-methoxy-5-propyl-6,7-benzomorphan (II) Methiodide.**—Ethereal methylmagnesium iodide (from 2.7 g. of methyl iodide, 2.2 g. of magnesium, and 100 ml. of ether) was added dropwise to a stirred suspension of 6.6 g. of I in 50 ml. of anhydrous ether. The mixture was stirred and refluxed for 44 hr., then poured onto ice (26 g.), potassium iodide (15 g.), and concentrated hydrochloric acid (14.5 ml.). After stirring for 2 hr., the solid was filtered, washed with ether, and crystallized from methanol–acetone to give 4.1 g. of II methiodide, m.p. 200–202°. The analytical sample melted at 209–210°.

*Anal.* Calcd. for $C_{19}H_{30}INO_2$: C, 52.9; H, 7.0; N, 3.3. Found: C, 52.5; H, 6.8; N, 3.5.

The **base** II was prepared in a yield of 0.19 g. (90%) by dry distillation (0.1 mm., bath temperature 180–185°) of 0.3 g. of II methiodide; prismatic crystals from ligroin (30–60°), m.p. 101–102°, $\nu_{max}^{CCl_4}$ 3445 cm.$^{-1}$ (OH–N bonding).[8]

*Anal.* Calcd. for $C_{18}H_{27}NO_2$: C, 74.7; H, 9.4; N, 4.8. Found: C, 74.5; H, 9.3; N, 4.6.

**α-2,9-Dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan (VI).**

**A. From IV.**—Phosphoric acid (200 ml., 85%) and 24 g. of IV (regenerated from the picrate with aqueous lithium hydroxide and ligroin) were kept at a bath temperature of 180–185° for 48 hr., poured into ice, made alkaline with aqueous ammonia, and the liberated material was extracted with chloroform. Evaporation of the dried extracts in *vacuo* left a residue which crystallized from acetone (cooling to 0°) in a yield of 10.9 g. (46%), m.p. 208–211°. After a recrystallization from ethanol or acetone it melted at 210–211°; $\lambda_{max}^{Nujol}$ 6.15 (w), 6.3 (m) μ.

*Anal.* Calcd. for $C_{17}H_{25}NO$: C, 78.7; H, 9.7. Found: C, 78.9; H, 9.8.

The **hydrobromide** crystallized from acetone–ether; m.p. 230–232° dec.

*Anal.* Calcd. for $C_{17}H_{26}BrNO$: C, 60.0; H, 7.7. Found: C, 59.7; H, 7.8.

**B. From II *via* III.**—Thionyl chloride (25 ml.), 0.5 ml. of pyridine, and 2.5 g. of II were kept at 40° for 2 hr. (stirring).[13] Volatile materials were removed at the water pump, and the residue was treated with ice, made alkaline with aqueous am-

(12) B. W. Harrom and H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 721 (1950); G. B. Diamond and M. D. Soffer, *ibid.*, **74**, 4126 (1952). Attempts to prepare this compound from ethylene and *m*-methoxyphenylacetyl chloride according to J. H. Burckhalter and J. R. Campbell, *J. Org. Chem.*, **26**, 4232 (1961), were unsuccessful, although β-tetralone could be readily obtained by us using their procedure.

(13) With the 5,9-dimethyl homolog of II,[5] the reaction time was 50 hr. However, thin layer chromatograms of aliquots taken at various times indicated that the reaction products (in the present case) were essentially constant after 0.5–1 hr. and remained so to 50 hr.

monia, and extracted with three 50-ml. portions of ether. After drying ($Na_2SO_4$), the ether was evaporated to give 2.3 g. of crude residue which was evaporatively distilled (bath temperature 150–170°, 0.1 mm.) to give 1.8 g. of a viscous, yellow oil. This oil in ligroin (b.p. 66-75°) was chromatographed over a column of alumina (55 g., Woelm grade III, neutral) using increasing proportions of benzene in ligroin. The fractions eluted by 30:55 benzene–ligroin were combined to give 0.6 g. of crude **9-methylene derivative (III)**, $\lambda_{max}^{smear}$ 6.05 and 11.1 $\mu$. This III (0.32 g.), 50 ml. of ethanol, and 0.16 g. of platinum oxide were shaken under hydrogen; the theoretical amount of hydrogen was absorbed in 1 hr. Evaporation of the filtered solution to dryness left 0.3 g. of an oil which was converted to 0.2 g. of hydrochloride (acetone, hydrogen chloride, cooling to −5°). Refluxing 0.5 hr. with 2.5 ml. of 48% hydrobromic acid, making alkaline with aqueous ammonia, and extraction with three 20-ml. portions of chloroform gave, after drying and evaporation of the chloroform, 0.2 g. of residue. It was triturated in acetone to give 0.15 g. of VI, m.p. 211-213°, identical (infrared and melting point comparison of bases and hydrobromides) with that prepared from 3-methyl-4-propylpyridine *via* IV.

**β-Isomer (V) Hydrobromide. A. From III.**—Ethanol (10 ml.), 0.43 g. of III, 20 ml. of 15% hydrochloric acid, and 0.2 g. of platinum oxide absorbed the calculated amount of hydrogen in 2.5 hr. The filtered solution was evaporated to dryness leaving 0.44 g. of residue. This and 5 ml. of 48% hydrobromic acid were refluxed for 0.5 hr., made alkaline with aqueous ammonia, and extracted with three 25-ml. portions of chloroform. Evaporation of the dried extracts left 0.38 g. of residue which, after trituration with acetone (30–40 ml.), was stored at −5° overnight to give 0.13 g. of α-isomer (VI), m.p. 208-210°. Acidification of the filtrate with hydrogen bromide, addition of ether to slight turbidity, and storage at −5° gave 40 mg. of V hydrobromide, m.p. 250-252° (sinters at 225°). On recrystallization from acetone, prisms, m.p. 263–264°, were obtained.

*Anal.* Calcd. for $C_{17}H_{26}BrNO$: C, 60.0; H, 7.7; N, 4.1. Found: C, 59.9; H, 7.9; N, 4.1.

The **base V** was prepared by treating a methanolic solution of the hydrobromide with a few drops of aqueous ammonia and dilution with water; prisms from methanol–water, m.p. 171–172°, $\lambda_{max}^{Nujol}$ 6.2 (s) $\mu$.

*Anal.* Calcd. for $C_{17}H_{25}NO$: C, 78.7; H, 9.7; N, 5.4. Found: C, 78.9; H, 9.6; N, 5.4.

**B. From IV.**—The acetone filtrate from the 10.9 g. of VI above (in the preparation of VI from IV) was concentrated to *ca.* 15 ml. and cooled to −15° overnight to give 1.4 g. of crystals, m.p. 215–220°.[14] The filtrate was evaporated to dryness. The residue was evaporatively distilled at 0.05 mm. (bath temperature 180–190°) and the viscous distillate dissolved in 8–10 ml. of acetone. Cooling to −15° for several days gave 1.4 g. of solid, m.p. 183–191°, principally VI but containing also a little V and the isomeric by-product[14] as shown by thin layer chromatography. The filtrate was acidified to pH 2 with hydrogen bromide, diluted to a faint turbidity with ether, and seeded with V hydrobromide obtained from III. On cooling to −15° for a few days, 2.1 g. of the hydrobromide of V, m.p. 253–258°, was obtained. After a recrystallization from 3:1 acetone–ether, the m.p. was 264–266°. This hydrobromide and the free base prepared from it were identical (melting point, infrared, etc.) with those prepared from III. From the filtrate of the 2.1 g., 0.33 g. more β-hydrobromide was obtained; total yield 8%.

**Methiodide Rate Studies.**—By the method published earlier[10b] isomer VI was found to react with methyl iodide ten times more rapidly than V, leaving no doubt about their configuration at C-9.

**α-2,9-Dimethyl-2′-methoxy-5-propyl-6,7-benzomorphan Methiodide (VIII).**—Methanol (10 ml.), 1.0 g. of VI, and 15 ml. of *ca.* 3% ethereal diazomethane were stirred to solution. Two more portions of the diazomethane (10 ml. each) were added at 24-hr. intervals during 48 hr. Solvents were evaporated *in vacuo*. The residue was evaporatively distilled at 0.1 mm. (bath temperature 150–160°) to give 1.0 g. of distillate to which in 10 ml. of acetone was added 1.0 ml. of methyl iodide. After 2 hr. at 25–30° and cooling to −15°, 1.1 g. of methiodide separated; m.p. 213–215°, plates from ethanol.

*Anal.* Calcd. for $C_{19}H_{30}INO$: C, 54.9; H, 7.3. Found: C, 55.0; H, 7.0.

**β-2,9-Dimethyl-2′-methoxy-5-propyl-6,7-benzomorphan Methiodide (IX).**—As described for the α-isomer (VIII), this methiodide was obtained from V in a yield of 90%; prisms from acetone–ethyl acetate, m.p. 172–175°.

*Anal.* Calcd. for $C_{19}H_{30}INO$: C, 54.9; H, 7.3. Found: C, 55.2; H, 7.3.

**7-Methoxy-2-methyl-1-propylnaphthalene Picrate.**—The methiodide of α-2,9-dimethyl-2′-methoxy-5-propyl-6,7-benzomorphan (0.75 g.) and 10 ml. of 10% aqueous potassium hydroxide were kept on the steam bath for 2 hr. The liberated methine was dried in ether and mixed intimately with 0.6 g. of 5% palladium–charcoal in a small test tube which was then immersed in a bath preheated to 275°. The bath temperature was raised to 320° for 15 min. The mixture was extracted three times with ether and the combined extracts were shaken with dilute hydrochloric acid. Drying and evaporation of the ether left 0.15 g. of liquid which was treated with 0.2 g. of picric acid in 2–3 ml. of hot 80% aqueous methanol. On cooling to 0° 125 mg. (15%) of orange needles, m.p. 85-95°, separated. The analytical sample (from methanol) melted at 97–99°.

*Anal.* Calcd. for $C_{21}H_{21}N_3O_8$: C, 56.9; H, 4.8. Found: C, 57.0; H, 5.0.

Similar degradation of the methiodide of β-2,9-dimethyl-2′-methoxy-5-propyl-6,7-benzomorphan gave the same picrate as shown by infrared and melting point data.

The free hydrocarbon prepared from the pure picrate gave an n.m.r. spectrum consistent with the structure VII.

**Acknowledgment.**—We are indebted to the Reilly Tar and Chemical Corporation for 3-methyl-4-propylpyridine.[15]

(14) Recrystallization of this fraction from acetone–methanol raised the melting point to 228–230°. It proved to be isomeric with V and VI and its n.m.r. spectrum was compatible with an indano structure, one which would result from cyclization of IV to a five-membered ring compound. *Anal.* Calcd. for $C_{17}H_{25}NO$: C, 78.7; H, 9.7; N, 5.4. Found: C, 78.4; H, 10.0; N, 5.3. We have reported a similar finding in another series.[10a]

(15) Initially prepared in fair yield according to J. P. Wibaut and S. Vroonen, *Rec. trav. chim.*, **67**, 545 (1948).