were seen at 254 mμ (ε 3070), 298 mμ (ε 5250) and 306 mμ (ε 5370) and an inflection at 318 mμ (ε 2950).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; neut. equiv., 271. Found: C, 71.11; H, 6.31; neut. equiv., 270.

The *hydriodide* was prepared with dilute acetic acid and potassium iodide and recrystallized from water as prisms, m.p. 178–180° (reported[2a] 178°); ν_{max}^{KBr} 1759 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{18}NO_3I$: C, 48.13; H, 4.54. Found: C, 48.26; H, 4.61.

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[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. XVII.[1] Further Stereochemical Studies with 9-Oxobenzomorphans

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Addition of methylmagnesium iodide to 2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (II) has afforded the 9-methylcarbinol methiodide (III) with the hydroxyl oriented toward the *cis*-fused iminoethano system as shown by degradation to the known *cis*-fused furan derivatives IV and VIII. Pyrolysis of III in boiling 1-nonanol yielded the base VII. Methyllithium and the free base VI on the other hand produced the diastereoisomer (X) which was also degraded to a nitrogen-free compound, presumably the *trans*-fused furan XI. A similar stereochemical pattern was followed in the addition of hydrogen to II and VI. Spectral data furnished additional proof of our assignments which are in conformity with and confirmatory of those made in the 2′-methoxy series (*cf.* References 1 and 2). Compounds VII, X, XIII, XV, and the *O*-acetyl derivative of XV have been tested for analgesic activity.

In a previous paper[2] we reported that the addition of methyl metallo reagents to 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (I) afforded only one of the two possible methylcarbinols in 75% yield; when the free base corresponding to I was used, the stereochemistry of addition was reversed. As one aspect of the determination of configuration of these methyl carbinols it was decided to degrade them to nitrogen-free products by two Hofmann elimination reactions. Somewhat unexpectedly,[3] in both instances, the two final products, obtained in good yield, exhibited characteristics of tetrahydrofurano compounds which were not identical. To help distinguish between these two it was deemed relevant to degrade similarly the methylcarbinol methiodide (III)[4] which, if the hydroxyl were *cis* (equatorial for the hydroaromatic ring) to the *cis*-fused iminoethano system, should lead to the known synthetic 1,2,3a,9b-tetrahydro-*cis*-3a,9b-dimethylnaphtho[2,1-b]furan (IV).[5] In the present report details of this degradation, of the addition of methyllithium to the base, VI, of the addition of hydrogen to II and VI and of an improved synthesis of II and VI are given.

Double Hofmann degradation of the methylcarbinol methiodide (III)[4] yielded a nitrogen-free product whose infrared and ultraviolet spectra corresponded with those of 1,2,3a,9b-tetrahydro-*cis*-3a,9b-dimethylnaphtho[2,1-b]furan (IV) synthesized by Fry.[5] Hydrogenation of the IV obtained by degradation gave VIII also identical with synthetic material.[5] Furthermore, the infrared spectrum of the base VII (prepared from III in boiling 1-nonanol) in chloroform was indicative of OH—N bonding (broad, strong band at 3450 cm.$^{-1}$). These facts confirm the assignments for III and VII as well as those made in the 2′-methoxy series as stated before.[2] Hydrogenation of II (platinum oxide) produced the carbinol XV (after cleavage of methyl iodide consistent with results in the 2′-methoxy series.[1]

Also in analogy with the 2′-methoxy series, reaction of the base VI with methyllithium or with platinum oxide-catalyzed hydrogen afforded the diastereoisomers X and XIII respectively of VII and XV. Degradation of X gave a nitrogen-free product whose infrared and ultraviolet absorption data were compatible with the *trans*-fused furan structure (XI)[2] and which absorbed one mole of hydrogen to give presumably XII.

In the course of the above work an improved synthesis of the ketone methobromide II[6] was developed. This improvement hinged largely on the use of 3,4-dihydro-1-methyl-2(1*H*)naphthalenone prepared by the method of Stork.[7] Further exploration of the pyrolysis of II to VI, previously carried out unsatisfactorily by dry distillation of II[6] has been made also. In boiling 1-hexanol, heptanol, octanol, or nonanol, the principal product

(1) H. Kugita and E. L. May, *J. Org. Chem.*, in press. Hiroshi Kugita, Visiting Scientist, Osaka, Japan.

(2) E. L. May and H. Kugita, *J. Org. Chem.*, 26, 188 (1961).

(3) Molecular models indicate unfavorable geometry for closure of a *trans*-fused tetrahydrofuran ring.

(4) E. L. May and E. M. Fry, *J. Org. Chem.*, 22, 1366 (1957).

(5) E. M. Fry, *J. Org. Chem.*, 22, 1710 (1957).

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

(7) G. Stork, U. S. Pat. 2,773,099; *Chem. Abstr.*, 51, 9703d (1957).

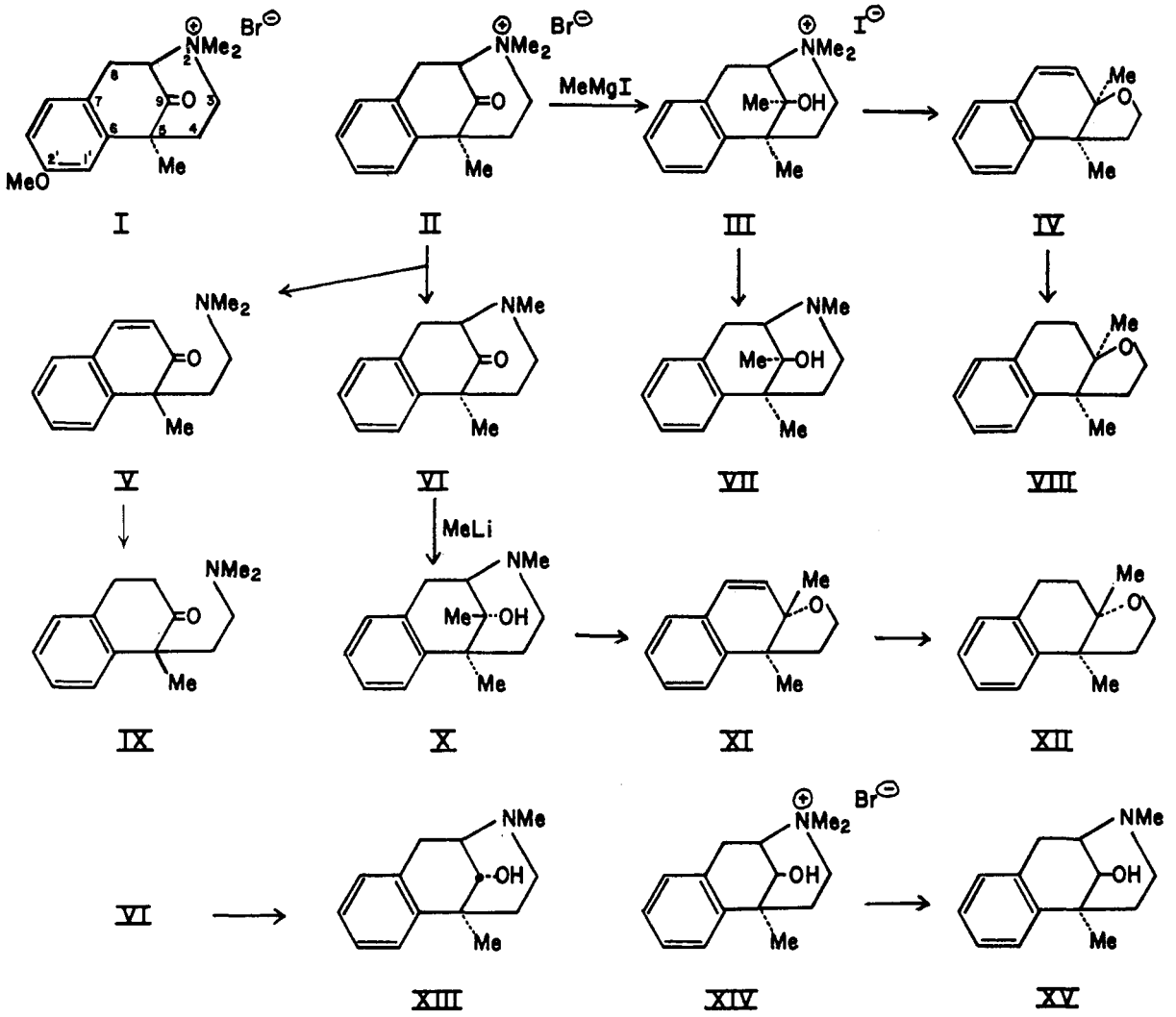

Figure 1

was the α,β-unsaturated ketone V (40%); the yield of the desired VI never exceeded 20%, octanol being optimal. Acidification of VI with hydrogen chloride gave a hydrochloride salt which generally showed no carbonyl absorption (Nujol) in the infrared and which gave an analysis agreeing with a hydrate, in analogy with previous findings in the 2′-methoxy series.[8] By rigorous exclusion of moisture (dry ether, hydrogen chloride gas) it was possible to obtain a hydrochloride salt of II showing normal carbonyl absorption. Apparently as in the 2′-methoxy series[8] there is strong affinity of the carbonyl group for water when the nitrogen is protonated.

Compounds VII, X, XIII, XV, and the *O*-acetyl derivative of XV have been tested in mice for analgesic effectiveness. In Table I are given analgesic activities for all the 9-hydroxy-6,7-benzomorphans tested to date. In general the α-9-hydroxy compounds are more effective than the β-derivatives. With only one exception (NIH 7806) the phenolic compounds were superior in effectiveness to the corresponding 2′-methoxy or 2′-deoxy analogs as expected. In one instance (7861) the substitution of phenethyl for methyl (7808) on the nitrogen increases potency more than one hundredfold; in another (compare 7831 with 7764) there is little change. It is also apparent that replacement of the 9-hydrogen by hydroxyl in the benzomorphan series[9] adversely affects analgesic potency. Particularly noteworthy, however, are the high degree of effectiveness of the di-*O*-acetyl compounds 7830 and 7802 (four and two times as potent respectively as morphine) and the good oral activity (three times that of codeine in mice) of the codeine-like substance 7656.

(8) Boiling 1-octanol and the 2′-methoxy derivative of II gave a 40% yield of the bicyclic ketone corresponding to VI and a 20–25% yield of the Hofmann product (J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

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

TABLE I

ANALGESIC ACTIVITY OF 9-HYDROXY-6,7-BENZOMORPHANS

NIH No.	α-9-Hydroxy-6,7-benzomorphan	ED_{50}, Mg./Kg.[a]
7858	2,5-Dimethyl (XV)	63.8 (58.2–69.9)
7863	*O*-Acetyl derivative	29.0 (23.4–36.1)
7832	2,5,9-Trimethyl (VII)	43.7 (41.0–46.5)
7807	2′-Methoxy-2,5-dimethyl[1]	ca. 100
7808	2′-Hydroxy-2,5-dimethyl[1]	79.9 (73.8–86.5)
7830	Di-*O*-Acetyl derivative[1]	0.51 (0.46–0.56)
7862	2′-Methoxy-5-methyl-2-phenethyl[1]	22.2 (18.9–26.1)
7861	2′-Hydroxy-5-methyl-2-phenethyl[1]	0.62 (0.53–0.71)
7656	2′-Methoxy-2,5,9-trimethyl[2]	19.7 (17.0–22.7) Oral: 13.5
7764	2′-Hydroxy-2,5,9-trimethyl[2]	6.91 (5.74–8.33)
7802	Di-*O*-Acetyl derivative[2]	1.07 (0.95–1.21)
7831	2′-Hydroxy-5,9-dimethyl-2-phenethyl[2]	7.49 (6.61–8.48)
	β-9-Hydroxy-6,7-benzomorphan	
7860	2,5,9-Trimethyl (X)	112.1 (83.9–150.0)
7809	2′-Methoxy-2,5-dimethyl[1]	47.3 (42.7–52.4)
7806	2′-Hydroxy-2,5-dimethyl[1]	>100
7811	2′-Methoxy-2,5,9-trimethyl[2]	>100
7810	2′-Hydroxy-2,5,9-trimethyl[2]	6.03 (5.25–6.93)

[a] Compounds were tested as hydrochloride or hydrobromide salts (subcutaneous administration, mice) by Dr. Nathan B. Eddy and staff, by a method described previously [N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953)]. The ED_{50} is derived by probit analysis of the data performed by Mrs. Wendy Ness; figures in parentheses are 1 × S.E. limits. The ED_{50} of morphine sulfate is 2.0 mg./kg.

EXPERIMENTAL

Melting points were taken in a capillary (Hershberg apparatus, total-immersion thermometers). Microanalyses are by Paula Parisius of the Analytical Services Unit of this laboratory, Harold McCann, director. Infrared determinations are by H. K. Miller and Ann Wright, also of this laboratory.

3,4-Dihydro-1-(2-dimethylaminoethyl)-1-methyl-2(1H)-naphthalenone (IX)[6] *hydrobromide.* To a stirred refluxing mixture of 8.2 g. of sodamide and 100 ml. of benzene was added during 5–10 min., 30 g. of 3,4-dihydro-1-methyl-2-(1H)naphthalenone (b.p. 90–91°/0.7 mm., n_D^{20} 1.5542).[7] The mixture was refluxed for 1 hr. and treated (while refluxing) with 23 g. of 2-chloro-*N*,*N*-dimethylethylamine in 100 ml. of benzene during 1 hr. After refluxing and stirring for an additional 9 hr., the mixture was shaken twice with water and then thrice with excess dilute hydrochloric acid. The combined acid extracts were made alkaline and extracted with ether. Drying and evaporation of the ethereal extracts left an oil which, after evaporative distillation (bath temperature 125–150°) at 0.3 mm., weighed 29 g. Neutralization of this in ether with 30% hydrogen bromide in acetic acid gave 37 g. of hydrobromide, m.p. 185–189°; leaflets from acetone-methanol, m.p. 187–189°.

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.54; H, 7.33.

2,5-Dimethyl-9-oxo-6,7-benzomorphan methobromide (II). To a stirred refluxing solution of 36.5 g. of IX hydrobromide in 185 ml. of acetic acid was added during 20 min. 6 ml. of bromine in 35 ml. of acetic acid. The solution was cooled under a swift stream of nitrogen, treated with 185 ml. of ether and left at −5° overnight to give 30–34 g. of bromo ketone hydrobromide, m.p. 142–145° dec.[8] This finely divided material (34 g.) in a separatory funnel was covered with cold water and 250 ml. of ether and 10–11 ml. of concd. ammonium hydroxide were added. The mixture was shaken to disappearance of almost all solid and the ether layer was taken to dryness at the water pump.[10] Digestion of the residue with warm acetone to complete crystallization, and cooling to −5° gave 21 g. (77% based on IX hydrobromide) of II, m.p. 198–200°, λ_{max}^{Nujol} 5.74 μ.

2,5-Dimethyl-9-oxo-6,7-benzomorphan (VI) *hydrochloride.* A mixture of 3.8 g. of II and 15 ml. of 1-octanol[11] were stirred and refluxed for 10 min., cooled under nitrogen, and treated with dilute hydrochloric acid and ether. The acid layer was made alkaline and extracted with ether. After drying and distillation of the ether the residue was evaporatively distilled (0.2 mm., 125°) giving 1.9 g. of oil, λ_{max}^{smear} 5.75 μ (VI) and 6.03 μ (V). The ratio of VI to V appeared to be 2 to 3.5 based on carbonyl band intensity. It was neutralized in ether with hydrogen chloride gas. After cooling the ether was decanted and the residue digested with acetone. After thorough cooling the yield of VI hydrochloride of m.p. 228–230°, was 0.7 g. (20%). It had an analysis corresponding to the hemihydrate and showed a medium hydroxyl (3.09 μ) and a strong carbonyl (5.74 μ) band in Nujol.

Anal. Calcd. for $C_{14}H_{18}ClNO \cdot {}^1/_2H_2O$: C, 64.48; H, 7.34; Cl, 13.60. Found: C, 64.27; H, 7.47; Cl, 13.21.

Recrystallization of this hydrochloride from alcohol-ether gave material melting partially at 145° and with decomposition at 230°; λ_{max}^{Nujol} 3.09 μ (no carbonyl band).[12]

Anal. Calcd. for $C_{14}H_{18}ClNO \cdot H_2O$: C, 62.41; H, 7.45. Found: C, 61.93; H, 7.56.

The filtrate from the above 0.7 g. of VI hydrochloride was evaporated to dryness *in vacuo*. The residual sirupy hydrochloride (1.4 g.) in 15 ml. of methanol with 0.5 g. of 10% palladium-charcoal absorbed 1.6 molar equivalents of hydrogen based on V) during 30 min. The reduced material was isolated as the hydrobromide salt (0.7 g.) which proved to be identical with the synthetic IX hydrobromide (m.p., infrared spectra of hydrobromide, and perchlorate[6]).

1,2-Dihydro-1-(2-dimethylaminoethyl)-2-hydroxy-1,2-dimethylnaphthalene methiodide. Compound II (1.4 g.)[4] and 15 ml. of 10% sodium hydroxide were kept on the steam bath for 3 hr. and extracted with ether. Evaporation of the dried extracts left an oil which was evaporatively distilled (0.2 mm./150–160°) to give 0.6 g. (60%) of base showing strongly associated hydroxyl in the infrared. With 0.3 ml. of

(10) It is necessary to work rapidly due to the rapid formation of the ether-insoluble, water-soluble II.

(11) Hexanol, heptanol, and nonanol gave similar results but octanol gave the best yield of VI.

(12) Analogous to the 2′-methoxy series (*cf.* Ref. 8).

methyl iodide (refluxing methanol) it gave 0.8 g. of methiodide; m.p. 195° (froth) after recrystallization from acetone; prisms λ_{max}^{Nujol} 2.95 μ and 5.82 μ (acetone of crystallization).

Anal. Calcd. for $C_{17}H_{26}INO.^1/_2CH_3COCH_3$: C, 53.93; H, 7.24; CH_3COCH_3, 6.97. Found: C, 53.68; H, 6.89; Loss (100°), 6.75.

1,2,3a,9b-Tetrahydro-cis-3a,9b-dimethylnaphtho[2,1-b]-furan (IV). The methiodide above (0.8 g.), 5.8 ml. of 0.23*M* thallous hydroxide, and 4 ml. of water were digested on the steam bath for 20 min. and filtered from thallous iodide. The filtrate was evaporated to dryness at the water pump, and the residual methohydroxide was dry-distilled at 80–90° (bath temperature)/0.3 mm. to give 0.27 g. of IV whose infrared and ultraviolet spectra (λ_{max}^{alc} 263 mμ, ϵ 9,630) were virtually identical to those of the synthetic compound reported by Fry.[5] Hydrogenation of our IV (palladium-charcoal, methanol) resulted in the absorption of 1 molar equivalent of hydrogen and the isolation of VIII also identical with synthetic material.[5]

β-9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (X) *methiodide.*[13] To the base from 1.0 g. of VI hydrochloride in 20 ml. of dry ether was added 15 ml. of 1.5*M* ethereal methyllithium (stirring). The clear solution was refluxed for 1–2 hr. and poured onto ice. The dried ethereal layer gave on distillation finally at 150° (bath temperature)/0.2 mm. 0.65 g. of viscous oil, $\lambda_{max}^{CHCl_3}$ 2.79 μ (3595 cm.$^{-1}$, sharp indicative of OH—π bonding) and 5.75 μ (weak, indicating some unchanged VI). Left for 1 week or refluxed for 24 hr. with 5 ml. of methanol and 0.4 ml. of methyl iodide, 0.7 g. (50% based on VI) of X methiodide, m.p. 219–222°, was obtained after evaporation of the methanol and crystallization of the residue from acetone; prisms from alcohol, m.p. 222–224°, λ_{max}^{Nujol} 3.05 μ.

Anal. Calcd. for $C_{16}H_{24}INO$: C, 51.47; H, 6.49. Found: C, 51.32; H, 6.46.

1,2,3a,9b-Tetrahydro-trans-3a,9b-dimethylnaphtho[2,1-b]-furan (XI). A mixture of 0.65 g. of X methiodide, 0.7 g. of sodium hydroxide and 7 ml. of water was kept on the steam bath for 1 hr., cooled and extracted with ether. Evaporation of the dried ethereal solution left 0.4 g. of oily *des*-base, $\lambda_{max}^{CHCl_3}$ 2.74 (weak), and 2.79 μ (medium). This was converted to the amorphous methiodide in acetone which was subjected to Hofmann degradation using thallous hydroxide as described in the preparation of IV. The yield of nitrogen-free product (after distillation at 110°/0.3 mm.) was 0.15 g. (70%), λ_{max}^{alc} 268 mμ[14] (ϵ 7,700), $\lambda_{max}^{CHCl_3}$ 9.2, 9.5, 10.07, 10.42, 11.09 μ.[15]

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.04. Found: C, 84.46; H, 8.20.

1,2,3a,4,5,9b-Hexahydro-3a,9b-trans-dimethylnaphtho[2,1-b]furan (XII). Hydrogenation of XI with platinum oxide (methanol as solvent) resulted in absorption of 1 molar equivalent of hydrogen. Distillation of the product at 0.3 mm. (bath temperature 90–100°) gave a colorless liquid, λ_{max}^{alc} 265.5, 272.5 mμ (ϵ 610), $\lambda_{max}^{CHCl_3}$ 9.15, 9.37, 10.0, 10.42 11.15 as major peaks.[16]

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.44; H, 9.28.

After chromatography on alumina (elution solvent 1:1 ether–petroleum ether, b.p. 30–60°), the infrared spectrum and analysis were essentially unchanged.

α-9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (VII) *hydrobromide.* 1-Nonanol (25 ml.) and 4.5 g. of III were refluxed (stirring) for 15 min. The cooled solution was treated with ether and extracted thrice with dilute hydrochloric acid. Addition of excess ammonium hydroxide and extraction with ether gave, after drying and evaporation of the ethereal extracts, 2.8 g. of crude VII. This, in ether, was neutralized with 30% hydrogen bromide in acetic acid giving 2.5 g. (66%) of VII hydrobromide, m.p. 252–254° (from alcohol).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.94; H, 7.21.

The *base* gave $\lambda_{max}^{CHCl_3}$ 2.92 μ (3425 cm.$^{-1}$) typical of OH—N bonding.

The *picrate* crystallized from acetone, then alcohol in yellow prisms, m.p. 168–170°; λ_{max}^{Nujol} 2.88 μ.

Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25. Found: C, 55.06; H, 4.96.

α-9-Hydroxy-2,5-dimethyl-6,7-benzomorphan methobromide (XIV). Platinum oxide (0.3 g.), 3.0 g. of II and 20 ml. of methanol absorbed nearly 1 molar equivalent of hydrogen during 4 hr. The filtered solution was evaporated to dryness at the water pump. Digestion of the residue with boiling acetone and cooling to −5° gave 2.7 g. (90%) of XIV, m.p. 224–226°; small prisms from alcohol-acetone.

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.70; H, 7.11. Found: C, 57.46; H, 7.27.

The *base* XV was prepared (60% yield) by pyrolysis of XIV as described in the preparation of VII; prisms from petroleum ether (b.p. 30–60°), m.p. 112–114°, λ_{max}^{Nujol} 2.9 μ (3450 cm.$^{-1}$, OH—N bonding).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.11; H, 8.51.

The *O-acetyl derivative* of XV was isolated as the *hydrobromide* salt which crystallized from acetone in prisms of m.p. 233–235°; λ_{max}^{Nujol} 5.71 μ.

Anal. Calcd. for $C_{16}H_{22}BrNO_2$: C, 56.48; H, 6.52. Found: C, 56.44; H, 6.70.

β-9-Hydroxy-2,5-dimethyl-6,7-benzomorphan (XIII). Platinum oxide (30 mg.), 80 mg. of VI and 3 ml. of alcohol absorbed 1 molar equivalent of hydrogen in 12–15 min. Evaporation of the filtered solution at the water pump left a residue which crystallized from ether in prisms, m.p. 129.5–131°, $\lambda_{max}^{CHCl_3}$ 2.78 μ (sharp) indicative of OH—π bonding; yield 60 mg. (75%).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.28; H, 8.69.

Hydrogenation of the hydrated (at the carbonyl function) hydrochloride salt of VI gave a 50% yield of XIII; the reduction in this instance proceeded very slowly.

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(13) The α and β designations are arbitrary.

(14) This absorption at 5 mμ longer wave length than IV is consistent with the methoxy series (*cf.* Ref. 2).

(15) The corresponding methoxy compound had $\lambda_{max}^{CHCl_3}$ 9.19, 9.44, 10.06, 10.4, and 11.08 μ (*cf.* Ref. 2).

(16) Major peaks for the methoxy series were 9.13, 9.43, 9.66, 9.77, 10.40, 11.13 μ.