Desacetyldihydroalloisotenulin (XI). R. D. (Fig. 4) in dioxane (c 0.102), 25°: $[\alpha]_{700}$ −7°, $[\alpha]_{589}$ −2°, $[\alpha]_{327.5}$ +1441°, $[\alpha]_{285}$ −1853°.

(8S, 9S)-(+)-Δ⁴-9-methyl-8-hydroxy-3-octalone (XII) (V. Prelog). R. D. (Fig. 3) in dioxane (c, 0.152), 25°: $[\alpha]_{700}$ +111°, $[\alpha]_{589}$ +161°, $[\alpha]_{405}$ +340° (sh.), $[\alpha]_{370}$ −16°, $[\alpha]_{362.5}$ +54°, $[\alpha]_{357.5}$ −14°, $[\alpha]_{342.5}$ +737°, $[\alpha]_{340}$ +692°, $[\alpha]_{275}$ +4550°.

(8S, 9R)-(−)-Δ⁴-9-methyl-8-hydroxy-3-octalone (XIII) (V. Prelog). R. D. (Fig. 3) in dioxane (c 0.104), 25°: $[\alpha]_{700}$ −100°, $[\alpha]_{589}$ −125°, $[\alpha]_{410-412.5}$ −345° (infl.), $[\alpha]_{380}$ −442° (sh.), $[\alpha]_{365}$ −258°, $[\alpha]_{357.5}$ −316°, $[\alpha]_{352.5}$ −160°, $[\alpha]_{315}$ −1980°, $[\alpha]_{312.5}$ −1900°, $[\alpha]_{280}$ −3390°.

Δ¹⁴-Cholesten-3β-ol-16-one benzoate (XIV) (K. Tsuda). R. D. (Fig. 3) in dioxane (c 0.10), 25°: $[\alpha]_{700}$ +77°, $[\alpha]_{589}$ +97°, $[\alpha]_{360}$ +1332°, $[\alpha]_{305}$ −845°, $[\alpha]_{290}$ −555°.

Desacetylneotenulin (XVII) (D. H. R. Barton, W. Herz). R. D. (Fig. 2) in dioxane (c 0.085), 24°: $[\alpha]_{700}$ −41°, $[\alpha]_{589}$ −48°, $[\alpha]_{337.5}$ +318°, $[\alpha]_{290}$ −800°.

Geigerin (XVIII) (G. W. Perold). R. D. (Fig. 2) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ −52°, $[\alpha]_{589}$ −30°, $[\alpha]_{357.5}$ −499°, $[\alpha]_{352.5}$ −481°, $[\alpha]_{345}$ −623°, $[\alpha]_{330}$ −376° (infl.), $[\alpha]_{300}$ +180°, $[\alpha]_{275}$ −175°.

Dihydrogeigerin (XIX) (G. W. Perold). R. D. (Fig. 5) in methanol (c 0.085), 24°: $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ +102°, $[\alpha]_{312.5}$ +2720°, $[\alpha]_{275}$ −2827°, $[\alpha]_{255}$ −2144°.

Isophotosantonic lactone (XX) (D. H. R. Barton). R. D. (Fig. 2) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ +56°, $[\alpha]_{589}$ +117°, $[\alpha]_{405}$ +224°, $[\alpha]_{370}$ −74°, $[\alpha]_{360}$ +26°, $[\alpha]_{352.5}$ −48°, $[\alpha]_{275}$ +2836°.

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

Structures Related to Morphine. VIII. Further Syntheses in the Benzomorphan Series*[1,2]

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2,5,9-Trimethyl-6,7-benzomorphan (VIII) has been synthesized from 3,4-lutidine methiodide (V) and benzylmagnesium chloride or from β-tetralone, while the hydroxy derivative (X) results from V and *p*-methoxybenzylmagnesium chloride. Compound VIII has also been converted to X *via* nitration, reduction, and diazotization and has been degraded to 1,2-dimethylnaphthalene.

Compound X, a close chemical relative of the potent analgesic racemorphan (IIIb) is an effective analgesic in mice with relatively low toxicity.

Recent studies in our laboratories have shown that 2,5-dimethyl-6,7-benzomorphan (IVa)[3] and the phenolic congener (IVb)[4] possess lower analgesic activity and lower toxicity than *N*-methylmorphinan (IIIa) and racemorphan (IIIb)[5,6] respectively. Stereochemically, structure IV simulates structure III except at carbon 9 (carbon 14 in III). The introduction of a methyl substituent at position 9 would complete this stereochemical approximation, and might be expected to enhance the analgesic effectiveness of IV. The present report is concerned with such an alteration of IV, the synthesis of 2,5,9-trimethyl 6,7-benzomorphan (VIII) and the hydroxy analog (X), compounds in which the C-methyl groups may be regarded as fragments of ring C of III. Attempts were first made to synthesize VIII by the sequence of reactions employed in the preparation of IVa.[3] However, the Knoevenagel reaction with 5-dimethylamino-3-methyl-3-phenyl-2-pentanone, a key step in this scheme of reactions, failed.[2] We then turned our attention to the synthesis developed by Grewe[5] for the morphinans (III and analogs)[6] which is outlined in Fig. 1. Transposing to our own case would merely involve substituting 3,4-lutidine methiodide (V) for 2-methyl-5,6,7,8-tetrahydrohydroisoquinoline methiodide (I).

In 1909 Freund and Bode[7] reported the formation of unstable dihydropyridines when pyridine methiodides and Grignard reagents were brought to reaction in ether. When we utilized benzylmagnesium chloride and V in this manner, a readily autoxidizable dihydro derivative (VI) was obtained. It was quickly distilled at 0.5 mm. and hydrogenated (palladium–barium sulfate) to the more stable tetrahydro compound (VII) which was cyclized (after distillation) to VIII with 85% phosphoric acid. The overall yield of VIII, based on 3,4-lutidine methiodide, was 20%. No attempt was made to characterize VI and VII. Similarly 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (X) resulted from *p*-methoxybenzylmagnesium chloride

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) The benzomorphan nomenclature was proposed by Dr. J. A. Barltrop [*J. Chem. Soc.*, 399 (1947) and private communication (1956).]

(2) Paper VII, E. L. May, *J. Org. Chem.*, **22**, 593 (1957).

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

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

(5) R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948); R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

(6) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949).

(7) M. Freund and G. Bode, *Ber.*, **42**, 1746 (1909).

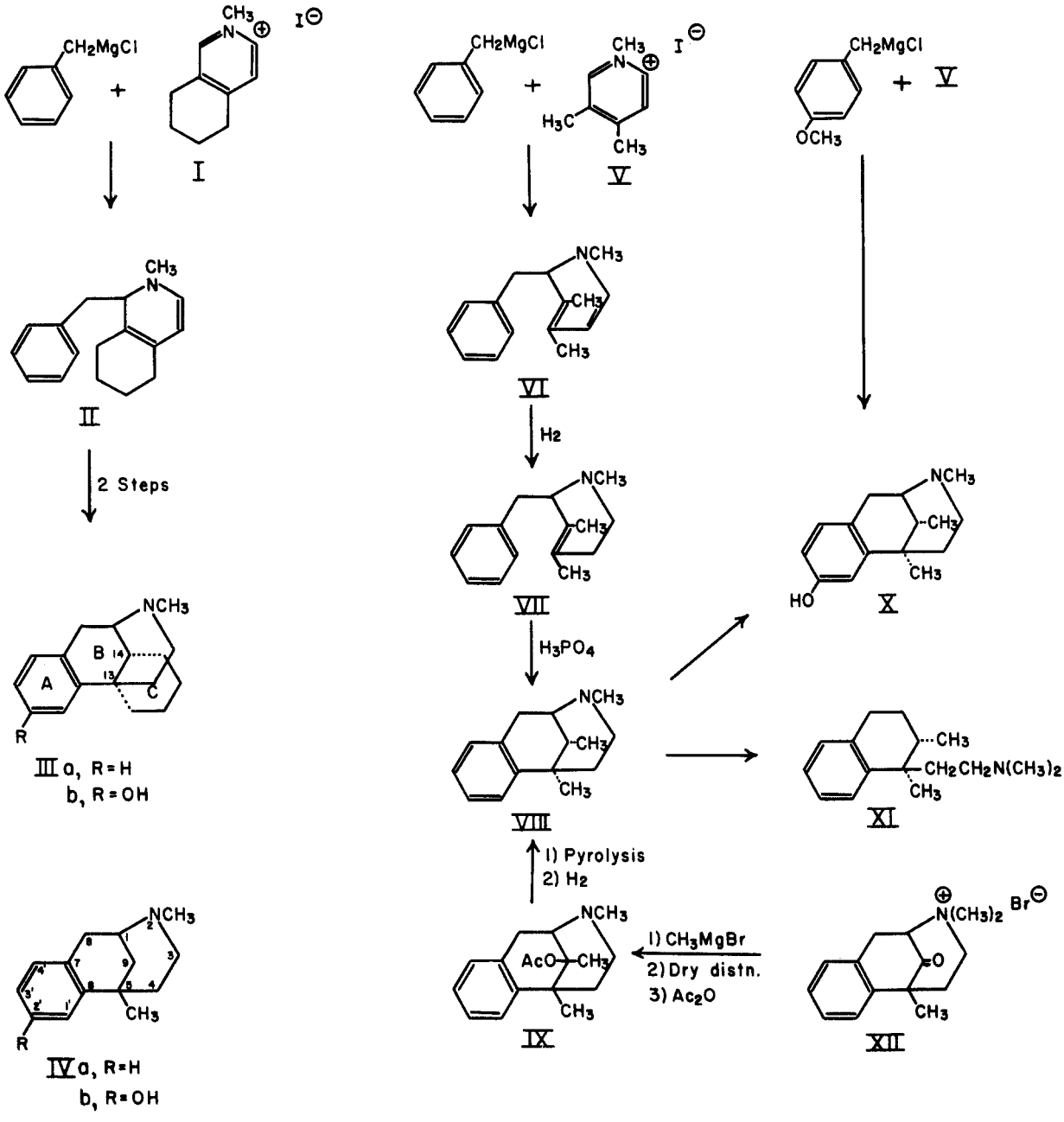

FIGURE 1.

and V. Ring closure in this instance was effected with either phosphoric or hydrobromic acid, methyl ether cleavage taking place simultaneously. Compound X could also be obtained from VIII by nitration, hydrogenation, and diazotization.

The structure of VIII (and thus X) was confirmed by subjecting its methiodide to Hofmann elimination, hydrogenating the resulting methine to 1,2-dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (XI) and aromatizing XI (palladium-charcoal) to the known 1,2-dimethylnaphthalene. Furthermore, an alternative synthesis was developed for VIII. In this synthesis 2,5-dimethyl-9-oxo-6,7-benzomorphan methiodide (XII)[3] was first brought to reaction with excess methylmagnesium iodide. Dry distillation of the resultant methylcarbinol methiodide in high vacuum followed by acetylation of the distilled base yielded the ester IX. On pyrolysis, IX lost acetic acid; hydrogenation of the methylene derivative resulting afforded VIII. This alternative synthesis is potentially useful for the preparation of homologs of VIII and X.

Regarding the stereochemistry of VIII and X, the iminoethano system is undoubtedly *cis*-fused to the hydroaromatic ring. With less certainty the methyl groups at C-5 and C-9 are assigned as *cis* for the newly formed hydroaromatic ring B in analogy to the morphinans (III)[5] where it has been shown that rings B and C are *cis*-fused. This is

consistent with an expected *trans* addition[8] (on ring closure) to the olefinic double bond of VII or the dihydrogenated II. It is noteworthy that a diastereoisomer[9] of VIII could not be detected in either of the methods employed for its synthesis.

Compounds VIII and X are from one third to two thirds as potent, in mice, as the morphinan analogs IIIa and IIIb respectively. They are also less toxic than IIIa and IIIb. A more detailed account of their pharmacology is presented in the following communication.[4]

EXPERIMENTAL

Microanalyses are from the Institute's service analytical laboratory under the direction of Dr. William C. Alford. Infrared data are from Mr. William Jones of this Institute.

3,4-Lutidine methiodide (V). A mixture of 5 ml. of 3,4-lutidine,[10] 3 ml. of methyl iodide, 15 ml. of benzene, and 15 ml. of acetone, left for 2 hr. (occasional shaking and ice-cooling) and cooled at 0° for 4 hr. gave 11 g. (96%) of V; long prisms from acetone, m.p. 123–124°.

Anal. Calcd. for $C_8H_{12}IN$: C, 38.57; H, 4.85. Found: C, 38.24; H, 4.90.

2,5,9-Trimethyl-6,7-benzomorphan (VIII) *hydrochloride.* To a stirred suspension of 12 g. of V and 100 ml. of dry ether (cooled in ice water) was added during 5 min., 100 ml. of 0.5*M* ethereal benzylmagnesium chloride. The mixture was then stirred without cooling for 1.5 hr., poured into ice water–ammonium chloride, and basified with ammonium hydroxide. The ethereal layer was extracted three times with 10% hydrochloric acid in *ca.* twofold excess. The combined extracts were basified with cold ammonium hydroxide and the liberated base was dried in ether and distilled at 0.5 mm. (air-bath temperature 125°). The resultant 5.8 g. of air-sensitive VI was quickly dissolved in 100 ml. of normal hydrochloric acid and hydrogenated with 2.0 g. of 5% palladium–barium sulfate. During 6 hr. 0.8 molecular equivalent of hydrogen was absorbed; uptake had practically ceased. The mixture was filtered through Super-Cel, basified with ammonium hydroxide, and the liberated VII dried in ether. Distillation as described for VI gave 3.8 g. of VII which, with 38 g. of 85% phosphoric acid, was kept at 145–150° for 2.5 days. The cooled, dark solution was poured into ice and made alkaline with ammonium hydroxide. After drying and distillation, as described before, 3.3 g. of base was obtained. It was dissolved in 50 ml. of ethyl acetate and acidified to Congo Red with gaseous hydrogen chloride. On seeding, 2.5 g. (20% overall yield from V) of VIII hydrochloride, m.p. 167–170°[11] eventually separated. It was at first hygroscopic but quickly changed to a stable powder which appeared to contain about 0.5 mole of solvate water. The solvent-free hydrochloride was obtained by conversion of the above hydrochloride to the base and acidifying this base with ethereal hydrogen chloride; small prisms, m.p. 203–205°, from acetone.

Anal. Calcd. for $C_{16}H_{22}ClN$: C, 71.54; H, 8.80. Found: C, 71.70; H, 8.62.

The *picrate*, prepared from the hydrochloride with alcoholic picric acid, melted at 122–123°. A recrystallization of this picrate from alcohol gave another crystalline modification, large, yellow prisms of m.p. 114–115°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.72; H, 5.26.

The *methiodide* crystallized from acetone in rods; m.p. 227.5–228°.

Anal. Calcd. for $C_{16}H_{24}NI$: C, 53.79; H, 6.77. Found: C, 53.72; H, 6.77.

2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (X). To 12.5 g. (0.05 mole) of V and 100 ml. of dry ether was added during 10 min. (stirring, 25°) 300 ml. (0.075 mole) of 0.25*M* ethereal *p*-methoxybenzylmagnesium chloride.[12] The mixture was stirred for 1.5 hr. and treated as described for the corresponding reaction above. The base obtained from the dried ether solution was distilled evaporatively at 0.5 mm. (air-bath temperature 150–160°). The resultant 6.4 g. of distillate, 2.0 g. of 5% palladium–barium sulfate and 85 ml. of normal hydrochloric acid absorbed 0.8 molecular equivalents of hydrogen during 4 hr. when reaction ceased. The filtered (through Super-Cel) solution was basified with aqueous ammonia and the liberated tetrahydro base was dried in ether and distilled at 150° (air bath/0.5 mm.). The 4.5 g. of distillate and 45 ml. of 48% hydrobromic acid were kept at 135–140° (oil-bath temperature) for 30 hr., cooled, poured into 1–2 volumes of ice water and basified with concentrated ammonium hydroxide. The semisolid was filtered and dissolved in the minimum (8–10 ml.) of boiling methanol. On cooling, finally to −5°, 1.6 g. (14% based on V) of X, m.p. 228–232° was obtained; the analytical sample melted at 232–235°; plates from methanol-water.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.13; H, 9.10.

The *hydrochloride* crystallized from absolute alcohol-ether as the monohydrate in rods of m.p. 194–196°.

Anal. Calcd. for $C_{15}H_{22}ClNO\cdot H_2O$: C, 63.03; H, 8.46; H_2O, 6.30. Found: C, 63.34; H, 8.28; Loss in wt. (117°), 6.22.

Analysis of the dried sample gave the following values: Calcd.: C, 67.27; H, 8.28. Found: C, 67.00; H, 8.50.

The *tosyl* derivative of X gave a crystalline picrate which crystallized from alcohol-acetone in small yellow prisms, m.p. 191–193°.

Anal. Calcd. for $C_{28}H_{30}N_4O_{10}S$: C, 54.71; H, 4.92. Found: C, 54.57; H, 5.04.

The tosyl derivative did not yield VIII on treatment with Raney nickel W-7 in boiling alcohol; mainly starting material was recovered.

2'-Nitro-2,5,9-trimethyl-6,7-benzomorphan picrate.[13] To a stirred, ice-cooled mixture of 8 ml. of fuming nitric acid (Sp. Gr. 1.49–1.50) and 5 ml. of acetic acid was added during 1.5 hr., 1.5 g. of VIII in 3 ml. of acetic acid. The solution was kept overnight at 25°. Acetic acid was evaporated with water-pump vacuum (bath temperature 55–60°). Addition of ice and aqueous ammonia gave an oil which was dried in ether. Evaporation of the ether left a residue which, in 8 ml. of acetone, was added to a solution of 2.0 g. of picric acid in 40 ml. of acetone. On standing for 2 hr. at room temperature and 3 hr. at 0°, 2.0 g. (60%) of picrate was deposited; m.p. 240–242° (dec.); yellow prisms from acetone, m.p. 248–250° (dec.).

Anal. Calcd. for $C_{21}H_{23}N_5O_9$: C, 51.52; H, 4.74. Found: C, 51.28; H, 4.48.

The *hydrochloride* crystallized from acetone in needles of m.p. 253–254° (dec.).

(8) M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., N. Y., Chapman Hall Limited, London, 1956, p. 242.

(9) A small yield of *N*-methylisomorphinan (M. Gates, R. B. Woodward, W. F. Newhall, and R. Künzli, *J. Am. Chem. Soc.*, **72**, 1141 (1950)) epimeric with IIIa at C_{14} was isolated along with IIIa.[5]

(10) We are indebted to Dr. F. E. Cislak, Director of Research, Reilly Tar and Chemical Corp., for a generous supply of 3,4-lutidine.

(11) Prolonged boiling of the ethyl acetate solution occasionally gave another modification (needles) of the hydrochloride which melted at 204–206°.

(12) M. G. Van Campen, D. F. Meisner, and S. M. Parmerter, *J. Am. Chem. Soc.*, **70**, 2296 (1948).

(13) The procedures used in this and the subsequent hydrogenation and diazotization experiments were taken from the paper by Schnider and Grüssner.[6]

Anal. Calcd. for $C_{15}H_{21}ClN_2O_2$: C, 60.67; H, 7.13. Found: C, 60.13; H, 7.06.

Conversion of 2'-nitro-2,5,9-trimethyl-6,7-benzomorphan to X. A mixture of 0.5 g. of 2'-nitro-2,5,9-trimethyl-6:7-benzomorphan hydrochloride, 0.2 g. of 5% palladium-barium sulfate, and 3 ml. of methanol absorbed three molecular equivalents of hydrogen quickly, when reduction stopped. The filtered solution was evaporated to dryness *in vacuo* to give an amorphous hydrochloride which was dissolved in 4 ml. of 3*N* sulfuric acid. To the stirred, ice-cooled solution was added during 25 min. 0.14 g. of sodium nitrite in 1 ml. of water. The yellow solution was then treated dropwise (at 60–70°) with 2.4 ml. of sulfuric acid in 2.4 ml. of water. During the next 30 min. the mixture was warmed to 80°, cooled, poured into ice water, and basified with ammonium hydroxide (total volume 100 ml.). Some intractable solid was filtered and the filtrate was extracted three times with chloroform. The dried chloroform extracts were evaporated to dryness and the residue was triturated with ether to give 180 mg. (46%) of 2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (X) which melted at 232–235° after a recrystallization from methanol. It proved to be identical with that prepared as described above.

9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan methiodide. To 11.2 g. of 2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (XII)[3] was added 170 ml. (5 molecular equivalents) of 1.0*M* methylmagnesium bromide. Only a portion of the solid reacted at once, the adduct apparently coating unreacted solid. The ether was distilled until the liquid adduct became much more fluid. The magma was then manually manipulated with a stirring rod until all the solid passed into the fluid state. The mixture was decomposed with water and the solids were dissolved in 30 ml. of 6*N* hydrochloric acid. Excess aqueous potassium iodide was added with the formation of the crystalline methiodide. Purified from alcohol, it melted at 247–249°; yield 9.4 g. (70%).

Anal. Calcd. for $C_{16}H_{24}INO$: C, 51.48; H, 6.48. Found: C, 51.25; H, 6.26.

9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan. A distilling flask containing 5.9 g. of the above methiodide was kept in a salt bath at 275–280° under a pressure of 0.1–0.4 mm. The solid did not melt but decomposed to an oil which distilled. The small amount of solid which sublimed was decomposed with a free flame. The colorless distillate weighed 3.6 g. (98%); b.p. 112–115°/0.5 mm.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.04; H, 9.03.

9-Acetoxy-2,5,9-trimethyl-6,7-benzomorphan (IX). The above alcohol (3.6 g.), 7 ml. of acetic anhydride, and 0.7 ml. of pyridine were refluxed for 3 hr., excess reagent was removed under reduced pressure, and the product was distilled at *ca.* 122°/0.1 mm.; yield 3.9 g. (93%).

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.29; H, 8.46.

The *perchlorate*, made by addition of perchloric acid to an ethereal solution of IX, crystallized from alcohol in high yield; m.p. 265–267° (gas).

Anal. Calcd. for $C_{17}H_{24}ClNO_6$: C, 54.62; H, 6.47. Found: C, 54.60; H, 6.42.

9-Methylene-2,5-dimethyl-6,7-benzomorphan. The acetate IX (2.8 g.), in a distilling flask immersed in a salt bath at 325–340° lost acetic acid during about 30 min. The pressure was then reduced to 0.2 mm. with distillation of the product at 95–110°. Dissolved in ether, it was converted to the crystalline perchlorate by the addition of 60% perchloric acid. The crude salt (1.23 g., 38%) melted at 204–219°. After purification from alcohol the m.p. was 218–220°.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.52; H, 6.45.

2,5,9-Trimethyl-6,7-benzomorphan (VIII) *methiodide.* The crude perchlorate of the methylene compound above (0.3 g.) in alcohol with platinum oxide absorbed almost one molecular equivalent of hydrogen. The filtered solution gave 0.2 g. of a perchlorate of m.p. 201–210°. Recrystallization from alcohol did not improve the melting point. It was converted to the base (aqueous alkali-ether) and the latter was converted to the methiodide. The methiodide, after crystallization from alcohol–ethyl acetate, melted at 225–226.5° alone or when mixed with the VIII methiodide prepared from V as described above. Furthermore, infrared spectra diagrams of specimens of the methiodides prepared by the two methods were virtually identical.

1,2-Dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (XI) *hydrochloride.* The methiodide of VIII (4.0 g.), 4.0 g. of sodium hydroxide and 36 ml. of water were kept on the steam bath for 1.5–2 hr., cooled, and extracted with ether. The dried ether extract was evaporated to dryness leaving a liquid which was dissolved in 10 ml. of methanol and hydrogenated (35 mg. of platinum oxide) to the absorption of one molecular equivalent of hydrogen (1 hr.). The filtered solution was evaporated to dryness at reduced pressure. The residue, in ether, was acidified with dry hydrogen chloride to give 2.9 g. (97%) of XI hydrochloride, m.p. 199–202°; needles from acetone, m.p. 203–204°.

Anal. Calcd. for $C_{16}H_{26}ClN$: C, 71.76; H, 9.78. Found: C, 71.62; H, 9.65.

1,2-Dimethylnaphthalene from XI. A stoppered test tube fitted with a vent and containing an intimate mixture of 0.3 g. of XI (oily base) and 0.2 g. of 5% palladium-charcoal was immersed in an oil bath preheated to 250°. During 10 min. the temperature was raised to 310° and kept at 310–320° for an additional 20 min. The tube was then cooled and extracted three times with benzene. The benzene extracts were evaporated *in vacuo* and the residue was distilled at 0.1 mm. (bath temperature 115°) to give 0.1 g. of distillate which was treated with 2.3 ml. of saturated alcoholic picric acid. The yield of picrate, m.p. 130–131.5°,[14] was 125 mg. (25%), undepressed in melting point by picrate prepared from authentic 1,2-dimethylnaphthalene furnished by The Aldrich Chemical Co., Inc.

Anal. Calcd. for $C_{18}H_{15}N_3O_7$: C, 56.11; H, 3.92. Found: C, 56.39; H, 3.99.

The infrared diagram of the 1,2-dimethylnaphthalene prepared from XI was identical with that of authentic 1,2-dimethylnaphthalene.

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(14) If the temperature rise was very slow the m.p. was 133–134°, indicating dimorphism.