Anal. Calcd. for $C_{32}H_{44}O_2$: C, 79.95; H, 10.37. Found: C, 80.51; H, 10.80.

11-Methyl-5β-pregn-9(11)-ene-3,20-dione-3,20-bis(cyclic Ethylene Acetal) (XIX).—A solution of 5.0 g. (0.0158 mole) of 11-methyl-5β-pregn-9(11)-ene-3,20-dione (II), 50 mg. of *p*-toluenesulfonic acid, and 5 ml. of ethylene glycol in 70 ml. of benzene was heated to reflux overnight and the water collected in a Dean-Stark water separator. The reaction mixture was cooled, washed with sodium bicarbonate solution, water, and dried (Na_2SO_4), evaporated to about 10 ml., and adsorbed onto 225 g. of Florisil. Fractions eluted with 2% acetone–petroleum ether contained 5.52 g. (83.5%) of crude bisketal. Crystallization from petroleum ether afforded 4.1 g. (68%) of colorless prisms, m.p. 132–135°. A portion of this material was recrystallized once for analysis, m.p. 134–135°.

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 75.15; H, 10.13.

Ozonization of 11-Methyl-5β-pregn-9(11)-ene-3,20-dione, Bis(cyclic Ethylene Acetal).—A solution of 11-methyl-5β-pregn-9(11)-ene-3,20-dione-3,20-bis(cyclic ethylene acetal) (5.52 g., 0.013 mole) in 100 ml. of ethyl acetate was treated at −20° to 10° over a 20-min. period with 1.33 g. (0.0277 mole) of 2% ozone in oxygen. The solution was diluted with 100 ml. of *t*-butyl alcohol and 1 ml. of 30% hydrogen peroxide in 10 ml. of water and was allowed to stand overnight at room temperature. The resulting solution was extracted with ether and the combined ether extracts washed consecutively with water, 5% alkali solution, water, and dried over anhydrous sodium sulfate. The basic extracts were acidified and yielded a negligible amount of solid. The dry ether solution was evaporated under reduced pressure and the residue chromatographed on 250 g. of Florisil. A 5% acetone–petroleum ether mixture eluted 1.578 g. of a crystalline ozonide, several recrystallizations from petroleum ether gave colorless prisms, m.p. 149–151°. This material liberates iodine from acid potassium iodide solution. The infrared spectrum is compatible with the assigned structure and exhibits a multitude of absorption bands in the C—O region.

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 67.08; H, 8.80.

Further elution with 5–10% acetone in petroleum ether afforded 2.771 g. of a gum whose infrared spectrum was consistent with that of the expected dione XXI; γ_{max} 1720 cm.$^{-1}$ (very strong and broad). This material was not characterized further since it could not be crystallized.

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Structures Related to Morphine. XXIV.[1] Further Application of the Stevens Rearrangement in the Synthesis of Diastereoisomeric 6,7-Benzomorphans from 3-Ethyl-4-methyl- and 4-Ethyl-3-methylpyridines

S. E. FULLERTON, J. H. AGER, AND E. L. MAY

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, Department of Health, Education, & Welfare, Bethesda, Maryland

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Sodium borohydride reduction of 3-ethyl-1,4-dimethyl- and 4-ethyl-1,3-dimethylpyridinium halides (I) has given good yields of the tetrahydropyridines (II). Quaternization of II with *p*-methoxybenzyl chloride and Stevens rearrangement of the resultant III with phenyllithium leads in part to the 2-*p*-methoxybenzyltetrahydropyridines (IV) which have also been prepared from I *via* the Freund reaction (using *p*-methoxybenzylmagnesium chloride) and subsequent sodium borohydride or catalytic reduction. Cyclization of IV with 48% hydrobromic acid results in the formation of diastereoisomeric (at C-9) benzomorphans (V, VI) in a ratio of about 10:1, respectively. Also isolated in low yield in the cyclization of IVb was an isomeric compound which may have the indano rather than the tetrahydronaphthaleno type structure. Compounds Va and Vb have been converted to open nitrogen analogs (VIIa and VIIb desired also for pharmacological study), and Va has been degraded to 1-ethyl-7-methoxy-2-methylnaphthalene (VIII). Both V and VI are potent analgesics, VIa (racemate) exceedingly so, with about forty times the activity of morphine.

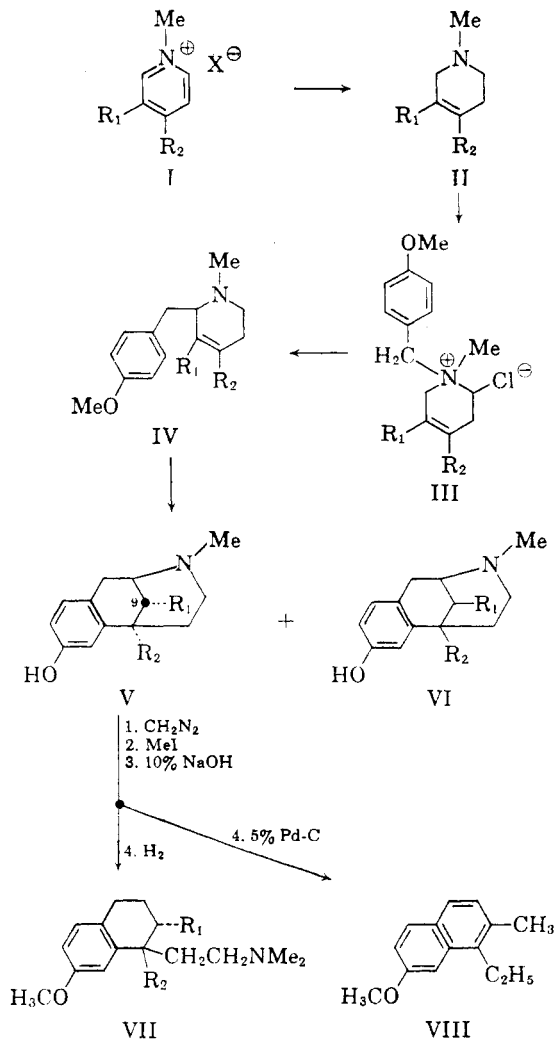
In previous communications[2] it has been shown that 3,4-lutidine and 3,4-diethylpyridine may be converted to corresponding diastereoisomeric (at C-9) pairs of 5,9-dialkyl-6,7-benzomorphans by the Grewe morphinan synthesis or by a more practicable sequence involving the Stevens rearrangement.[3] More recently[1] we have demonstrated unequivocally that the 5,9-dialkyl groups of the predominant isomers (designated α) are in *cis* juxtaposition for the hydroaromatic ring. The ratio of α to β (lesser) isomer was approximately 12:1 in the dimethyl series and 8:1 with the diethyl homologs.[4] In contrast to the dimethyl series, the α and β diethyl compounds exhibited pronounced infrared spectral differences which could be utilized in their separation and identification.[2] Further

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

(2) (a) J. H. Ager and E. L. May, *ibid.*, **27**, 245 (1962). (b) E. L. May and J. H. Ager, *ibid.*, **24**, 1432 (1959).

(3) E. M. Fry and E. L. May, *ibid.*, **26**, 2592 (1961).

(4) As noted before (*cf.* ref. 2) these dialkylbenzomorphans possess marked neuropharmacologic properties and show a pronounced separation of activity and physical dependence capacity in animal species. Peak analgesic activity and thereapeutic ratio were shown by the β-diethyl compound.



a. R_1 = Me, R_2 = Et
b. R_1 = Et, R_2 = Me

Figure 1

interesting chemical, stereochemical, spectral, and pharmacological considerations are apparent when the 5 and 9 positions are unsymmetrically, ethylmethyl substituted as in compounds V and VI. The synthesis, stereochemistry of some degradation reactions, infrared data, and analgesic activity of V and VI are herein described.

Starting bases used in the synthesis of α- (Va) and β- (VIa) 5-ethyl-2′-hydroxy-2,9-dimethyl-6,7-benzomorphans and α- (Vb) and β- (VIb) 9-ethyl-2′-hydroxy-2,5-dimethyl-6,7-benzomorphans were 4-ethyl-3-methylpyridine and 3-ethyl-4-methylpyridine, respectively.[5] Sodium borohydride reduction of the methiodides (I. X^- = iodide) of these bases in aqueous methanolic[6] sodium hydroxide produced the tetrahydropyridines (II), isolated as the *p*-methoxybenzyl chloride quarternary salts (III) in 53–56% yields, calculated from I. Stevens rearrangement of III with ethereal phenyllithium[3] afforded in about 40% yields, the 2-(*p*-methoxybenzyl)tetrahydropyridines (IV) which were purified and characterized as the picrates. These tetrahydropyridines were also synthesized from I (X = Br) by the Freund reaction[2,7] and hydrogenation of the resulting 2-(*p*-methoxybenzyl)-1,2-dihydropyridines with palladium–barium sulfate or preferably reduction with sodium borohydride[8] in aqueous methanol. Cyclization of IV was effected as usual[2] with 48% hydrobromic acid to give V and VI in a ratio of 12:1. From the cyclization of IVb there was obtained in addition (2% yield) an *isomeric* product which may be an indano type compound resulting from five-membered ring closure (*cf.* footnote 15).

The stereochemistry of V and VI was firmly established by a determination of their reaction rates with methyl iodide.[1] In addition Va was degraded to 1-ethyl-7-methoxy-2-methylnaphthalene (VIII as reported for similar series),[2,8] while both Va and Vb have been converted in four steps to the open-nitrogen analogs VIIa and VIIb, which were desired for pharmalogical study.

Like the dimethyl series no pronounced infrared (Nujol) spectral differences were noted for Vb and VIb (9-ethyl,5-methyl). However, distinct differences in the 6–6.5, 8, and 11.6 μ regions were apparent for Va and VIa comparable to those seen in the diethyl series.[2a] Further studies and possible correlations with other physical properties and neuropharmacologic activity are contemplated.

Compounds V and VI were assessed for analgesic activity. The results parallel those obtained with the lower homologs[2] in that the β-isomers are much more potent than the α-isomer with some increase though not nearly a corresponding increase in toxicity. Of the *N*-methyl compounds (5,9-dimethyl, 5,9-diethyl, 5-ethyl-9-methyl, and 9-ethyl-5-methyl) synthesized to date, peak activity is seen in racemate Vb (ED_{50} 1.5 mg./kg. compared with 2.1 mg./kg. for morphine); in the β-series, maximum activity is shown by the remarkably potent VIa racemate (ED_{50} *ca.* 0.07 mg./kg.), to our best knowledge by far the most potent analgesic, morphine-like in structure, yet reported.[9]

Experimental

Melting points were taken in a capillary (Hershberg apparatus, total-immersion thermometers). Microanalyses are by the Institute's service analytical unit, Harold Mc-

(5) We are indebted to Dr. Frank E. Cislak, Reilly Tar and Chemical Company, for generous supplies of these materials.

(6) The use of methanol minimizes contamination of II with dihydropyridines which quickly disproportionate in alcohol as followed by ultraviolet measurements.

(7) M. Freund and G. Bode, *Ber.*, **42**, 1746 (1909); E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957). Since publication of the diethyl compounds (*cf.* ref. 2a), the β-5,9-diethyl isomer has likewise been degraded to 1,2-diethyl-7-methoxynaphthalene leaving no doubt about the basic skeletal structure of both the α and β isomers.

(8) We are indebted to Dr. E. M. Fry of this laboratory for the observations that, in the Freund reaction, bromide is better than iodide and that sodium borohydride reduction of the dihydro compounds is superior to catalytic reduction.

Cann, Director. Infrared spectra (Perkin-Elmer 21) are by H. K. Miller and Mrs. Ann Wright, also of this laboratory.

4-Ethyl-1,3-dimethylpyridinium Iodide (Ia. X = iodine).—4-Ethyl-3-methylpyridine[5] (5 g.), 10 ml. of acetone, 5 ml. of benzene, and 3 ml. of methyl iodide were ice-cooled for 20 min. and then kept at room temperature (heat evolution) for 2–3 hr., diluted with 3 ml. of ethyl acetate, and left at −15° overnight to give 10.1 g. (93%) of crystals; needles from acetone–ethyl acetate, m.p. 121.5–124.5° (dec.).

Anal. Calcd. for $C_9H_{14}IN$: C, 41.07; H, 5.36. Found: C, 40.46; H, 5.35.

The **bromide** (Ia. X = Br) crystallized from ethanol–ether as prisms, m.p. 158–159°.

Anal. Calcd. for $C_9H_{14}BrN$: C, 50.01; H, 6.53; Br, 36.97. Found: C, 50.08; H, 6.66; Br, 37.22.

4-Ethyl-1-(*p*-methoxybenzyl)-1,3-dimethyl-1,2,5,6-tetrahydropyridinium Chloride (IIIa).—To 26 g. of Ia (X = I), 7.4 g. of sodium hydroxide, 100 ml. of water, and 80 ml. of methanol[6] was added 3.8 g. of sodium borohydride (stirring). The temperature rose to around 60° and was maintained at 55–65° for 90–100 min. The mixture was diluted with cold water and extracted thrice with ether. The combined extracts were washed once with water, dried (sodium sulfate), and evaporated at the water pump leaving 11.5 g. of crude IIa, which was treated with 15 g. of *p*-methoxybenzyl chloride and 35 ml. of acetone. After 2 hr. at room temperature and 12 hr. at −15° the hygroscopic IIIa was filtered and washed with acetone–ether (2:1) and finally ether; yield 16.2 g. (56%), m.p. 140–143°. The analytical sample (plates from acetone–ether) melted at 143–144°, (hygroscopic).

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.02; H, 8.86. Found: C, 68.18; H, 9.01.

4-Ethyl-2-(*p*-methoxybenzyl)-1,3-dimethyl-1,2,5,6-tetrahydropyridinium (IVa) Picrate.—To 15.5 g. of IIIa was added as rapidly as possible (stirring) 130 ml. of 0.9 *M* ethereal phenyllithium. The brisk refluxing subsided after a few minutes. The mixture was stirred for 2 hr., refluxed for 30 min., poured into ice water, and the ethereal layer extracted thrice with excess dilute hydrochloric acid. The acid extracts were made alkaline with aqueous ammonia, and the liberated base was dried in ether. Evaporation of the ether left 12.6 g. of base (crude IVa) which, in 25 ml. of ethanol, was added to 8.2 g. of picric acid in 100 ml. of ethanol. Left at room temperature for 2 hr. and at 0° for 3 hr. the solution deposited 11.9 g. (46%) of IVa picrate, m.p. 135–137°. The analytical sample (plates from acetone–water) melted at 139–140°.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.54; H, 5.77; N, 11.48. Found: C, 56.76; H, 5.99; N, 11.60.

α-5-Ethyl-2′-hydroxy-2,9-dimethyl-6,7-benzomorphan (Va).—To 11.9 g. of IVa picrate was added an excess of 3% lithium hydroxide solution and the mixture extracted five times with petroleum ether (b.p. 30–60°). The combined extracts were dried (sodium sulfate) and evaporated at the water pump leaving 6.3 g. (46% based on IIIa) of IVa. This and 60 ml. of 48% hydrobromic acid were kept at 140–150° (bath temperature) for 24 hr., poured onto ice, made alkaline with concentrated ammonium hydroxide, and extracted with chloroform. Evaporation of the dried chloroform extracts at the water pump left a residue which crystallized from 5–10 ml. of acetone (cooling eventually to −5°) in a yield of 3.9 g.[10] (66%), m.p. 246–250° (dec.); prisms from methanol, m.p. 249–254° (dec.), λ_{max}^{Nujol} 6.16m, 6.31s, 8.05s, 11.61 mμ.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.30; H, 9.45. Found: C, 78.22; H, 9.47.

The *hydrochloride* of Va crystallized from methanol–ether in prisms of m.p. 253–255.5° (dec.); λ_{max}^{Nujul} 6.16s, 6.31s μ.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 68.21; H, 8.58; Cl, 12.58. Found: C, 68.07; H, 8.72; Cl, 12.51.

The acetone filtrate, from the 3.9 g. of Va above, was evaporated to dryness and the residue dissolved in 2–3 ml. of acetone. On cooling for 12 hr. at −15°, 0.45 g. of solid, m.p. 179–185°, separated. It was dissolved in 5 ml. of methanol and acidified with gaseous hydrogen chloride. After the addition of ether and cooling to −15° for 4 hr., 0.4 g. (6% based on IVa)[11] of the hydrochloride of VIa, m.p. 245–249°, was obtained. It crystallized from methanol–ether in needles, m.p. 251–255.5°, λ_{max}^{Nujol} 6.19s μ.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 68.21; H, 8.58. Found: C, 68.47; H, 8.91.

The VIa **base** prepared from the hydrochloride in aqueous methanolic ammonia, crystallized from methanol in needles, m.p. 189.5–192.5°, λ_{max}^{Nujol} 6.19s, 7.96, 8.03, 11.5, 11.65 μ.[12]

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.30; H, 9.45. Found: C, 78.59; H, 9.21.

α-5-Ethyl-2′-methoxy-2,9-dimethyl-6,7-benzomorphan Methiodide.—Methanol (15 ml.), 1.3 g. of Va, and 20 ml. of 3% ethereal diazomethane were stirred to solution (3 hr.). An additional 30 ml. of the diazomethane solution was added and the mixture kept at 25° (*ca.*) for 2–3 days. Solvents were distilled *in vacuo* and the residue evaporatively distilled (bath temperature 160°) at 0.4 mm. The 1.3 g. of distillate readily gave 1.8 g. (86%) of crystalline methiodide (acetone as solvent) which was recrystallized from acetone–ether; prisms, m.p. 222–223° (dec.).

Anal. Calcd. for $C_{18}H_{28}INO$: C, 53.89; H, 7.03; N, 3.49. Found: C, 54.01; H, 7.21; N, 3.48.

α-1-Ethyl-7-methoxy-2-methyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (VIIa) Hydrochloride.—The above methiodide (1.8 g.), 1.8 g. of sodium hydroxide, and 20 ml. of water were refluxed for 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 (15 mg. of platinum oxide) to the absorption of 1 mol. equiv. of hydrogen (1 hr.). The filtered solution was evaporated to dryness at reduced pressure. The residue (VIIa) in ethanol was acidified with dry hydrogen chloride. On addition of ether the hydrochloride gradually crystallized. It was kept at 5° for 4 hr. and filtered; yield 1.1 g. (79%), m.p. 190–194°; needles from ethanol–ether, m.p. 195–196°.

Anal. Calcd. for $C_{18}H_{30}ClNO$: C, 69.33; H, 9.70; N, 4.49; Cl, 11.37. Found: C, 69.44; H, 9.85; N, 4.57; Cl, 11.54.

1-Ethyl-7-methoxy-2-methylnaphthalene (VIII) Picrate.—5-Ethyl-2′-methoxy-2,9-dimethyl-6,7-benzomorphan methiodide (0.9 g. prepared as described above) and 15 ml. of 10% sodium hydroxide were refluxed for 2 hr. and the resultant methine isolated as described under VIIa. The 0.5 g. of methine and 0.5 g. of 5% palladium charcoal were intimately mixed in a test-tube fitted with an air-vent. The tube was then immersed in an oil bath preheated to 250°. The temperature of the bath was raised to 315° during 10 min. and kept at 310–320° for an additional 20 min. The cooled residue was extracted thrice with ether. The ether extracts were washed with dilute hydrochloric acid, dried, and evaporated leaving a residue which was evaporatively distilled at an air-bath temperature of 120° (0.15 mm.). The

(9) Testing was performed by Mrs. Louise Atwell and Mrs. Josephine Goodwin of this laboratory after the method of N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Therap.*, **107**, 385 (1953). Statistical analyses are by Mrs. Wendy Ness, also of this laboratory.

(10) Over-all yield of Va, 16%.

(11) Over-all yield of VIa, 1.5%. A previous attempt, using the same method of synthesis but without purification of the tetrahydro base (IVa) *via* the picrate, resulted in an over-all yield of 12% of Va. No diastereoisomer (VIa) was obtained, even after distillation of the mother liquors and chromatography of the distillate on a florisil column. Gas chromatography was also unsuccessful in this respect. Va was also prepared using the Grewe type synthesis (*cf.* ref. 8 and 2). An over-all yield of 8.5% of Va was obtained (starting with Ia, X = I) when the dihydro compound was reduced to IVa by hydrogenation over 5% palladium–barium sulfate: when sodium borohydride was used as the reducing agent (and starting with Ia. X = Br), an 11.5% yield of Va resulted.

(12) The differences in absorption, particularly in the phenyl region, are distinct for Va (6.16, 6.31 μ) and VIa (6.19 μ only).

distillate (0.25 g.),[13] 0.25 g. of picric acid, and 6–7 ml. of 95% ethanol were warmed to solution, then gradually cooled to −15° to give 220 mg. (23% based on starting methiodide) of the picrate of IX, m.p. 106–108.5° (dec.), orange needles from methanol.

Anal. Calcd. for $C_{20}H_{19}N_3O_8$: C, 55.94; H, 4.66. Found: C, 56.15; H, 4.52.

3-Ethyl-1,4-dimethylpyridinium Iodide (Ib. X = I).—3-Ethyl-4-methylpyridine[5] (20 g.) was treated with 11 ml. of methyl iodide in acetone–benzene, as described above under Ia (X = I), to give 38.7 g. (87%) of crystals; needles from acetone–ethyl acetate, m.p. 153–154°.

Anal. Calcd. for $C_9H_{14}IN$: C, 41.07; H, 5.36. Found: C, 40.78; H, 5.34.

The **bromide** (Ib. X = Br) crystallized from ethanol–ether as rods, m.p. 227–228.5°.

Anal. Calcd. for $C_9H_{14}BrN$: C, 50.01; H, 6.53; N, 6.48. Found: C, 49.73; H, 6.41; N, 6.53.

3-Ethyl-1-(*p*-methoxybenzyl)-1,4-dimethyl-1,2,5,6-tetrahydropyridinium Chloride (IIIb).—A mixture of 38.7 g. of Ib (X = I), 9.5 g. of sodium hydroxide, 160 ml. of water, and 75 ml. of methanol was treated with 5.7 g. of sodium borohydride, as described above under IIIa, to give 17.8 g. of crude IIb. This was treated with 23 g. of *p*-methoxybenzyl chloride and 30 ml. of acetone, and the solution was left at 25–30° for 24 hr. Addition of 30 ml. of dry ether, thorough stirring by hand, and decantation left a white dough which was similarly treated with another portion of ether. The residual chloride (IIIb) was dried to constant weight at the water pump at a bath temperature of 45° (1–2 hr.); a nearly white, fluffy, hygroscopic, amorphous powder[14] weighing 23 g. (53%) resulted.

3-Ethyl-2-(*p*-methoxybenzyl)-1,4-dimethyl-1,2,5,6-tetrahydropyridine (IVb) was a constituent of an oil obtained after rearrangement of 23 g. of chloride (IIIb). Its picrate was isolated in 39% yield and was purified from acetone–water, plates, m.p. 135–137°.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.54; H, 5.77; N, 11.48. Found: C, 56.70; H, 5.84; N, 11.55.

α-9-Ethyl-2′-hydroxy-2,5-dimethyl-6,7-benzomorphan (Vb).—The picrate (15.8 g.) above gave 8 g. of oily base (IVb) and this was ring-closed with 48% hydrobromic acid as described for IVa above. The residue obtained gave 5.9 g. of crystals from 10–15 ml. of acetone[15] (cooling to −5°), m.p. 210–215°. This was dissolved in *ca.* 350 ml. of boiling acetone, the solution was concentrated to 100–125 ml. (crystallization had already begun) and kept at 25° overnight, then at −15° for 2 hr. Filtration and washing with cold acetone gave 5.2 g. (69% based on IVb)[16] of Vb, m.p. 217–221°; prisms from acetone, m.p. 218.5–222.5° (dec.).

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.30; H, 9.45. Found: C, 78.12; H, 9.35.

The hydrochloride of Vb crystallized from methanol–ether in prisms of m.p. 238–242° (dec.).

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 68.21; H, 8.58; Cl, 12.58. Found: C, 68.35; H, 8.63; Cl, 12.21.

The combined filtrate and washings from the 5.2 g. of Vb above were concentrated to 15 ml. and kept at −15° for 3 hr. to give 0.4 g. of prisms judged to be 70% of VIb and 30% of Vb by methiodide-rate studies.[1] The resulting filtrate concentrated to 2–3 ml. and kept at −15° for 24 hr. yielded 235 mg. of nearly pure[1] VIb, m.p. 182–186°, which was dissolved in 5 ml. of boiling acetone and acidified (to pH 3) with gaseous hydrogen chloride. The yield of VIb **hydrochloride** (after cooling to −15°) was 0.25 g. m.p. 253–256°; prisms from methanol–acetone, m.p. 254–257°.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 68.19; H, 8.58. Found: C, 67.99; H, 8.55.

The VIb (**base**), prepared from the hydrochloride salt in aqueous methanolic ammonia, melted at 186–187.5°; cubes from acetone.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.30; H, 9.45. Found: C, 78.42; H, 9.59.

Similar conversion of the 0.4 g. of prisms above to the hydrochloride and careful recrystallization of the latter from absolute ethanol gave an additional 0.25 g. (total yield 0.5 g., 6% based on IVb)[17] of pure hydrochloride of VIb.

α-9-Ethyl-2′-methoxy-2,5-dimethyl-6,7-benzomorphan Methiodide. Methanol (20 ml.), 1.5 g. of Vb and 25 ml. of 3% ethereal diazomethane were stirred to solution (2 hr.). An additional 35 ml. of the diazomethane solution was added and the mixture kept at 25° (*ca.*) for 2–3 days. Solvents were distilled *in vacuo*, and the residue gave 1.9 g. (78%) of methiodide (acetone as solvent) which was crystallized from acetone-ether; m.p. 228–233° (dec.).

Anal. Calcd. for $C_{18}H_{28}INO$: C, 53.89; H, 7.03; I, 31.80. Found: C, 54.12; H, 7.15; I, 31.73.

2-Ethyl-7-methoxy-1-methyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (VIIIb) Hydrochloride.—The above methiodide (1.8 g.) was treated with aqueous sodium hydroxide, as described under VIIa. The dried ether extract was evaporated to dryness leaving a liquid which was hydrogenated (as previously described) over platinum oxide. The residue (VIIIb) obtained was dissolved in methanol–acetone and acidified with dry hydrogen chloride. On addition of ether (and cooling to 5°) the hydrochloride crystallized and was filtered; yield 0.85 g. (61%); needles from methanol–acetone–ether, m.p. 180.5–181.5°.

Anal. Calcd. for $C_{18}H_{30}ClNO$: C, 69.33; H, 9.70; Cl, 11.37. Found: C, 69.56; H, 9.89; Cl, 11.66.

(13) $\lambda_{max}^{C_2H_5OH}$ 234, 271, 280, 287, 315, 330, (ε 63,516, 3,468, 4,209, 3,604, 1,100, 1,418). These values were determined using the crude distillate.

(14) This powder (m.p. 50–70° to a glass) could not be obtained crystalline. It gave a correct analysis for chlorine, lost 1.6% on drying *in vacuo* at 65°, and gave characteristic bands in the infrared at 2.97 and 4.06 μ (in $CHCl_3$).

(15) The acetone filtrate was evaporated to dryness at the water-pump, and the residue evaporatively distilled at 190°/0.15 mm. The distillate was treated with acetone and careful fractional crystallization gave 0.29 g. of prisms, m.p. 200–219° (mainly Vb), and 0.17 g. of rods, m.p. 200–206°. The 0.17-g. fraction was dissolved in acetone and acidified with gaseous hydrogen chloride to give a quantitative yield of hydrochloride salt, m.p. 275–283°. It crystallized from methanol-acetone in prisms, m.p. 285–288°. The base prepared from this hydrochloride crystallized from acetone in rods, m.p. 208–210°. Analysis of this compound and its hydrochloride salt indicated isomerism with Vb and VIb; methiodide rate studies[1] and analgesic activity, infrared and particularly NMR data were suggestive of an indano structure which would result from a five-membered ring closure of IV.

(16) Over-all yield of Vb, 13%.

(17) Over-all yield of VIb, 1.1%. A previous attempt, using the same method of synthesis but without purification of the tetrahydro base (IVb) *via* the picrate, resulted in an over-all yield of 8% of Vb. NO diastereoisomer (VIb) was obtained. Vb was also prepared using the Grewe type synthesis (*cf.* ref. 8 and 2). An over-all yield of 17% of Vb was obtained, starting with Ib (X = Br) and using sodium borohydride as the reducing agent. No diastereoisomer (VIb) was detected.