4-Methoxy-1-methylpyridinium Iodide. Grignard Products and Transformations Thereof

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Reaction of 4-methoxy-1-methylpyridinium iodide (1) with benzyl- or *p*-methoxybenzylmagnesium chloride, followed by borohydride reduction, has produced (depending upon solvent media) 2-benzyl-1-methyl derivatives of 4-methoxy-1,2,3,6-tetrahydropyridine (**4a,b**) or 4,4-dimethoxypiperidine (**5a,b**), apparently through the 2-benzyl-4-methoxy-1-methyl-1,2-dihydropyridines (**2a,b**). Treatment of **2a,b** with methanol–aqueous sodium hydroxide gave 4(1H)-pyridones, **6a,b**. Direct quenching of the Grignard mixture from 1 and benzylmagnesium chloride with ammonium chloride–ammonium hydroxide yielded, instead of **2a**, 4-amino-2-benzyl-2,3-dihydro-1-methylpyridinium iodide (**3**), readily converted into **6a** or the 4-aminopiperidine (**7**). Acid treatment of **4** or **5** afforded 4-piperidones (**8**) and reduction of **6** led to diastereoisomeric 4-piperidinols (**9**) which were also obtained in low yield, directly from **2**. Piperidinol **9b** was also obtained from **8b**. Known benzomorphans **10a,c** resulted from cyclodehydration of **9a,b**. The mechanism for the formation of the anomalous (when compared with the 4-alkyl series) products is discussed.

The interesting nonquaternary-carbon analgesics, 2-methyl- and 2′-hydroxy-2-methyl-6,7-benzomorphans (**10a,c**) have been synthesized from pyridine or 4-phenylpyridine.[2] About the same time, 4-methoxypyridine was also considered as a starting material because it could provide entry not only to **10a,c** but also to 5-hydroxy analogs. Described herein are the conversion of 4-methoxy-1-methylpyridinium iodide (**1**) into **10a,c** and some unpredicted transformations of products resulting from the reaction of **1** with benzylmagnesium chlorides.

Upon treating an ethereal benzylmagnesium chloride–**1** reaction mixture with aqueous ammonium chloride–ammonium hydroxide, 4-amino-2-benzyl-2,3-dihydro-1-methlpyridinium iodide (**3**) was obtained instead of the expected[3] 2-benzyl-4-methoxy-1-methyl-1,2-dihydropyridine (**2a**). Compound **3** was reduced to 4-amino-2-benzyl-1-methylpiperidine (**7**).

When the Grignard mixture was quenched with dilute hydrochloric acid, then made basic with sodium hydroxide, a crude, unstable product (presumably **2a**)[3] was obtained. Immediate sodium borohydride reduction of **2a** in aqueous methanolic sodium hydroxide gave a mixture of 2-benzyl-4-methoxy-1-methyl-1,2,3,6-tetrahydropyridine (**4a**) and 2-benzyl-4,4-dimethoxy-1-methylpiperidine (**5a**) in a ratio of 2:5.[4] Pure **4a** and **5a** were obtained *via* their picrates. On substitution of dioxane for methanol in the reduction, **4a** was formed in good yield and was recovered unchanged when treated with boiling aqueous methanolic sodium hydroxide. Partial conversion of **4a** into **5a** was noted, however, during preparation of the picrate in methanolic picric acid. Acid hydrolysis of **4a** or **5a** gave 2-benzyl-1-methyl-4-piperidone (**8a**).

In boiling aqueous methanolic sodium hydroxide, **2a** (and **3**) were hydrolyzed into 2-benzyl-2,3-dihydro-1-methyl-4(1H)-pyridone (**6a**). Platinum-catalyzed hydrogenation or, more stereospecifically, sodium borohydride reduction of **6a**, gave a mixture of diastereoisomeric 4-piperidinols (**9a**).[5] Polyphosphoric acid (PPA) cyclodehydration of **9a** yielded the known **10a**.[2]

Similarly, **1** and *p*-methoxybenzylmagnesium chloride have afforded **4b**, **5b**, and **6b**. Piperidinols **9b**, obtained from either **6b** or **8b**, gave **10c** on PPA cyclodehydration–O-demethylation, after acid hydrolysis of a stable phosphate ester.[2] See Scheme I.

Structural assignments for **3**, **4**, **5**, and **6**, anomalous products when compared with the 4-alkyl series,[3] were made largely from nmr measurements, complemented by infrared, ultraviolet, and mass spectral data. Thus, **3** showed absorptions for an unsaturated amine in the ir and for a conjugated system of double bonds in the uv.[6] The nmr spectrum indicated the two olefinic protons as doublets at 5.12 (J = 6 Hz, **H**—C=C—NH_2) and 7.79 (J = 6 Hz, —$\overset{+}{N}$=C**H**) ppm. Chemical shifts for the remaining protons, compatible with structure **3**,[6] are given in the Experimental Section.

Infrared and nmr spectra showed the presence of an enol ether group in **4a** by strong absorption at 5.95 μ and a singlet at δ 3.48 for the methoxyl group and one olefinic proton at 4.54 (t, J = 3 Hz); similar absorptions were noted for **4b**. The triplet observed for this proton was indicative of its position on carbon 5, but 100-MHz spectra, double-irradiation techniques, and synthesis of the Δ^3 isomer of **4b** were necessary for definite assignments and for rigid proof of the double-bond location in **4**. This will be discussed in the following paper.

The presence of two methoxyl groups in **5** was evident from the nmr spectrum. Their chemical shifts at δ 2.90 and 3.10, the lack of absorption for a proton on a carbon bearing a methoxyl (which would be expected to be considerably deshielded), and the absence of olefinic proton absorption indicated that a ketal moiety was present in a piperidine system.

Evidence for a γ-amino-α,β-unsaturated ketone in **6** was obtained from its characteristic[7] uv and ir spectra: λ_{max}^{EtOH} 325 mμ (ϵ 12,500); λ_{max}^{Nujol} 6.16, 6.29 μ. The two

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(2) K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 405 (1969).

(3) (a) See N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957). (b) E. L. May and E. M. Fry, *ibid.*, 1366. (c) M. Takeda, A. E. Jacobson, and E. L. May, *ibid.*, **34**, 4158 (1969).

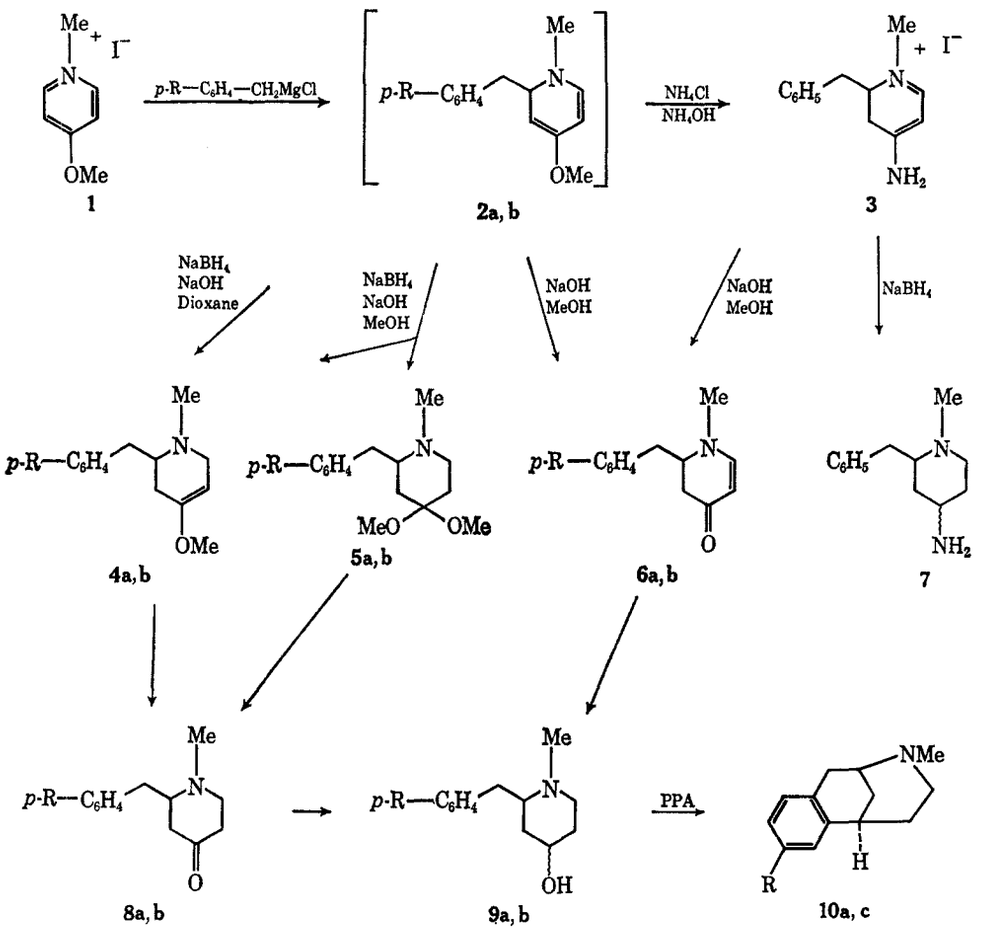
(4) Determined by glpc and by integration of the methoxy signals in the nmr spectrum.

(5) Obtained also in low yield by either method used in the reduction of **2a,b**.

(6) In good agreement with data given for a similar system by A. I. Myers, A. H. Reine, and R. Gault, *Tetrahedron Lett.*, 4049 (1967); see Experimental Section.

(7) A. I. Myers, A. H. Reine, J. C. Sircar, K. B. Rao, S. Singh, H. Weidman, and M. Fitzpatrick, *J. Heterocycl. Chem.*, **5**, 151 (1968).

SCHEME I



a, R = H; b, R = OMe; c, R = OH

olefinic protons of **6** appeared as doublets (J = 7 Hz) at 4.89 and 6.89 ppm.

The formation of **3**, **4**, **5**, and **6** may be explained by the sequence of reactions shown in Scheme II. Thus, protonation of **2** at the terminal position of the diene system would give intermediate A[8] which may be reduced to **4** (in dioxane) as the major reaction, and, being susceptible to nucleophilic attack[6] at position 4, A could add MeO^-, NH_2^-, or OH^- to yield D, C, or B, respectively. Borohydride reduction of D would lead to **5**,[9] and expulsion of methoxide ion from C with simultaneous quaternization in the presence of I^- would give **3**. α,β-Unsaturated ketone **6** could be formed either by elimination of MeO^- and subsequent ketonization of the dienol formed or by abstraction of hydrogen from the 4-OH with elimination of MeO^-.

Unexplained by the above mechanistic speculations is the 5:1 ratio of attack on A by methoxide anion in preference to HO^-, under the sodium hydroxide methanol–borohydride conditions. Yet, in the reaction of A with methanol–sodium hydroxide alone, apparently only HO^- attacks to form **6** eventually. One might further expect **1** to follow the same reaction path in sodium hydroxide–methanol–borohydride as **2a**, through the comparable intermediate, A, without a 2-*p*-methoxybenzyl group. However, neither a ketal nor a piperidinol is formed from **1** under these conditions, the enol ether being isolated as the preponderant product.[3c]

(8) See R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Lett.*, 553 (1962).

(9) That **5a** was not formed *via* **4a** was indicated by a quantitative recovery of **4a** after it was heated in CH_3OH–1 *N* NaOH for 3 hr.

Experimental Section[10]

4-Amino-2-benzyl-2,3-dihydro-1-methylpyridinium Iodide (3).—Benzylmagnesium chloride (0.068 mol) in ether (50 ml) was added to a suspension of 4-methoxy-1-methylpyridinium iodide[11] (1, 10 g. 0.04 mol) in ether (50 ml). The mixture was stirred for 6 hr, poured into ice–water containing NH_4Cl, and made alkaline with NH_4OH. Extraction of the mixture with ether[12] caused precipitation of a crystalline solid which was collected and washed with H_2O to give **3** (4.25 g, mp 204–210°). An additional 1 g of **3** separated from the filtrate during 2 days (total yield 40%). Recrystallization from acetone–ethanol gave plates: mp 212–214°; λ_{max}^{Nujol} 3.02, 3.17, 6.03, 6.12, 6.42 μ; λ_{max}^{EtOH} 345 mμ (ϵ 25,000)[6]; nmr (DMSO) 2.95 (m, 2, $PhCH_2$), 3.25 (s, 3, N^+Me), 7.32 (s, 5, Ph) ppm.

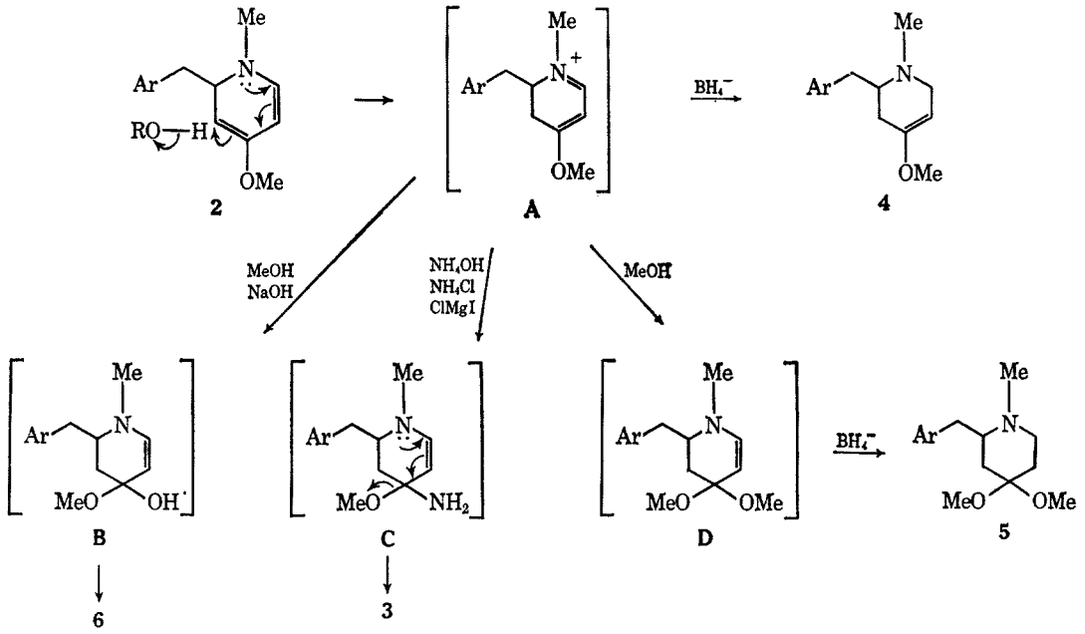
Anal. Calcd for $C_{13}H_{17}N_2I$: C, 47.57; H, 5.22; N, 8.54; I, 38.67. Found: C, 47.56; H, 5.17; N, 8.59; I, 38.77.

(10) Microanalyses and nmr (Varian A-60, 60 MHz, TMS at δ 0.00 as internal standard, $CDCl_3$ as solvent unless otherwise stated) and mass (Hitachi RMU-6E double-focusing spectrometer at 80 eV) spectral data are from the Microanalytical Services and Instrumentation Section of this institute. Ir spectra were obtained with a Perkin-Elmer 137 Infracord or a 237-B grating spectrophotometer (polystyrene film calibration). Glpc was done isothermally on a 3-ft, 3% SE-30 (Chromosorb W, acid washed) column (flame-ionization detector), all tlc on Analtech silica gel GF, precoated plates (unless otherwise stated) by development in a $CHCl_3$–CH_3OH (9:1) system with detection by iodine vapor.

(11) Prepared by PCl_3 reduction of 4-methoxypyridine N-oxide (Aldrich) followed by treatment with CH_3I (80% yield, mp 143–145°, dec); *cf.* R. R. Renshaw and R. C. Conn, *J. Amer. Chem. Soc.*, **59**, 297 (1937).

(12) This ethereal solution was extracted with HCl. Ether extraction of the basified extract gave 1.7 g of a multicomponent mixture (by tlc).

SCHEME II



4-Amino-2-benzyl-1-methylpiperidine Dihydrochloride (7).—Compound **3** (1.5 g), 1 *N* NaOH (25 ml), methanol (25 ml), and $NaBH_4$ (1 g) were heated at 60° for 2 hr, diluted with H_2O, and extracted with ether. The extracts were dried[13] and evaporated. The residue was distilled [120–140°, bath temperature, (0.2 mm)] to give 0.6 g of colorless oil. The oil was dissolved in ether and a dihydrochloride prepared with dry HCl. The solid (**7**, 0.72 g, 57%) was recrystallized from acetone–ethanol–ether: mp 120–125° (partially, resolidifies), 262–265° dec; λ_{max}^{Nujol} 3.0 (H_2O), 6.1 and 6.3 μ; nmr (free base) 1.32 (s, 2, NH_2 disappeared on addition of D_2O), 2.39 (s, 3, NCH_3), and 7.2 (s, 5, Ph) ppm; *m/e* 204 (M^+), 70 (base).

Anal. Calcd for $C_{13}H_{22}N_2Cl_2 \cdot H_2O$: C, 52.88; H, 8.19; N, 9.49; Cl, 24.02. Found: C, 52.66; H, 8.00; N, 9.58; Cl 23.80.

2-Benzyl-1,2-dihydro-4-methoxy-1-methylpyridine (2a) and Its Reduction.—Benzylmagnesium chloride (0.108 mol) in ether (75 ml) was added to **1** (18.7 g, 0.075 mol) in ether (100 ml) and stirred for 3 hr. The mixture was poured into 12 *M* HCl (45 ml) and ice–water (180 ml). The cold, aqueous layer was washed with ether, made basic with 40% NaOH and extracted with ether. Drying[13] and evaporation of solvent gave **2a** (13 g) as an air-sensitive, red oil.

A.—$NaBH_4$ (1.45 g) was added to **2a** (4.3 g) in methanol (75 ml) and 1 *N* NaOH (25 ml) and the mixture gently refluxed for 2.5 hr. Methanol was removed *in vacuo*, and the residue was diluted with H_2O and extracted with ether. The extracts gave a yellow oil (3.7 g) after removal of solvent, a mixture of **2-benzyl-4-methoxy-1-methyl-1,2,3,6-tetrahydropyridine (4a)** and **2-benzyl-4,4-dimethoxy-1-methylpiperidine (5a)** in a ratio of 2:5,[14] and a third component (**9a**) (see below) by tlc.

A picrate (5.1 g, mp 142–150°) was prepared from the mixture in methanol. It crystallized from methanol (35 ml)–acetone (10 ml) (2.63 g, 37% based on **1**) and recrystallized from acetone as yellow plates, giving the ketal (**5a**) picrate, mp 165–167°.

Anal. Calcd for $C_{21}H_{26}N_4O_9$: C, 52.71; H, 5.48; N, 11.71. Found: C, 52.65; H, 5.73; N, 11.48.

The **5a** free base was regenerated from its picrate and evaporatively distilled [140°, bath temperature (0.05 mm)]; nmr 2.38, (s, 3, NCH_3) and 7.18 (s, 5, Ph) ppm; *m/e* 249 (M^+), 158 (base).

Solvent was removed from the filtrate of the 5.1 g of picrate, and the residue was treated with warm methanol (4 ml). Decantation from an insoluble oil and refrigeration gave the enol ether (**4a**) picrate (0.67 g, 6% based on **1**,[14] mp 110–116°): yellow needles from methanol, mp 116–118°.

Anal. Calcd for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97; N, 12.55 Found: C, 53.92; H, 4.86; N, 12.66.

The **4a** free base was regenerated from the picrate and distilled [140–150°, bath temperature (0.05 mm)]: nmr 2.42 (s, 3, NCH_3) and 7.18 (s, 5, Ph) ppm; *m/e* 217 (M^+), 126 (base).

Solvent was removed from the picrate's mother liquor (all combined). Regeneration of free base from the residue, and its refrigeration in *n*-hexane (20 ml)–ether (5 ml) gave a solid, **2-benzyl-1-methyl-4-piperidinol** [(α-**9a**), 0.56 g, 11% based on **1**, mp 113–118°], which was recrystallized in ethyl acetate–*n*-hexane (mp 117–120°): λ_{max}^{Nujol} 3.20 μ (OH).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.13; H, 9.29; N, 6.82.

Solvent was removed from the mother liquor of α-**9a** and a picrate was prepared in methanol (20 ml)–acetone (4 ml). An additional 1.75 g of **5a** picrate was obtained (total yield of **5a** picrate, 36.7% based on **1**).

B.—$NaBH_4$ (1.45 g) was added to a mixture of **2a** (4.3 g), dioxane (50 ml), and 1 *N* NaOH (25 ml). The mixture was refluxed for 2.5 hr and worked up in the usual manner to give a yellow oil (3.5 g), which, according to tlc, was a mixture of **4a** and **9a**. The oil in methanol (40 ml) and picric acid (3.8 g) gave 5.3 g of picrate, mp 100–115°. It was digested with hot methanol (20 ml) to give, after decantation from insoluble oil, 2.6 g (23% based on **1**) of **4a** picrate, mp 114–118°.

The methanol-insoluble oil was crystallized from methanol–acetone (1:1), and found to be **5a** picrate (0.8 g, mp 165–167°), evidently formed from **4a** during picrate preparation.

All of the picrate mother liquors were evaporated *in vacuo;* the residue was converted into free base (LiOH–$CHCl_3$). Crystallization of residual material from ether–*n*-hexane gave α-**9a** (0.22 g, 4.3% based on **1**, mp 115–118°).

2-Benzyl-1-methyl-4-piperidone (8a) Picrate.—Ketal **5a** (from 7 g of **5a** picrate) was heated (70–80°) in 6 *N* HCl (60 ml) for 1 hr. The solution was cooled, basified with NH_4OH, and extracted with ether. Removal of solvent from the dried[13] ethereal extracts gave an oil, **8a** (3.2 g), converted into its picrate salt in ethanol.[15] Recrystallization from ethanol gave needles: mp 143–145°, dec; λ_{max}^{Nujol} 5.8 μ (C=O).

Anal. Calcd for $C_{19}H_{20}N_4O_8$: C, 52.78; H, 4.66; N, 12.96. Found: C, 53.05; H, 4.90; N, 12.54.

The free base had λ_{max}^{film} 5.8 μ (C=O); nmr 2.51 (s, 3, NCH_3), and 7.20 (s, 5, Ph) ppm; *m/e* 203 (M^+), 112 (base).

(13) With Na_2SO_4.

(14) During conversion of pure **4a** into its picrate in methanol, some **5a** picrate was also formed. Thus the 2:5 ratio of **4a** into **5a** initially isolated was changed into 1:6 during separation *via* the picrates.

(15) If **8a** is converted into the picrate in methanol, the hemiketal (**2-benzyl-4-methoxy-1-methyl-4-piperidinol**) **picrate**, mp 146–148° dec, is obtained in 93% yield: λ_{max}^{Nujol} 2.78, 2.91 μ (OH), no C=O absorption. *Anal.* Calcd for $C_{20}H_{24}N_4O_9$: C, 51.72; H, 5.21; N, 12.06. Found: C, 51.91; H, 5.28; N, 11.83. Regeneration of the free base (aqueous LiOH–$CHCl_3$) gave **8a**, convertible into **8a** picrate in ethanol; *cf.* J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

The piperidone **8a** was also obtained from **4a** (100 mg) by heating it for 1 hr at 70° in 6 *N* HCl (10 ml). Work-up as above gave **8a** picrate (150 mg, 75%), identical (mixture melting point, ir, tlc) with that prepared from ketal **5a**.

2-Benzyl-2,3-dihydro-1-methyl-4(1H)-pyridone (6a). A. From 2a.—A mixture of **2a** (4.3 g), methanol (75 ml), and 1 *N* NaOH (25 ml) was refluxed 2.5 hr. Methanol was removed *in vacuo*, and the residual mixture was diluted with H_2O and extracted with ether. Solvent was removed from the dried[13] ethereal extracts to give an oil which was evaporatively distilled [180–190°, bath temperature (0.05 mm)]. The distillate (2.1 g, 41.7%) slowly crystallized. Recrystallization from ether gave needles: mp 68–70°; nmr 2.85 (s, 3, NCH_3), 7.2 (s, 5, Ph) ppm; *m/e* 201 (M^+), 110 base).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.33; H, 7.74; N, 6.81.

B. From 3.—A mixture of **3** (4.7 g), 10% NaOH (15 ml), and methanol (25 ml) was refluxed for 2 hr. The usual work-up gave a yellow oil. Distillation, crystallization, and recrystallization as above gave **6a** (2.1 g, 73%) identical with the above material.

2-Benzyl-1-methyl-4-piperidinol (α-9a, β-9a).[16] **A. Catalytic Hydrogenation of 6a.**—Compound **6a** (1 g) was reduced over PtO_2 (200 mg) in methanol (50 ml) until 2.2 equiv of hydrogen was absorbed to give an oil (1.1 g) which consisted of two compounds (tlc). Refrigeration of the oil in ether (8 ml)–*n*-hexane (3 ml) gave α-**9a** (0.455 g, 45%) which after recrystallization from ethyl acetate–*n*-hexane had mp 117–120° and was identical with the α-**9a** obtained from **2a** (by either reduction method).

Solvent was removed from the ether–hexane filtrate to give an oil which was purified by preparative tlc to give the diastereoisomer, β-**9a** (0.27 g, 26%, mp 117–121°). Recrystallization from ethyl acetate–*n*-hexane (1:2) gave needles: mp 121–123°, depressed by α-**9a**; λ_{max}^{Nujol} 3.13 μ (OH).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.03; H, 9.06; N, 6.60.

B. $NaBH_4$ Reduction.—$NaBH_4$ (0.38 g) was added to **6a** (0.8 g) in methanol (30 ml) and 1 *N* NaOH (10 ml), and the mixture was refluxed for 2.5 hr. The usual work-up gave an oil (0.85 g) which crystallized from ether (10 ml)–*n*-hexane (5 ml) to give α-**9a** (0.482 g, mp 116–120°). The mother liquor subjected to preparative tlc gave an additional 0.12 g of α-**9a** (total 73%), 60 mg of β-**9a** (8%, mp 118–121°), and 77 mg of **6a**.

2-Methyl-6,7-Benzomorphan (10a).—A mixture of α- and β-**9a** (1 g) in PPA (10 g) was heated at 200–205° for 6 hr, cooled, and diluted with water (50 ml). The solution was basified with NH_4OH and extracted with ether. Removal of solvent from the dried[13] extracts left an oil which was evaporatively distilled [120–130°, bath temperature (0.05 mm)] to give **10a**. The hydrochloride (0.565 g, 52%, mp 224–226°, dec) was prepared in ether (25 ml)–acetone (15 ml) and found to be identical (ir, tlc, glpc, and mixture melting point) with an authentic sample.[2]

1,2-Dihydro-4-methoxy-2-*p*-methoxybenzyl-1-methylpyridine (2b) and Its Reduction.—*p*-Methoxybenzylmagnesium chloride[17] (0.224 mol in 660 ml of ether) was added to a suspension of **1** (40 g, 0.16 mol) in ether (180 ml). The mixture was stirred for 3.5 hr and poured into a mixture of 12 *M* HCl (90 ml) and ice–water (360 ml). The cold, aqueous solution was washed with ether, made alkaline with 40% NaOH, and extracted with ether. The ethereal extracts were washed with water and dried.[13] Solvent was removed *in vacuo* to give an air-sensitive red oil (**2b**, 26 g).

A.—$NaBH_4$ (2.9 g) was added to **2b** (8.7 g) in methanol (100 ml) and 1 *N* NaOH (35 ml), and the mixture was heated at 85° for 2 hr. Methanol was removed *in vacuo*. The residues were diluted with H_2O and extracted with ether. Removal of solvent from the dried[13] extracts gave an oil (7.5 g) which was a 1:1.8 mixture[4] of **4b** and **5b**. Nmr data for the mixture (**4b** and **5b**) follow: 3.52 (s, 3, OCH_3) and 4.57 ppm for **4b**;[18] 2.95 (s, 3, OCH_3) and 3.12 (s, 3, OCH_3) ppm for **5b**.[19]

The mixture (6 g) was dissolved in 6 *N* HCl (40 ml) and heated (70–80°, 30 min). The cooled solution was then basified with NH_4OH and extracted with ether. The dried,[13] ethereal extracts were evaporated *in vacuo* to give a red oil (4.8 g). A picrate was prepared from the oil in acetone (10 ml), to give **2-*p*-methoxybenzyl-1-methyl-4-piperidone (8b) picrate** (4.3 g, 22% based on **1**). Recrystallization from acetone gave plates, mp 157–158° dec.

Anal. Calcd for $C_{20}H_{22}N_4O_9$: C, 51.95; H, 4.80; N, 12.12. Found: C, 52.05; H, 4.65; N, 12.10.

The hydrobromide of **8b** (prisms from 2-propanol–ether) had mp 175–177°, λ_{max}^{Nujol} 5.75 μ (C=O).

Anal. Calcd for $C_{14}H_{20}BrNO_2$: C, 53.51; H, 6.42; N, 4.46. Found: C, 53.58; H, 6.47; N, 4.64.

The solvent was removed from the **8b** picrate mother liquor. The residual material was converted to free base and triturated with a small amount of ether. Refrigeration give **2-*p*-methoxybenzyl-1-methyl-4-piperidinol (9b**, 0.55 g, 5.5% based on **1**). Recrystallization from ethyl acetate–*n*-hexane gave needles: mp 102.5–104°; λ_{max}^{Nujol} 3.1 μ (OH); *m/e* 235 (M^+), 114 (base).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.16; H, 8.91; N, 5.74.

B.—$NaBH_4$ (2.9 g) was added to the dihydropyridine (**2b**, 8.7 g) in dioxane (100 ml) and 1 *N* NaOH (35 ml), and the mixture was heated (85°, 2 hr). Work-up as above gave an oil[20] (7.2 g), 1 g of which was purified by preparative tlc to give **2-*p*-methoxybenzyl-4-methoxyl-1-methyl-1,2,3,6-tetrahydropyridine**[21] **(4b**, 0.57 g, 31% from **1**). A **picrate** was prepared in ether, using ethereal picric acid. Recrystallization from methanol–acetone gave plates, mp 126.5–127°.

Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 52.86; H, 5.32; N, 11.65.

The free base had λ_{max}^{film} 5.96 μ (C=COMe); nmr 1.87–2.10 (m, 2, C_3 H's), 2.47 (s, 3, NCH_3), 3.52 (s, 3, enol ether), 3.77 (s, 3, aromatic OCH_3), 4.57 (broad t, 1, J = 3 Hz, olefinic H), 6.82 and 7.11 (4, AA'BB' multiplet, J_{AB} ~ 8.5 Hz, aromatic) ppm; *m/e* 247 (M^+), 126 (base).

Acid hydrolysis of the remaining crude base (5.7 g) followed by the usual work-up and picrate formation, resulted in the isolation of piperidone (**8b**) picrate (4.4 g, 22.7% based on **1**, mp 155–157°) and the piperidinol (**9b**, 0.2 g, 2%, mp 98–102°).

2-*p*-Methoxybenzyl-1-methyl-4-piperidinol (9b). A. From 6b.—Dihydropyridine (**2b**, 8.7 g) was refluxed for 2 hr in a mixture of methanol (100 ml) and 1 *N* NaOH (35 ml). The usual work-up resulted in a brown oil (7 g) which was evaporatively distilled [220–240°, bath temperature, (0.03 mm)] to give crude **6b** (6.2 g): λ_{max}^{film} 6.12 and 6.29 μ (NC=CC=O).[7]

$NaBH_4$ (2.5 g) was added to **6b** (5 g) in methanol (150 ml) and 1 *N* NaOH (50 ml), and the mixture was refluxed overnight. The usual work-up gave 4.8 g of an oil (**9b**) which crystallized from ether (6 ml)–*n*-hexane (10 ml) (3.16 g, 32% based on **1**). Recrystallization from ethyl acetate–hexane gave a solid (mp 102–104°) identical with the piperidinol **9b** previously described.

B. From Reduction of 8b.—$NaBH_4$ (0.75 g) was added to 2-*p*-methoxybenzyl-1-methyl-4-piperidone (**8b**, from 2.15 g of picrate) in methanol (25 ml) and the mixture refluxed 2 hr. The usual work-up gave piperidinol **9b** (0.765 g, 70%, mp 100–103°).

2′-Hydroxy-2-methyl-6,7-benzomorphan (10c).—2-*p*-Methoxybenzyl-1-methyl-4-piperidinol (**9b**, 0.45 g) was heated in PPA (8 g) for 5 hr (205°, bath temperature). The mixture was cooled and H_2O (30 ml) and 12 *M* HCl (18 ml) were added. This solution was refluxed 15 hr, filtered through Norit, made basic with NH_4OH, and extracted with chloroform–ethanol (9:1). Solvent was removed from the dried[13] organic extracts. The residue was triturated in a small amount of acetone, then refrigerated overnight to give **10c** (0.21 g, 54%, mp 218–221°, dec). Recrystallization from methanol gave a solid, mp 228–230° dec, identical with an authentic sample.[2]

Registry No.—**1**, 21823-37-0; **2a**, 21876-32-4; **2b**, 21876-33-5; **3**, 21823-47-2; **4a**, 21823-48-3; **4a**, picrate, 21823-49-4; **4b**, 21823-50-7; **4b**, picrate, 21823-51-8; **5a**, 21823-52-9; **5a**, picrate, 21823-53-0; **6a**, 21823-54-1; **7**, dihydrochloride, 21823-55-2; **8a**, 21823-56-3; **8a**, picrate, 21823-57-4; **8b**, picrate, 21886-97-5; **8b**, hydrobromide, 21823-58-5; α-**9a**, 21823-94-9; β-**9a**, 21823-95-0; **9b**, 21850-66-8; (2-benzyl-4-methoxy-1-methyl-4-piperidinol) picrate, 21823-59-6.

(16) The α and β prefixes for **9** are arbitrary diastereoisomer designations.

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

(18) Physical data for pure **4b** are given in reduction B.

(19) Structure **5b** is assigned by analogy with **5a**.

(20) The nmr spectrum of this oil indicated the absence of **5b**.

(21) Homogeneous by tlc and glpc.