4-Methoxy-1-methylpyridinium Iodide. Stevens Rearrangement of Borohydride Reduction Product

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Stevens rearrangement of 4-methoxy-1-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridinium chloride (**3**) monohydrate, prepared from 4-methoxy-1-methylpyridinium iodide (**1**), has given ring-fission products, *p*-methoxybenzyl-N-methylamine (**4**), 3-methoxy-5-(N-*p*-methoxybenzyl-N-methyl)amino-1,3-pentadiene (**5**), and 5-(N-*p*-methoxybenzyl-N-methyl)amino-3-phenyl-1-penten-3-ol (**9**), in addition to 4-*p*-methoxybenzyl-1-methyl-2-phenyl-1,2,5,6-tetrahydropyridine (**8**) (a 1,4-rearrangement-addition product) and the desired 4-methoxy-2-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridine (**6**). The nmr spectral properties of **6** were intimately compared with those of the corresponding Δ^4 isomer (**10**).[2]

In the foregoing paper,[2] 4-methoxy-2-*p*-methoxybenzyl-1-methyl-1,2,3,6-tetrahydropyridine (**10**, Δ^4 unsaturation) was described as an unexpected product from borohydride reduction of the corresponding 1,2-dihydro compound. To establish the structure of **10** with greater certainty and to investigate alternative routes to 3-benzazocines (6,7-benzomorphans), the 1,2,5,6 (Δ^3) isomer (**6**) has been synthesized from 4-methoxy-1-methylpyridinium iodide (**1**).

Reduction of **1** with sodium borohydride gave 4-methoxy-1-methyl-1,2,3,6-tetrahydropyridine (**2**), which was converted into a stable hydrate of quaternary salt **3**, with *p*-methoxybenzyl chloride. Treatment of this hydrate with excess, ethereal phenyllithium produced a mixture[3] which could be separated by thick layer chromatography into N-*p*-methoxybenzyl-N-methylamine (**4**), the 1,3-pentadiene (**5**),[4] the expected 4-methoxy-2-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridine (**6**), 4-*p*-methoxybenzyl-1-methyl-2-phenyl-1,2,5,6-tetrahydropyridine (**8**), and the 1-penten-2-ol (**9**) (Scheme I)

The structure of **5**, a Hofmann elimination product of **3**, was assigned from spectral data. The secondary amine **4**[5] could arise from **5** during the work-up procedure *via* acid cleavage of the C–N linkage of **5** with formation of stabilized cation **A**, the product from which would be lost during further work-up. Alcohol **9**, with the longest glpc retention time and highest boiling point of the five compounds isolated, could also derive from **5** through addition of phenyllithium to hypothetical ketone **B**, formed after enol ether hydrolysis of **5**. Infrared absorption at 3.1–3.3 μ (OH), nmr chemical shifts for an ABX unsaturated system along with those for two aromatic rings, and other data were proof of structure **9** (see Scheme II and Experimental Section.

As for **8** (fourth in glpc retention time), nmr and mass spectral data indicated an additional, monosubstituted phenyl residue. A broad signal at 5.35 ppm (olefinic proton) which did not change on addition of trifluoroacetic acid, the uv spectrum [λ_{max}^{EtOH} 235, 277, 284 mμ (ϵ 2800, 2350, 2080)], and an *m/e* of 293 for the molecular ion (172, base peak) provided the principal basis for its structure.[6]

Finally, the normal rearrangement product, **6**, was found to be similar to the isomeric **10** in its ir (5.95 μ, enol ether)[7] and mass (*m/e* 247, M^+, 126, base peak for both **6** and **10**)[8] spectral characteristics. The nmr spectrum of **6** was similar to that of **10** in the chemical shifts for N–CH_3, aromatic O–CH_3, and aromatic protons. However, the signals for the protons of the allylic methylene group (at C-5 for **6** and C-3 for **10**) and for the olefinic protons are distinctly different (Scheme III). The olefinic proton in **6** (δ 4.38 broad) is diamagnetically shifted 0.16–0.19 ppm compared with its normal position (δ 4.54–4.57, broad t, J = 3 Hz) in **10**, **10a**,[2] and **2**, owing to the anisotropy effect of the aromatic ring. The allylic (C-3) methylene protons of **10** and **10a** (at δ 1.87–2.10) were similarly affected by this anisotropy, being shifted diamagnetically by 0.2–0.3 ppm (12–18 Hz) compared with the C-5 methylene protons of **6** and **2** at 2.1–2.4. The broad triplet (olefinic proton) observed for **10a** was resolved by double irradiation at 100 MHz. Decoupling by irradiation of the C-6 protons (about 3.15) collapsed the triplet to a singlet (broad owing to long-range coupling with the C-3 protons). When the C-3 protons were irradiated, the olefinic proton appeared as a much sharper triplet, J = 3 Hz. These data are consistent with a structure containing a double bond in the Δ^4 (4,5) position in **10a** (and **10** because of the similarity of their nmr spectra). Thus, the double bond of **6** must be in the Δ^3 position.

Experimental Section[9]

4-Methoxy-1-methyl-1,2,3,6-tetrahydropyridine (2) Picrate.—NaOH (1 *N*, 110 ml) was slowly added to a below −15°[10] suspension of **1** (22.5 g) in methanol (35 ml). The ice bath was removed and $NaBH_4$ (6 g) was rapidly added. The temperature rose

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(2) M. Takeda, A. E. Jacobson, K. Kanematsu, and E. L. May, *J. Org. Chem.*, **34**, 4154 (1969).

(3) Glpc examination showed five substances in ratios of 17:13:14:6:16 in the order of increasing retention time.

(4) Presumably the solvate water of **3** which would convert the PhLi into LiOH was largely responsible for this product.

(5) The structure was deduced from spectral data. The hydrochloride of **4** was reported by M. Tiffeneau, *Bull. Soc. Chim. Fr.*, **9**, 826 (1911); *Chem. Abstr.*, **5**, 3803 (1911).

(6) These nmr and uv data, the latter showing no conjugated aryl chromophore, rule out Δ^2 unsaturation as well as reversed positions for the phenyl and *p*-methoxybenzyl groups. Other significant data, given in the Experimental Section, are consistent with **8**.

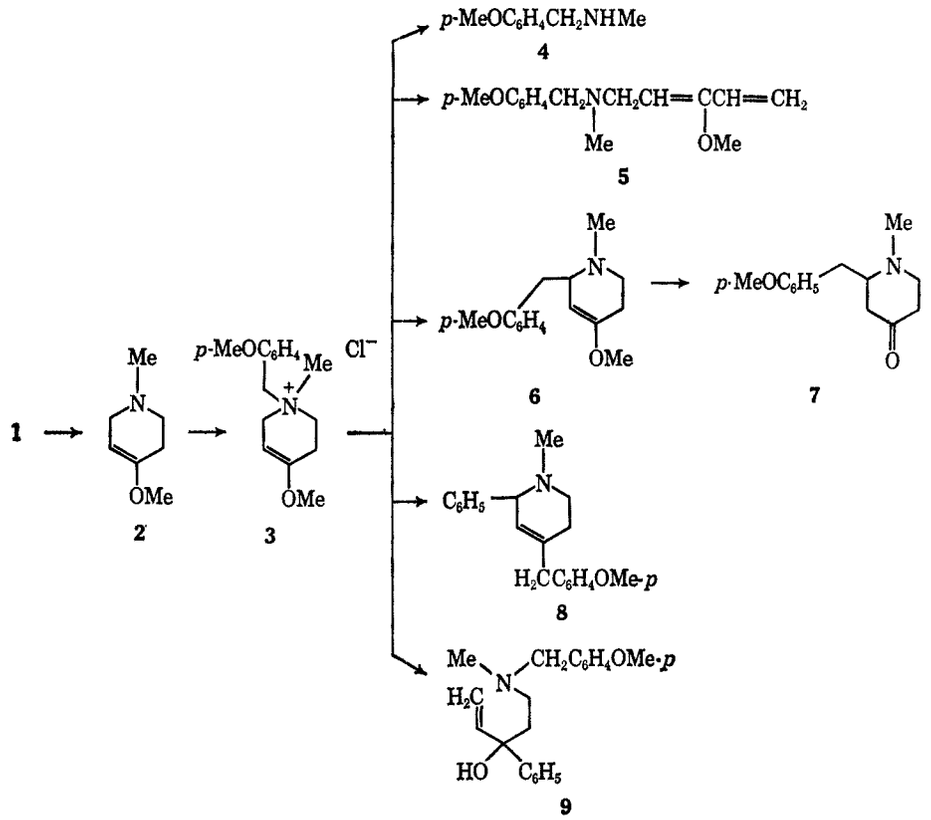
(7) Major differences were observable in the "fingerprint" region.

(8) Differences arose in the relative abundance of a few of the fragment ions.

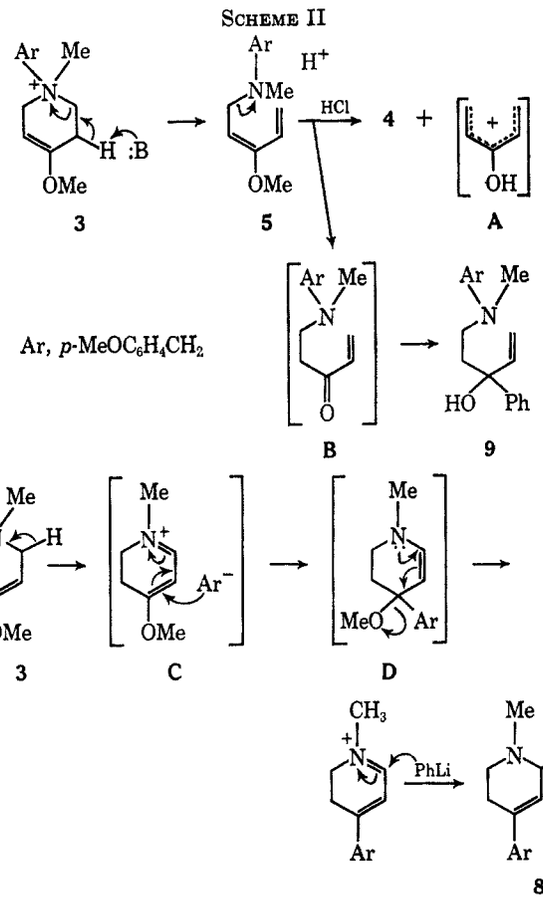
(9) See footnote 10 of ref 2. A Varian HA-100 instrument was used for 100-MHz spectra.

(10) Higher temperatures or a larger amount of NaOH reduced the yield of **2** with increased formation of water-soluble materials. In one run, the aqueous layer (after ether extraction) gave on continuous methylene chloride extraction a 15% yield of 1-methyl-4(1H)pyridone: $\lambda_{max}^{CHCl_3}$ 6.02 (sh), 6.09 and 6.35 (both strong) μ; nmr 3.7 (s, 3, NCH_3), 6.32 (d, 2, J = 7.5 Hz, C=CHC=O), 7.39 (d, 2, J = 7.5 Hz, NHC=C) ppm; *m/e* 109 (M^+ and base); λ_{max}^{EtOH} 261.5 mμ, $\lambda_{max}^{EtOH\text{-}12\%\ HCl}$ 239.5 mμ.

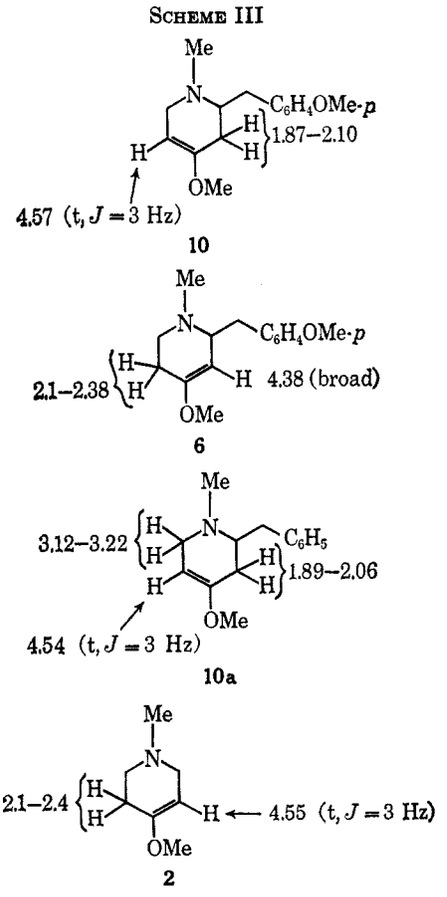
Scheme I



Scheme II



Scheme III



slowly to 35° during 20 min, and the mixture was then heated at 70° for 90 min. The cooled mixture was saturated with NaCl and extracted with ether. Solvent was distilled at 740–760 mm (bath temperature <60°) to give **2** (10.2 g, 90%, bp 168–170°): λ_{max}^{film} 5.95 μ (enol ether); nmr 2.33 (s, 3, N-CH_3), 3.48 (s, 3, O-CH_3) ppm. A picrate was prepared in ether: needles, mp 109.5–111.5°

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53; N, 15.73. Found: C, 43.83; H, 4.38; N, 15.90.

4-Methoxy-1-*p*-methoxybenzyl-1-methyl-1,2,3,6-tetrahydro-

pyridinium Chloride (3).—*p*-Methoxybenzyl chloride[11] (12.7 g) was added to **2** (10.2 g) in ether (100 ml)–acetone (30 ml), and the mixture was kept for 2 days at 25°, giving a hygroscopic solid (**3**, 18.2 g, 75%) which was washed with acetone–ether (1:1). Recrystallization from acetone–methanol–ether gave needles: mp 158–162°; λ_{max}^{Nujol} 3.0 (H_2O), 5.95 (enol ether) μ; nmr (D_2O) 3.07 (s, 3, N^+–CH_3), 3.67 (s, 3, C=$COCH_3$), 3.93 (s, 3, $PhOCH_3$), 4.53 (s, 2, $PhCH_2$), ~4.85 (center of broad band, 1, HC=C), 7.12 and 7.57 (4, AA'BB' multiplet, J_{AB} = 9.5 Hz, aromatic) ppm.

Anal. Calcd for $C_{15}H_{22}ClNO_2 \cdot H_2O$: C, 59.69; H, 8.02; N, 4.64; Cl, 11.75. Found: C, 59.49; H, 8.03; N, 4.89; Cl, 11.90.[12]

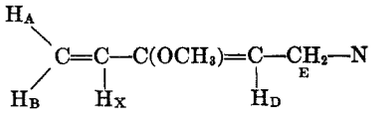
Stevens Rearrangement of 3.—Phenyllithium (16 ml, 1.91 *M*)[13] was rapidly added to a stirred suspension of **3** (hydrate, 4.5 g) in ether (10 ml). An exothermic reaction occurred, ebullition quickly subsiding. The mixture was stirred for 3 hr at 25°, poured into ice–water and extracted with ether. The ethereal solution was extracted, as rapidly as possible, with cold 1% HCl. The acidic extracts were washed with ether, basified with NH_4OH and extracted with ether. Removal of solvent from the dried (Na_2SO_4) ethereal extracts gave a red oil (2.23 g). The crude base was shown to be a mixture (by glpc) of what proved to be **4**, **5**, **6**, **7**, **8**, and an unknown sixth compound in the ratio of 17:13:14:6:16:4, respectively. The various components were isolated from the mixture by repeated thick layer chromatography.

N-*p*-Methoxybenzylmethylamine (4).—The bottom fraction of the thick layer chromatographic plate gave **4**[14] which was purified as its hydrochloride, mp 174–176° (lit.[5] mp 166°).

Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.47. Found: C, 57.47; H, 7.27; N, 7.67.

The free base had λ_{max}^{film} 3.0 μ (NH); nmr 1.90 (broad s, 1, NH disappeared on D_2O addition), 2.42 (s, 3, NCH_3), 3.67 (s, 2, $PhCH_2$), 3.76 (s, 3, OCH_3), 6.84 and 7.23 ppm (AA'BB' multiplet, 4, J_{AB} = 8.5 Hz, aromatic H's); *m/e* 151 (M^+), 121 (base).

3-Methoxy-5-(N-*p*-methoxybenzyl-N-methyl)amino-1,3-pentadiene (5).—Compound **5**[15] was isolated as a colorless oil: bp 120–140° (bath temperature), (0.1 mm); λ_{max}^{film} 6.05 (enol ether), 10.25 and 10.9 ($CH=CH_2$) μ; λ_{max}^{EtOH} 210, 228, 247, 281 mμ (ϵ 11500, 16,500, 12,800, 2050); nmr 2.20 (s, 3, NCH_3), 3.46 (s, 2, $PhCH_2$), 3.62 (s, 3 =$COCH_3$), 3.80 (s, 3, aromatic OCH_3), 6.84 and 7.24 (AA'BB' multiplet, 4, J_{AB} = 8.5 Hz, aromatic H's) ppm.



The following nmr data apply to the structure above: H_A, 5.61 (q, 1, J_{AB} = 2 Hz, J_{AX} = 17 Hz); H_B, 5.15 (q, 1, J_{AB} = 2 Hz, J_{BX} = 11 further split with 2 Hz coupling); H_X, 6.52 (q, 1, J_{AX} = 17 Hz, J_{BX} = 11 Hz); H_D, 4.80 (broad t, 1, J_{DE} = 7.5 Hz); H_E, 3.13 (d, 2, J = 7.5 Hz) ppm. Mass spectrum: *m/e* 247 (M^+), 121 (base).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.58; H, 8.62; N, 5.90.

4-Methoxy-2-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridine (6) Picrate.[16]—A picrate was prepared and recrystallized from acetone to give cubes, mp 162–163°.

Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.22; H, 4.88; N, 11.75.

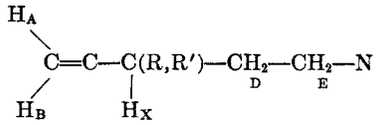
The free base had λ_{max}^{film} 5.95 μ (enol ether); nmr 2.48 (s, 3, NCH_3), 3.42 (s, 3, C=C—OCH_3), 3.76 (s, 3, aromatic OCH_3), 6.82 and 7.12 (AA'BB' multiplet, 4, J_{AB} = 8.5 Hz) ppm (see text for other chemical shifts).

Compound **6** was hydrolyzed (6 *N* HCl) to the known[2] **7**, isolated as the picrate, in 90% yield.

4-*p*-Methoxybenzyl-1-methyl-2-phenyl-1,2,5,6-tetrahydropyridine (8).[17]—A mixture of **8** and **9**, inseparable by silica gel tlc, was separated by alumina thick layer chromatography. Compound **8** was distilled [200–220°, bath temperature (0.3 mm)]; λ_{max}^{EtOH} 235, 277, 284 mμ (ϵ 2800, 2350, 2080); nmr 2.16 (s, 3, NCH_3), 3.28 (broad s, 2, $PhCH_2$), 3.77 (s, 3, OCH_3), 5.35 (broad, 1, C=C**H**), 6.82 and 7.12 (AA'BB' multiplet, 4, J_{AB} = 8.7 Hz), and 7.32 (s, 5, monosubstituted phenyl) ppm; nmr (CF_3CO_2D) 2.98 (s, 3, NCH_3), 3.57 (s, broad, 2, CH_2Ph), 4.0 (s, 3, OCH_3), 5.62 (broad, 1, C=CH), 7.08 and 7.32 (AA'BB' multiplet, 4, J_{AB} = 8.5 Hz), and 7.52 (s, 5, monosubstituted phenyl) ppm; *m/e* 293 (M^+), 172 (base).

Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.51; H, 7.90; N, 4.97.

5-(N-*p*-Methoxybenzyl-N-methyl)amino-3-phenyl-1-penten-3-ol (9).[18]—The base **9** was isolated as a colorless oil and distilled [bath temperature, 240°, (0.8 mm)]: λ_{max}^{film} 3.1–3.3 (OH), 10.15, 10.95 ($CH=CH_2$) μ; λ_{max}^{EtOH} 219, 275, 281 mμ (ϵ 13,000, 2640, 2440); nmr 2.13 (s, 3, NCH_3), 3.39 (s, 2, $PhCH_2$), 3.79 (s, 3, OCH_3), 6.86 and 7.23 (AA'BB' multiplet, 4, J_{AB} = 9 Hz), 7.2–7.5 (m, 5, monosubstituted phenyl) ppm. The following nmr



data apply to the structure above: H_A, 5.36 (q, 1, J_{AX} = 16.8 Hz, J_{AB} = 2 Hz); H_B, 5.08 (q, 1, J_{AB} = 2 Hz, J_{BX} = 10.6 Hz); H_X, 6.14 (q, 1, J_{BX} = 10.6 Hz, J_{AX} = 16.8 Hz); H_D, 1.95–2.2 (2 H); H_E 2.58 (two doublets, 2, J = 5 Hz, J = 11 Hz) ppm. Mass spectrum: *m/e* 311 (M^+), 121 (base).

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 76.86; H, 8.27; N, 4.43.

Registry No.—Sodium borohydride, 1303-74-8; **1**, 21823-37-0; **2** (picrate), 21823-38-1; **3**, 21823-39-2, **4**, 702-24-9; **5**, 21823-41-6; **6**, 21823-42-7; **6** (picrate), 21823-43-8; **8**, 21823-44-9; **9**, 21823-45-0.

Acknowledgment.—The authors wish to thank Dr. R. J. Highet and Mr. E. Sokoloski, National Heart Institute, NIH, for the 100-MHz, double-irradiation spectra.

(11) Eastman Kodak Co. See also S. Saito and E. L. May, *J. Org. Chem.*, **27**, 948 (1962).

(12) After **3** was dried at 60° overnight *in vacuo* its ir spectrum still indicated the presence of hydrate H_2O.

(13) Alfa Inorganics, Inc., 70:30 benzene–ether.

(14) Lowest boiling point, 20 sec glpc (160°) retention time.

(15) Three-minute (160°) glpc retention time, next to highest tlc R_f value.

(16) Glpc retention time 3.5 min (160°), middle tlc fraction.

(17) Glpc retention time 2.8 min (200°), highest R_f on tlc.

(18) Retention time 3.4 min at 200°.