Notes

Δ^3 and Δ^4 Isomers of 4-Alkyl-2-*p*-methoxybenzyl-1-methyltetrahydropyridines

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It has been tacitly assumed that *4-alkyl*-2-*p*-methoxybenzyl-1-methyltetrahydropyridines,[2] prepared by palladium-catalyzed hydrogenation or alkaline sodium borohydride reduction of corresponding 1,2-dihydropyridines,[3] bear Δ^3 unsaturation. Recent investigations[4] demonstrating that a similar sequence of reactions beginning with 4-methoxypyridine has given exclusively 2-benzyl-*4-methoxy*-1-methyl-1,2,3,6-tetrahydropyridines (Δ^4 unsaturation) has prompted us to reexamine the 4-alkyl series. We present here the synthesis and structure proof of 1,4-dimethyl-2-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridine (**5a**), the Δ^4 isomer (**6a**), and their 4-ethyl homologs (**5b**, **6b**).

Sodium borohydride reduction of the product **3**, obtained from 1,4-dimethylpyridinium iodide (**2a**) and ethereal *p*-methoxybenzylmagnesium chloride,[3a] gave an 8:3 mixture (glpc) of **5a** and **6a**, respectively, after distillation and separation *via* their picrate salts.

The position of the double bond in **5a** and **6a** was determined by nmr spectral data (Scheme I). Thus, **5a** showed a broad signal at 5.18 ppm compared with 5.38 for **6a**.[5] This diamagnetic shift of 0.2 ppm (12 Hz) can be ascribed to the anisotropy effect of the aromatic ring of **5a** and was observed in the 4-methoxy series.[4b] A similar diamagnetic shift (for the same reason) was seen for the two C-3 protons (chemical shift centered at 1.85 ppm) of **6a**. The multiplet for the C-5 protons of **5a** is centered at 2.00 ppm. The 4-CH_3 signals were almost identical (1.65 and 1.63 ppm, respectively) for **5a** and **6a**.

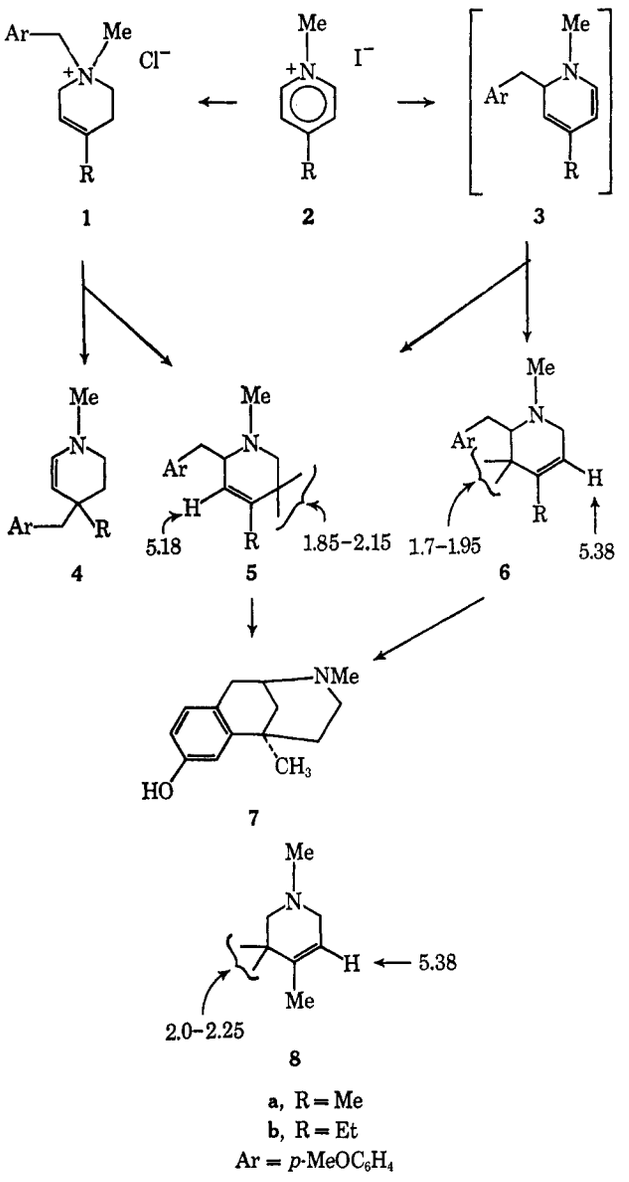
Similar treatment of 4-ethyl-1-methylpyridinium iodide (**2b**) also gave two major products (**5b**, **6b**) in a 3:1 ratio. The major product was assigned the Δ^3 structure for reasons given above (olefinic proton at 5.20 ppm).

Compounds **5a,b** were synthesized unambiguously by borohydride reduction of **2a,b** and Stevens rearrangement of the *p*-methoxybenzylchloride-quaternized products (**1a,b**). A minor 1,4-rearrangement product was isolated in each instance and proved to be 4-alkyl-4-*p*-methoxybenzyl-1-methyl-1,2,3,4-tetrahydropyridines (**4a,b**)[6] principally by spectral data (see Experimental Section).

Polyphosphoric acid (PPA) treatment of either **5a** or **6a** gave 2,5-dimethyl-2′-hydroxy-6,7-benzomorphan (**7**).[3a,c,7] These cyclizations take place almost certainly through an identical C-4, carbonium-ion intermediate.

From the above results, it is apparent that, in the

SCHEME I



a, R = Me
b, R = Et
Ar = *p*-$MeOC_6H_4$

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(2) These compounds are precursors of interesting and important 3-benzazocines (6,7-benzomorphans); see J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 288 (1969).

(3) (a) N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957). (b) S. Saito and E. L. May, *ibid.*, **27**, 948 (1962). (c) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

(4) (a) M. Takeda, A. E. Jacobson, K. Kanematsu, and E. L. May, *J. Org. Chem.*, **34**, 4154 (1969). (b) M. Takeda, A. E. Jacobson, and E. L. May, *J. Org. Chem.*, **34**, 4158 (1969).

(5) For comparison see 1,4-dimethyl-1,2,3,6-tetrahydropyridine (**8**).

(6) These minor products are analogous to previously isolated materials in other series; *cf.* A. E. Jacobson, *J. Org. Chem.*, **31**, 1569 (1966), and A. E. Jacobson and R. T. Parfitt, *ibid.*, **32**, 1894 (1967).

(7) J. G. Murphy, J. H. Ager, and E. L. May, *ibid.*, **25**, 1386 (1960).

borohydride reduction of 4-alkyl-2-*p*-methoxybenzyl-1-methyl-1,2-dihydropyridines (**3a,b**), proton attack (or the net result thereof) occurs at the C-5 (central) position of the dienamine system to give, ultimately, the expected **5a,b** (Δ^3 unsaturation)[8] and, to a lesser extent, at (terminal) C-3 leading to **6a,b** (Δ^4 unsaturation). As reported before,[4a] a *4-methoxy* substituent induces protonation at C-3 exclusively. At present, we cannot explain the directive influence of the 4 substituent in the protonation of systems such as **3** during alkaline borohydride reduction.

Experimental Section[9]

Preparation and $NaBH_4$ Reduction of 3a.—Ethereal *p*-methoxybenzylmagnesium chloride[10] (270 ml of 0.34 *M* solution) was added to a suspension of 1,4-dimethylpyridinium iodide (**2a**, 17.6 g) in ether (80 ml), and refluxed (2 hr) with stirring to give a two-layered mixture. The cooled mixture was poured into ice–water containing NH_4Cl (25 g), basified with NH_4OH, and extracted with ether. The ethereal solution was extracted with 10% HCl, washed with ether, made basic with NH_4OH, and extracted with ether. Solvent was removed *in vacuo* from the dried ethereal extracts to give an air-sensitive red oil (**3a**, 15 g). $NaBH_4$ (3.4 g) was added to this **3a** in methanol (200 ml) and 1 *N* NaOH (70 ml), and the mixture was heated overnight (60–70°). The methanol was removed *in vacuo*, and the residual material was extracted with ether. Solvent was removed from the dried ethereal extracts to give a yellow oil (13 g) which was found to be a mixture of **5a** and **6a** (8:3, by glpc). The oil was fractionally distilled (0.35 mm) to give **1,4-dimethyl-2-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridine** (**5a**, 5.3 g, bp 115–120°, contaminated with 15% **6a**) and **1,4-dimethyl-2-*p*-methoxybenzyl-1,2,3,6-tetrahydropyridine** (**6a**, 2.4 g, bp 120–123°, contaminated with 35% of **5a**). A picrate was prepared from the 115–120° fraction in methanol and recrystallized from methanol to give needles (**5a** picrate, mp 110–112°).

Anal. Calcd for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.27; N, 12.17. Found: C, 54.98; H, 5.01; N, 12.07.

The free base had λ_{max}^{film} 5.95, 11.7, 12.2 μ (C=C); nmr 2.47 (s, 3, NCH_3), 6.82, 7.11 (AA'BB' multiplet, 4, J_{AB} = 9 Hz) ppm; *m/e* 231 (M^+), 110 (base).

The 120–123° fraction (**6a**) was also purified through its picrate (1.7 g). Recrystallization (acetone–methanol) gave needles (**6a** picrate, mp 127–129°).

Anal. Calcd for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.27; N, 12.17. Found: C, 54.91; H, 5.52; N, 12.08.

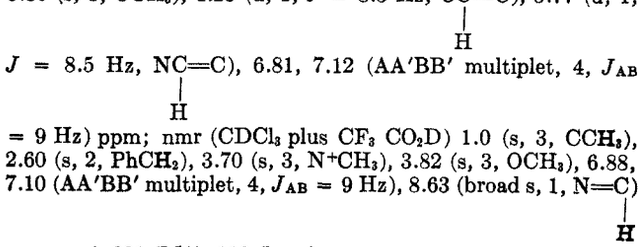
The free base had λ_{max}^{film} 5.95, 11.6, 12.1 μ (C=C); nmr 2.47 (s, 3, NCH_3), 3.79 (s, 3, OCH_3), 6.82 and 7.11 (AA'BB' multiplet, 4, J_{AB} = 9 Hz) ppm; *m/e* 231 (M^+), 110 (base).

Preparation and $NaBH_4$ Reduction of 3b.—4-Ethyl-1-methylpyridinium iodide (**2b**, 18.7 g) was treated with ethereal *p*-methoxybenzylmagnesium chloride[10] (270 ml of 0.34 *M*) as above to give a brown oil (**3b**, 15 g), which was reduced with $NaBH_4$ (3.4 g) under the above conditions to give an oil (14 g), mainly a two-component mixture of **4-ethyl-2-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridine** (**5b**) and a second compound[11] (25% by glpc). The oil was fractionally distilled (0.5 mm), and the fraction collected at 125–128° (**5b**, 5.3 g) was converted into its picrate (4.15 g) in methanol. Recrystallization (methanol) gave yellow needles, mp 82–84°.

Anal. Calcd for $C_{22}H_{26}N_4O_8$: C, 55.69; H, 5.52; N, 11.81. Found: C, 55.85; H, 5.42; N, 11.79.

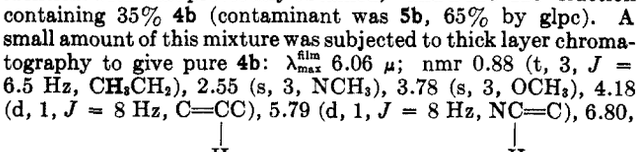
The free base had λ_{max}^{film} 5.95, 11.6, 12.15 μ (C=C); nmr 0.95 (t, 3, *J* = 7 Hz), 2.48 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 5.20 (broad, 1, C=CH), 6.85 and 7.17 (AA'BB' multiplet, 4, J_{AB} = 8.5 Hz) ppm; *m/e* 245 (M^+), 124 (base).

Stevens Rearrangement of 1a.—Phenyllithium (100 ml of 2.11 *M* in 70:30 benzene–ether) was added to a suspension of **1a**[12] (26.7 g) in ether (100 ml) and the usual procedure[13] and work-up gave a brown oil (19.8 g), mainly a two-component mixture of **5a** and **1,4-dimethyl-4-*p*-methoxybenzyl-1,2,3,4-tetrahydropyridine** (**4a**) in the ratio (glpc) of 3:1. Fractional distillation (0.1–0.2 mm) gave **5a** (10.2 g, 106–112°) which was converted into **5a** picrate in methanol (11.3 g). Recrystallization (methanol) gave needles, mp 110–112°, identical with those previously obtained.[12,14] The fraction collected at 112–117° (3.72 g) was found to be mixture of **5a** and **4a** (7:4), a portion of which was subjected to thick layer chromatography to give the pure **4a**: λ_{max}^{film} 6.06 (C=C) μ; nmr 0.95 (s, 3, CCH_3), 2.57 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 4.25 (d, 1, *J* = 8.5 Hz, CC=C), 5.77 (d, 1, *J* = 8.5 Hz, NC=C), 6.81, 7.12 (AA'BB' multiplet, 4, J_{AB} = 9 Hz) ppm; nmr ($CDCl_3$ plus CF_3CO_2D) 1.0 (s, 3, CCH_3), 2.60 (s, 2, $PhCH_2$), 3.70 (s, 3, N^+CH_3), 3.82 (s, 3, OCH_3), 6.88, 7.10 (AA'BB' multiplet, 4, J_{AB} = 9 Hz), 8.63 (broad s, 1, N=C) ppm; *m/e* 231 (M^+), 110 (base)



Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.74; H, 8.88; N, 6.07.

Stevens Rearrangement of 1b.—Phenyllithium (75 ml of 2.11 *M* in 70:30 benzene–ether) was added to a suspension of **1b**[3b] (22 g) in ether (100 ml). The usual procedure[13] and work-up gave a brown oil (17 g) which was found to be a mixture of **5b** and **4-ethyl-4-*p*-methoxybenzyl-1-methyl-1,2,3,4-tetrahydropyridine** (**4b**) (4:1 by glpc). Fractional distillation (0.3–0.4 mm) gave **5b**, bp 115–126°, 6.35 g, contaminated with 10% **4b** (by glpc), which was purified through its picrate to give **5b** picrate identical with that previously obtained,[3b] and a 126–128° fraction containing 35% **4b** (contaminant was **5b**, 65% by glpc). A small amount of this mixture was subjected to thick layer chromatography to give pure **4b**: λ_{max}^{film} 6.06 μ; nmr 0.88 (t, 3, *J* = 6.5 Hz, CH_3CH_2), 2.55 (s, 3, NCH_3), 3.78 (s, 3, OCH_3), 4.18 (d, 1, *J* = 8 Hz, C=CC), 5.79 (d, 1, *J* = 8 Hz, NC=C), 6.80, 7.11 (AA'BB' multiplet, 4, *J* = 9 Hz) ppm; nmr ($CDCl_3$ plus CF_3CO_2D) 0.95 (t, 3, *J* = 6.5 Hz, CH_3CH_2), 2.60 (s, 2, $PhCH_2$), 3.66 (s, 3, N^+CH_3), 3.80 (s, 3, OCH_3), 6.85, 7.07 (AA'BB' multiplet, 4, *J* = 9 Hz), 8.67 (broad, 1, N^+=CH) ppm; *m/e* 245 (M^+), 124 (base).



2'-Hydroxy-2,5-dimethyl-6,7-benzomorphan (**9**). **A. From 5a.**—A mixture of **5a** (regenerated from 1.4 g of picrate) and PPA (8 g) was stirred and heated at 200° for 8 hr. Water (40 ml) and 12 *M* HCl (20 ml) were added to the cooled mixture which was then refluxed for 15 hr. Basification (NH_4OH), extraction (chloroform–ethanol, 9:1), and removal of solvent from the dried extracts gave an oil (**7**, 0.6 g) which crystallized (0.509 g, 77%) from acetone (5 ml), mp 213–216° dec.[3,7]

B. From 6a.—PPA cyclization of **6a** (regenerated from 0.4 g of picrate) followed by acid hydrolysis as above gave **9** (0.145 g, 76.8%, mp 213–216°), identical with the product obtained from **5a**.

Registry No.—**4a**, 21779-24-8; **4b**, 21779-25-9; **5a**, 21779-26-0; **5a** picrate, 21779-27-1; **5b**, 21779-28-2; **5b** picrate, 21779-29-3; **6a**, 21779-30-6; **6a** picrate, 21850-62-4.

(8) P. S. Anderson and R. E. Lyle, *Tetrahedron Lett.*, 153 (1964), reported protonation at the central position for a similar system.

(9) See footnote 10 of the first paper[4a] of this series.

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

(11) Presumably **6b**, the isolation and characterization of which were not achieved.

(12) E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

(13) See Stevens-rearrangement experiment in S. Saito and E. L. May, *J. Org. Chem.*, **27**, 948 (1962).

(14) J. H. Ager, this institute, unpublished results.

Base-Catalyzed Addition Reactions of Benzaldehyde Anil

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Several years ago, the potassium *t*-butoxide catalyzed reaction of benzaldehyde anil (1) with dimethyl