Improved Synthesis of 2-Benzyl-1,2,5,6-Tetrahydropyridines, Precursors of Analgetic 6,7-Benzomorphans

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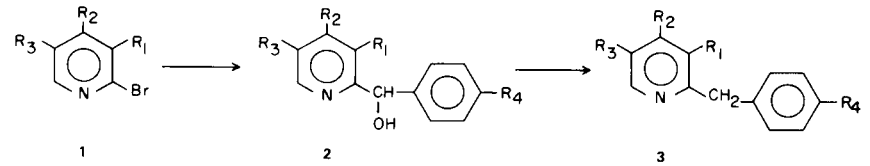
Received January 18, 1971

Pentazocine, phenazocine and related analgetic 6,7-benzomorphans are generally synthesized by intramolecular cyclization of appropriately substituted 1,2,5,6-tetrahydropyridines (*e.g.* **5**). The latter are made by (a) a Freund reaction between a benzylmagnesium chloride and 1-alkylpyridinium iodide followed by reduction (a) or (b) Stevens rearrangement of an *N*-benzylpyridinium chloride (3). These procedures, while making possible the synthesis of a variety of 6,7-benzomorphans for pharmacological evaluation (4) do not always afford satisfactory yields of the desired product. Side-products are encountered in the Stevens rearrangement (5a) and the Grignard reaction gives unstable (2) and at times (5b) unpredicted products. We now report a new approach to the preparation of 2-benzyl-1,2,5,6-tetrahydropyridines in which the 2-benzyl group is introduced in a direct and improved sequence.

2-Bromopyridine (**1a**) can be alkylated with anisaldehyde (6) to give *p*-methoxyphenyl-2-pyridylcarbinol (**2a**), the chloride of which undergoes reductive dehalogenation to 2-*p*-methoxybenzylpyridine (**3a**) (6). The unambiguity of the substituent in the 2-position made this synthesis attractive for a route to **5**. Quaternization of **3a** with methyl iodide gave excellent yields of methiodide, **4a**.



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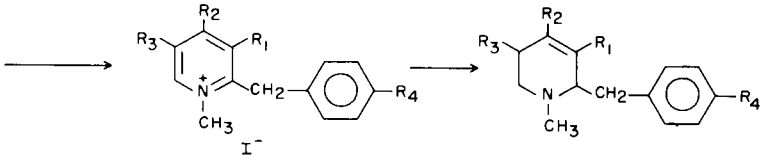

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a: $R_1 = R_2 = R_3 = R_4 = H$
b: $R_1 = R_2 = R_3 = H$; $R_4 = OCH_3$
c: $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$
d: $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = OCH_3$

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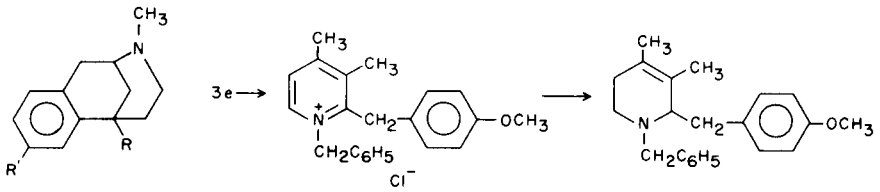
e: $R_1 = R_2 = CH_3$; $R_3 = H$; $R_4 = OCH_3$
f: $R_1 = R_3 = H$; $R_2 = CH_3$; $R_4 = OCH_3$
g: $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = OCH_3$



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a: R = R' = H
b: R = H; R' = OH
c: R = CH_3; R' = OH

TABLE I

2-Benzyl-1-methyl-1,2,5,6-tetrahydropyridines

Compound	B.P.°/mm/m.p.°	Yield % (a)	Molecular Formula	Analyses Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
5a	95/0.4 (b) (c)	70	$C_{13}H_{17}N$	83.37	83.24	9.15	8.98	7.48	7.28
5b	170/5 (b) (d)	75	$C_{14}H_{19}NO$	77.38	77.17	8.81	8.51	6.45	6.29
5c	87-89/0.3 (e) HCl, 168	56	$C_{14}H_{20}ClN$	70.69	70.95	8.50	8.34	5.89	5.85
5d	138/0.5 (e) (f) HCl, 205	65	$C_{15}H_{22}ClNO$	67.27	66.91	8.25	7.96	5.21	4.92
5e	115-120/0.2 (g)	56	$C_{16}H_{23}NO$	78.32	78.41	9.45	9.56		
5f	116-118/0.8 (h)	65							

(a) Yields are based on a limited number of experiments and do not necessarily represent the maximum obtainable. (b) Glc showed this to be a 4:1 mixture of Δ^3- and Δ^4-isomers. (c) This was cyclized under conditions previously reported (7) from this laboratory to 2-methyl-6,7-benzomorphan (**6a**), b.p. 105°/2mm in 80% yield. *Anal.* Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.64. H, 9.42; N, 7.29. Hydrochloride, m.p. 223° [lit (7) 224-225°]. (d) Picrate, m.p. 123-124° [lit. (7) 123-124°]. Cyclization with PPA gave 50% yield of 2'-hydroxy-2-methyl-6,7-benzomorphan (**6b**); m.p. 230° [lit. (7) m.p. 230°]; (e) Glc showed this to contain 5% of the Δ^4-isomer. (f) Nmr absorptions: δ 1.58 (d, J = 2 Hz, 3, C-Me), 2.32 (s, 3, NCH_3), 2.78 (s, 2, CH_2), 3.63 (s, 3, OMe), 5.42 (m, 1, C-4H), 6.74, 7.16 (AA'BB' multiplet, 4, J_{AB} = 9 Hz), ring methylene absorptions between 1.9-3.0 ppm; total integration satisfactory. (g) Nmr: δ 1.58 (s, 6, C-3 Me and C-4 Me), 2.32 (s, 3, NMe), 3.70 (s, 3, OMe), 6.74, 7.12 (AA'BB' multiplet, 4, J_{AB} = 9 Hz), methylene absorptions between 1.8-2.8 ppm. Integrals of trace absorptions at 1.0 and 5.8 ppm indicated negligible amounts of Δ^4-isomer. (h) The nmr data and m.p. of the picrate (129-130°) correspond to properties reported (6) for 1,4-dimethyl-2-*p*-methoxybenzyl-1,2,3,6-tetrahydropyridine. Cyclization in PPA gave 78% yield of 2,5-dimethyl-2'-hydroxy-6,7-benzomorphan (**6c**) m.p. 213-216° [lit. (6) 213-216°].

TABLE II

2-Benzyl-1-methylpyridinium Iodides 4

Compound	M.P. °C	Formula	Analyses Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
4a	159	$C_{13}H_{14}IN$					4.50	4.68
4b	229-230	$C_{14}H_{16}INO$	49.26	49.05	4.73	4.65	4.11	3.83
4c	88 dec (a)	$C_{14}H_{16}IN$	51.71	51.58	4.95	5.15	4.31	4.23
4d	127-129	$C_{15}H_{18}INO$	50.71	50.47	5.10	4.93	3.95	3.84
4e	222-223	$C_{16}H_{20}INO$	52.04	51.76	5.46	5.39	3.79	3.89
4f	186-187	$C_{15}H_{18}INO$	50.71	50.64	5.10	4.96	3.95	3.82
4g	182-183	$C_{15}H_{18}INO$	50.71	50.78	5.10	5.10	3.95	4.20

(a) The yellow crystalline compound rapidly turns brown in air.

This was reduced with sodium borohydride in methanolic solution giving a 75% yield of a 4:1 mixture of 1,2,5,6-(Δ^3)- (**5a**) and 1,2,3,6-(Δ^4)-tetrahydropyridines. Cyclization of the mixture with PPA afforded the known (7) 2'-hydroxy-2-methyl-6,7-benzomorphan (**6a**).

Following this success, we prepared a series of 2-benzylpyridines (**3b-g**) from appropriate 2-bromopyridines (**1b-g**) and converted them *via* the methiodides (**4**) to the corresponding tetrahydropyridines (**5**, Scheme I, Table I). In cases where an alkyl substituent is present in the 3-position, sodium borohydride reduction afforded almost entirely (95%) the Δ^3-isomer. An exclusively methanol medium was used after it was noticed that reduction in aqueous alkali-methanol mixtures gave considerably lower yields

of **5**, difficult to purify (extensive resinification on distillation).

The accessibility of substituted 2-amino- and 2-bromopyridines and the ease of conversion to the 2-benzylpyridines give the described procedure broad potential for the unambiguous synthesis of specifically substituted 6,7-benzomorphans. As an example, we have applied this sequence to the synthesis of 1-benzyl-3,4-dimethyl-2-(*p*-methoxybenzyl)-1,2,5,6-tetrahydropyridine (**8**), an intermediate for an improved preparation of pentazocine (8). Thus, quaternization of **3e** with benzyl chloride gives 1-benzyl-3,4-dimethyl-2-*p*-methoxybenzylpyridinium chloride (**7**) which is reduced by sodium borohydride in 65% yield to **8**, isolated as the oxalate, m.p. 154-158° (8).

EXPERIMENTAL

Melting points are corrected. Microanalyses and nmr measurements (Varian A-60) were done by the Instrumentation and Analytical Services Section of this Institute. Unless otherwise stated, deuteriochloroform was used as solvent for nmr. Chemical shifts are reported as δ values in parts per million (ppm) relative to internal tetramethylsilane.

Bromopyridines (**1**).

2-Bromo-3-methyl- (9) and 2-bromo-4-methylpyridine (10) were prepared by published procedures. The method of Mariella and Kwinge (9) was used for preparing new bromopyridines.

2-Bromo-3,4-dimethylpyridine.

This was prepared from 2-amino-3,4-dimethylpyridine (11) in 85% yield, as a colorless oil, b.p. 110°/10 mm, crystallizing to a solid, m.p. 49-50°; nmr: δ 2.25 (s, 6, C-3 Me and C-4 Me), 6.93 (d, 1, C-5 H), 7.92 (d, 1, C-6 H, $J_{5,6}$ = 5 Hz).

Anal. Calcd. for C_7H_8BrN: C, 45.17; H, 4.33; N, 7.52. Found: C, 45.21; H, 4.17; N, 7.35.

2-Bromo-5-methylpyridine.

This compound, m.p. 45°, was obtained in 95% yield from 2-amino-5-methylpyridine (Aldrich Chemical Co.). Vacuum distillation gave a colorless oil, b.p. 65°/0.5 mm, crystallizing to a solid m.p. 46-47°; nmr: 2.25 (s, 3, Me), 7.32, 7.35 (s, 1 each, C-3 H and C-4 H), 8.15 (m, C-6 H).

Anal. Calcd. for C_6H_6BrN: C, 41.86; H, 3.52. Found: C, 41.91; H, 3.27.

2-Benzylpyridines (**3**).

The preparation of 2-*p*-methoxyphenyl-3,4-dimethylpyridine (**3e**) *via* (3,4-dimethyl-2-pyridyl)-*p*-methoxyphenyl carbinol (**2e**) illustrates the general procedure used for obtaining new substituted 2-pyridyl carbinols and the corresponding 2-benzylpyridines.

2-Bromo-3,4-dimethylpyridine (**1e**, 55.8 g., 0.3 mole) in anhydrous ether (100 ml.) was slowly added to a stirred solution of butyllithium (Alfa Inorganics, 0.5 mole, 225 ml. of 25.3 wt % solution in hexane) cooled to -30° to -40° in acetone-dry ice. The resultant brownish mixture was stirred for 0.5 hour and anisaldehyde (49 g., 0.36 mole) was added dropwise (temperature below -25°). The mixture was allowed to warm to -15°, stirred for 1 hour and poured into a dilute hydrochloric acid-ice mixture. The acidic layer was separated and rendered basic with gaseous ammonia to liberate the carbinol as a crystalline solid. This was dissolved in chloroform, filtered through carbon, dried and evaporated to give 68.0 g. (93%) of **2e**, m.p. 122°; nmr: 1.97, 2.20 (s, 3 each, C-3 and C-4 Me), 3.72 (s, 3, OMe), 5.75 (s, 1, C*H*OH), 5.90 (broad, 1, CHO*H* exchanged by deuterium oxide), 6.78, 7.16 (AA'BB' multiplet, 4, J_{AB} = 9 Hz), 7.0 (d, 1, J = 5 Hz, C-5 H), 8.29 (d, 1, J = 5 Hz, C-6 H) ppm. The analytical sample was crystallized from benzene and sublimed at 60° (0.1 mm).

Anal. Calcd. for $C_{15}H_{17}NO_2$: N, 5.76. Found: N, 5.96.

Thionyl chloride (36 g., 0.3 mole) was added dropwise to a stirred, cooled solution of **2e** (61 g., 0.25 mole) in benzene (300 ml.) at such a rate that the temperature did not exceed 20°. The mixture was stirred for one hour at room temperature, cooled, and made alkaline with 25% aqueous sodium hydroxide. The benzene layer was separated and the aqueous solution extracted once with benzene. The combined organic extract was dried and concentrated under reduced pressure to a dark red liquid. This was dissolved in glacial acetic acid (300 ml.) and reduced with powdered zinc dust (40 g.) added portionwise with stirring. The mixture was stirred and gently refluxed for 4 hours, cooled and filtered from the inorganic salts. The acetic acid was distilled under reduced pressure and the residue basified with 25% sodium hydroxide solution. The product was extracted in ether (3 x 400 ml.), dried and concentrated to give 52 g. of **3e**. Distillation *in vacuo* afforded 33.5 g. (60%) of pure product (homogenous by glc) as a yellowish oil, b.p. 145-148°/0.2 mm; nmr: 2.08, 2.12 (s, 3, 3, C-3 Me and C-4 Me), 3.63 (s, 3, OMe), 2.47 (s, 2, CH_2), 6.73-7.09 (m, 5, phenyl and C-5 H), 8.24 (d, 1, J = 5 Hz, C-6 H).

Anal. Calcd. for $C_{15}H_{17}NO$: N, 6.16. Found: N, 5.78.

p-Methoxyphenyl-2-pyridylcarbinol (**2b**).

This compound had m.p. 132-133° (12), 95% yield from 2-bromopyridine; nmr: 3.77 (s, 3, OMe), 4.83 (b, 1, CHO*H* exchanged by deuterium oxide), 5.70 (s, 1, C*H*OH), 6.78-7.67 (m, 7, phenyl, C-3, C-4, and C-5 H), 8.58 (m, 1, C-6 H).

2-*p*-Methoxybenzylpyridine (**3b**).

This compound was obtained in 60% yield from **2b**, colorless oil, b.p. 132-134°/0.2 mm. [lit. (6) b.p. 145-147°/2 mm] 45% yield; nmr: 3.60 (s, 3, OMe), 3.93 (s, 2, CH_2), 6.68-7.25 (m, 7, phenyl, C-3, C-4 and C-5 H), 8.33 (m, 1, C-6 H).

Phenyl(3-methyl-2-pyridyl)carbinol (**2c**).

This compound had b.p. 120-123°/0.4 mm [lit. (6) b.p. 134-137°/1 mm] 60% yield; nmr: 2.0 (s, 3, Me), 5.75 (s, 1, C*H*OH), 6.16 (b, 1, CHO*H*) 7.23 (s, 5, phenyl), 7.0-7.4 (m, 2, C-4 H and C-5 H), 8.42 (m, 1, C-6 H).

2-Benzyl-3-methylpyridine (**3c**).

This compound had b.p. 93°/0.2 mm [lit. (6) b.p. 101-106°/0.5 mm] 70% yield from **2c**; nmr (carbon tetrachloride): 2.0 (s, 3, Me), 3.97 (s, 2, CH_2), 6.7-7.2 (m, 7, phenyl, C-4 H and C-5 H), 8.20 (m, 1, C-6 H).

p-Methoxyphenyl(3-methyl-2-pyridyl)carbinol (**2d**).

This compound had b.p. 180°/0.5 mm, m.p. 63-64°, 68% yield from 2-bromo-3-methylpyridine; nmr: 2.02 (s, 3, Me), 3.67 (s, 3, OMe), 5.70 (3, 1, C*H*OH), 5.80 (s, 1, CHO*H*), 6.7-7.4 (m, 6, phenyl, C-4 H and C-5 H), 8.42 (m, 1, C-6 H).

Anal. Calcd. for $C_{14}H_{15}NO_2$: N, 6.11. Found: N, 5.98.

2-*p*-Methoxybenzyl-3-methylpyridine (**3d**).

This compound had b.p. 140-142°/0.3 mm, colorless oil turning yellow on standing, 60% yield from **2d**; nmr: 2.15 (s, 3, Me), 3.62 (s, 3, OMe), 4.08 (s, 2, CH_2), 6.7-7.3 (m, 6, phenyl, C-4 H and C-5 H), 8.38 (m, 1, C-6 H).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.62; H, 7.41; N, 6.37.

p-Methoxyphenyl(4-methyl-2-pyridyl)carbinol (**2f**).

This compound had m.p. 94-95° (from acetone), 71% yield from **1f**; nmr: 2.20 (s, 3, Me), 3.67 (s, 3, OMe), 5.42 (b, 1, CHO*H*), 5.68 (s, 1, C*H*OH), 6.78, 7.28 (4, AA'BB' multiplet, J_{AB} = 9 Hz) 6.84 (m, 1, C-5 H), 7.03 (m, 1, C-4 H), 8.26 (d, 1, C-6 H, $J_{5,6}$ = 5 Hz).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.42; H, 6.76; N, 5.81.

2-*p*-Methoxybenzyl-4-methylpyridine (**3f**).

This compound had b.p. 130°/0.5 mm, 74% yield from **2f**; nmr: 2.18 (s, 3, Me), 3.70 (s, 3, OMe), 4.03 (s, 2, CH_2), 6.79, 7.18 (AA'BB' multiplet, 4, $J_{A,B}$ = 9 Hz, 6.70-7.00 (m, 2, C-3 H and C-5 H), 8.33 (d, 1, C-6 H, $J_{5,6}$ = 6 Hz).

Anal. Calcd. for $C_{14}H_{15}NO$: C; 78.84; H, 7.09; N, 6.57. Found: C, 78.93; H, 7.00; N, 6.65.

p-Methoxyphenyl(5-methyl-2-pyridyl)carbinol (**2g**).

This compound had b.p. 175°/0.7 mm, 60% yield; nmr: 2.21 (s, 3, Me), 3.70 (s, 3, OMe), 5.25 (b, 1, CHO*H*), 5.68 (s, 1, C*H*OH), 6.80-7.30 (m, 6, phenyl, and C-3 H and C-4 H), 8.25 (m, 1, C-6 H).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.30; H, 6.40; N, 5.89.

2-*p*-Methoxybenzyl-5-methylpyridine (**3g**).

This compound had b.p. 140°/0.2 mm, 75% yield from **2g**; nmr: 2.20 (s, 3, Me), 3.68 (s, 3, OMe), 4.03 (s, 2, CH_2), 6.87-7.3 (m, 6, phenyl, C-3 H and C-4 H), 8.30 (m, 1, C-6 H).

Anal. Calcd. for $C_{14}H_{15}NO$: N, 6.57. Found: N, 6.76.

Quaternization of 2-Benzylpyridines.

Methyl iodide (15 ml.) was added portionwise to a stirred solution of the benzylpyridine (0.075 mole) in methanol (100 ml.). The mixture was stirred at room temperature for 1 hour, then refluxed for 2 hours. Evaporation gave the crystalline methiodide in 87-98% yields. The analytical sample was crystallized twice from acetone. The physical constants and elemental analyses are recorded in Table II.

Sodium Borohydride Reduction of the Methiodides.

Sodium borohydride (0.1 mole) was added portionwise in the cold to a stirred solution of the methiodide (0.1 mole) in methanol (200 ml.). The mixture was gently refluxed for 4 hours, cooled, diluted with cold water and extracted in ether. Solvent was removed from the dried extract leaving the crude **5** as an oil which was fractionated *in vacuo*. See Table I.

1-Benzyl-3,4-dimethyl-2-(*p*-methoxybenzyl)pyridinium Chloride (**7**).

Benzyl chloride (1.27 g.) and **3e** (2.28 g.) were heated at 150-160° for 4 hours and cooled. Trituration in ether (to remove any unchanged starting materials) gave a very hygroscopic solid which was dissolved in methanol (20 ml.), treated with *Norite*, filtered and concentrated leaving 3.5 g. of **7**. An analytical sample, m.p. 120°, was obtained by crystallizing the vacuum-dried product twice from absolute methanol, and drying for at least 6 hours at 60-70°/0.2 mm.

Anal. Calcd. for $C_{22}H_{24}ClNO$: N, 3.96. Found: N, 4.09.

1-Benzyl-3,4-dimethyl-2-(*p*-methoxybenzyl)-1,2,5,6-tetrahydropyridine (**8**).

The crude **7** (3.5 g.) was reduced in methanol with sodium borohydride as described above giving 1.8 g. of **8** as an oil. This was converted into its oxalate, m.p. 154-158° (from acetone-methanol) [lit (8) m.p. 153-158°].

Anal. Calcd. for $C_{22}H_{27}NO \cdot C_2H_2O_4$: N, 3.40. Found: N, 3.56.

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