

Chemical Research Department, Hoffmann-La Roche Inc.

Synthesis and Characterization of 6- and 7-Methoxy-1-benzyl-2-methyl-1,2,3,4-tetrahydro-6- and 7-Isoquinolinols

A. Brossi, A. I. Rachlin and S. Teitel

We would like to report the synthesis and physical characterization of 1-benzyl-7-methoxy-2-methyl-1,2,3,4-tetrahydro-6-isoquinolinol (VI), an isomer of the known 6-methoxytetrahydro substituted-7-isoquinolinol (1) (VIII). For the preparation of VI, 2-(3-benzyloxy-4-methoxyphenyl)ethylamine (I) (2) was treated with phenylacetyl chloride to form the amide (II) which was cyclized with phosphorus pentachloride to give the 3,4-dihydroisoquinoline (III), characterized as its hydrochloride. Quaternization of III with methyl iodide afforded the isoquinolinium iodide (IV) which was reduced with sodium borohydride to the *N*-methyltetrahydroisoquinoline (V). Treatment of the latter with concentrated hydrochloric acid at room temperature selectively cleaved (3) the 6-benzyloxy group to give the desired aminophenol (VI). *O*-Methylation of VI afforded the known (4) 6,7-dimethoxy substituted tetrahydroisoquinoline (VII).

By a similar sequence of reactions, but starting from 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (5), we obtained the isomeric 1-benzyl-6-methoxy-2-methyl-1,2,3,4-tetrahydro-7-isoquinolinol (VIII). The physical data were in full agreement with the structure indicated, but con-

siderably different from those previously reported (1). *O*-Methylation of our compound VIII afforded the same dimethoxy derivative (VII) which was obtained from the isomer VI.

EXPERIMENTAL (6)

N-(3-Benzyloxy-4-methoxyphenyl)phenylacetamide (II).

To a vigorously stirred mixture of 53.5 g. (0.18 mole) of 2-(3-benzyloxy-4-methoxyphenyl)ethylamine hydrochloride (I·HCl) (2) in 200 ml. of methylene chloride and 200 ml. of water containing 0.01 g. of phenolphthalein was added 33 g. (0.22 mole) of phenylacetyl chloride dissolved in 100 ml. of methylene chloride over 1 hour. The mixture was maintained at 10-15° and slightly alkaline (pink) by the addition of 10% sodium hydroxide as needed. The mixture was stirred at room temperature for 1 hour and the organic layer was separated, washed, dried and evaporated. The residue was crystallized from a mixture of ethanol-petroleum ether (b.p., 30-60°) to give 60.7 g. (90%) of II, m.p. 115-117°. A specimen prepared from ethanol exhibited m.p. 116-117°; ν max (chloroform): 3415 (NH), 1660 (amide I), 1510 cm^{-1} (amide II).

Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 77.06; H, 6.76; N, 4.02.

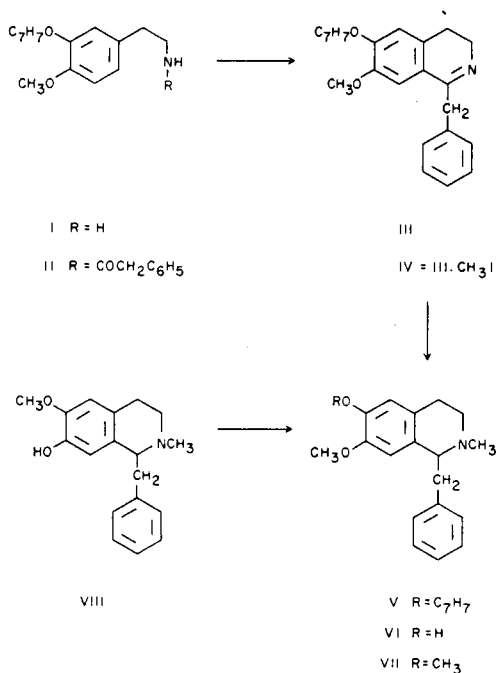
1-Benzyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline Hydrochloride (III·HCl).

To a stirred solution of 58.7 g. (0.155 mole) of II in 600 ml. of chloroform, maintained at 25-30°, was added 61 g. (0.29 mole) of phosphorus pentachloride over 15 minutes. The reaction mixture was stirred at 50-60° for 1 hour, cooled and rendered turbid with petroleum ether. The resulting crystals were filtered and washed with petroleum ether b.p., 30-60° to give 45.7 g. (75%) of III·HCl, m.p. 201-203°. An analytical specimen prepared from ethanol exhibited m.p. 204-205°, ν max (KBr): 2500, 1910 cm^{-1} (immonium salt).

Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_2\cdot\text{HCl}$: C, 73.18; H, 6.14. Found: C, 73.17; H, 6.21.

1-Benzyl-6-benzyloxy-7-methoxy-2-methyl-3,4-dihydroisoquinolinium Iodide (IV).

A solution of 19.7 g. (0.05 mole) of III·HCl in 400 ml. of water was rendered alkaline with ammonium hydroxide and the mixture extracted with three 250 ml. portions of benzene. The benzene extracts were combined, washed, dried, the water was removed by azeotropic distillation, the benzene solution was concentrated to 250 ml. and 24 ml. of methyl iodide was added. The solution was stored overnight at room temperature, the crystals were filtered and washed with benzene to give 21.3 g. (81%) of IV, m.p. 187-189°. An analytical specimen prepared from methanol exhibited m.p. 193-194°; λ max (EtOH): 248, 313, 366 μ (ϵ , 17,000, 10,000, 11,250).



Anal. Calcd for $C_{25}H_{26}INO_2$: C, 60.13; H, 5.25. Found: C, 59.94; H, 5.38.

1-Benzyl-6-benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (V·HCl).

To a stirred solution of 21.3 g. (0.042 mole) of IV in 300 ml. of methanol was added 19.2 g. (0.5 mole) of sodium borohydride over 1 hour. The reaction mixture was stirred at 40° for 2 hours and then evaporated. The residue was suspended in 150 ml. of water and the mixture was extracted with four 400 ml. portions of methylene chloride. The methylene chloride extracts were combined, washed, dried and evaporated. The solid residue was dissolved in 2-propanol, acidified with hydrogen chloride in 2-propanol and evaporated. The residue was crystallized from 2-propanol to give 11.4 g. (69%) of V·HCl; m.p. 188-189°; ν max (KBr): 2350 cm^{-1} (salt bands).

Anal. Calcd for $C_{25}H_{27}NO_2 \cdot HCl$: C, 73.24; H, 6.88; N, 3.42. Found: C, 73.23; H, 7.16; N, 3.74.

1-Benzyl-7-methoxy-2-methyl-1,2,3,4-tetrahydro-6-isoquinolinol Hydrochloride (VI·HCl).

A mixture of 20 g. (0.049 mole) of V·HCl in 80 ml. of concentrated hydrochloric acid and 80 ml. of benzene was stirred vigorously at room temperature under nitrogen for 17 hours and diluted with 50 ml. of water. The resulting crystals were filtered and dried to give 12.4 g. (79%) of VI·HCl, m.p. 243-245°. An analytical sample prepared from methanol exhibited m.p. 245-246°; ν max (KBr): 3230 (OH), 2630, 2560 cm^{-1} (salt bands). nmr (DMSO- d_6): δ 2.62 (doublet, $J = 5$ cps, NCH_3), 3.30 (singlet, OCH_3), 2.60-4.00 (CH_2 groups), 4.50 (broad, CH), 5.72, 6.68 (singlets, aromatic), 7.28 (broad, phenyl).

Anal. Calcd for $C_{18}H_{21}NO_2 \cdot HCl$: C, 67.59; H, 6.94. Found: C, 67.56; H, 6.91.

The base was obtained from an aliquot of VI·HCl which was dissolved in water, rendered alkaline with ammonium hydroxide and extracted with benzene. The benzene extracts were washed, dried and evaporated. The residue was crystallized from methanol to give VI which exhibited m.p. 157-158°; nmr (deuteriochloroform): δ 2.52 (singlet, NCH_3), 3.50 (singlet, OCH_3), 2.50-3.50 (CH_2 groups), 3.74 (multiplet, CH), 5.58 (broad, OH), 5.90, 6.60 (singlets, aromatic), 7.20 (broad, phenyl).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47. Found: C, 76.51; H, 7.60.

1-Benzyl-6-methoxy-2-methyl-1,2,3,4-tetrahydro-7-isoquinolinol (VIII).

A mixture of 5 g. (0.012 mole) of 1-benzyl-7-benzyloxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride, m.p. 238-239° (derived from the corresponding free base) (I) in 15 ml. of concentrated hydrochloric acid and 20 ml. of benzene was stirred vigorously at room temperature under nitrogen for 17 hours, diluted with water and rendered alkaline with ammonium hydroxide. The benzene layer was separated, washed, dried and evaporated. The residue was crystallized from ether to give 3.4 g. (100%) of VIII, m.p. 79-80°. An analytical specimen prepared from ether exhibited m.p. 82-83° (7); ν max (chloroform) (7): 3570 (OH), 2800 cm^{-1} (NCH_3). nmr ($CDCl_3$): δ 2.43 (singlet, NCH_3), 3.78

(singlet, OCH_3), 2.50-3.80 (CH_2 groups and CH), 5.87 (broad, OH), 6.17, 6.35 (singlets, aromatic), 7.18 (sharp, phenyl).

Anal. Calcd for $C_{18}H_{21}NO_2$ (7): C, 76.29; H, 7.47. Found: C, 76.54; H, 7.62.

1-Benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (VII·HBr).

a) Preparation from VI.

A solution of 300 mg. of VI in 25 ml. of methanol containing an excess of diazomethane in ether (8) was stored at 4° for 2 hours and then at room temperature for 17 hours. The volatile matter was evaporated at 35° in a stream of nitrogen. The residue was suspended in 50 ml. of water and the mixture was extracted with three 30 ml. portions of ether. The ether extracts were combined, acidified with ethanolic hydrogen bromide and the mixture was evaporated. The residue was crystallized from a mixture of ethanol and ether to give 200 mg. of VII·HBr, m.p. 202-204° (9).

b) Preparation from VIII.

By the above procedure, 300 mg. of VIII gave 120 mg. of VII·HBr; no mixture melting point depression with VII·HBr obtained from free base of VI.

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- (6) All melting points (corrected) were taken in open capillary tubes with a Thomas-Hoover melting apparatus. Infrared spectra were determined with a Beckman Model IR-5 recording spectrophotometer and ultraviolet spectra were measured with a Cary Model 14 M spectrophotometer. The nmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as an internal standard.
- (7) Reference 1 gives m.p. 130-131°, microanalytical data for the monohydrate, ν max (chloroform): 3650 (H_2O), 3517 (phenolic OH), 2800 cm^{-1} (NCH_3).
- (8) Freshly prepared from 6 g. of nitrosomethylurea according to the procedure of F. Arndt "Organic Synthesis", Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.
- (9) Reference 4: m.p. 205-206°.

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