Synthesis of 7-Methoxy-1,2,3,4-tetrahydro-5-isoquinolinol

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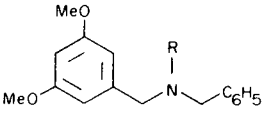
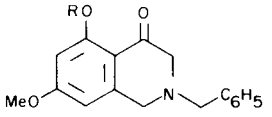
In connection with a study on the preferential *O*-demethylation of dimethoxy-substituted 3,4-dihydroisoquinolines (1), we needed an authentic sample of a 5,7-methoxyhydroxy-substituted tetrahydroisoquinoline. Since compounds with this substitution pattern have not been previously prepared, we chose to synthesize one of the isomers, namely, 7-methoxy-1,2,3,4-tetrahydro-5-isoquinolinol (V). This was accomplished by selective *O*-demethylation of 2,3-dihydro-4(1*H*)isoquinolones (2,3).

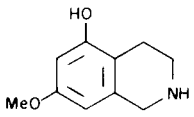
Condensation of 3,5-dimethoxybenzaldehyde and benzylamine followed by reduction with sodium borohydride provided the secondary amine I which was alkylated with ethyl bromoacetate and the resulting glycine ester II cyclized with 80% sulfuric acid to give the dimethoxy-substituted isoquinolone III. Treatment of III with 48% hydrobromic acid under controlled reaction conditions cleaved the methoxyl neighboring the carbonyl to afford the monophenol IV. The C-5 position of the phenolic hydroxyl in IV, predictable from the relative stability of the *p*-methoxyl in related dimethoxy-substituted carbonyl compounds (3,4), was established by ultraviolet spectroscopy. The monophenol IV (pK_a 10.1) showed absorption similar to *o*-hydroxyacetophenone (pK_a 10.3) rather than to *p*-hydroxyacetophenone (pK_a 8.1) and exhibited a principal electron transfer band (5) at 279 mμ which was in agreement with the calculated value for the anion of IV (285 mμ) rather than its isomer (334 mμ). Catalytic hydrogenation of IV under energetic conditions effected simultaneous elimination of the benzylic carbonyl and the *N*-benzyl group to afford the tetrahydroisoquinoline V.



I, R = H
II, R = $-CH_2CO_2Et$



III, R = Me
IV, R = H



V

EXPERIMENTAL (6)

N-Benzyl-3,5-dimethoxybenzylamine (I).

A solution of 10 g. (60 mmoles) of 3,5-dimethoxybenzaldehyde and 6.4 g. (60 mmoles) of benzylamine in 75 ml. of benzene was refluxed for 8 hours. Water (1 ml.) was removed in a Dean-Stark trap. The benzene was evaporated, the residue dissolved in 60 ml. of ethanol and stirred as 2.28 g. (60 mmoles) of sodium borohydride was added over 30 minutes. After stirring for an additional 4 hours, the mixture was evaporated, diluted with 30 ml. of water, heated at 95° for 5 minutes, cooled and extracted with ether. The extract was evaporated and the residual oil distilled to give 11.6 g. (75%) of I, b.p. 149° (0.05 mm.), n_D^{25} 1.5774; λ max (ethanol) 228 mμ (infl.) (ε, 8,500), 275 (2,220), 281 (2,150).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.63; H, 7.18.

N-Benzyl-*N*-(3,5-dimethoxybenzyl)glycine Ethyl Ester (II).

A mixture of 16.5 g. (64 mmoles) of I, 11.1 g. (66 mmoles) of ethyl bromoacetate and 13.4 g. (97 mmoles) of anhydrous potassium carbonate in 200 ml. of ethanol was stirred and refluxed overnight. The mixture was cooled, filtered and the filtrate evaporated. The residue was extracted with ether and the extract evaporated to leave 20.9 g. (95%) of II as a colorless oil. An aliquot was distilled and exhibited b.p. 195° (0.7 mm.), n_D^{20} 1.5374; λ max (ethanol) 228 mμ (infl.) (ε, 8,000), 276 (1,800), 282 (1,800); NMR, δ 1.18 (t, 3, *J* = 7 Hz, CCH_3), 3.23 (s, 2, NCH_2CO), 3.66, 3.72 (s, 4, 2 CH_2Ar), 3.71 (s, 6, 2 OCH_3), 4.07 (q, 2, *J* = 7 Hz, OCH_2), 6.35 (t, 1, *J* meta = 2.5 Hz, C_4-H), 6.51 (d, 2, *J* meta = 2.5 Hz, C_2-H, C_6-H), 7.31 (m, 5, phenyl).

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33. Found: C, 69.80; H, 7.47.

2-Benzyl-2,3-dihydro-5,7-dimethoxy-4(1*H*)-isoquinolone (III).

A solution of 8 g. (23 mmoles) of II in 35 ml. of sulfuric acid (80% by weight) was heated at 100° for 4 hours, cooled and poured onto ice. The mixture was adjusted to *p*H 10 with 50% sodium hydroxide and extracted with three 100 ml. portions of methylene chloride. The extracts were evaporated and the residual oil crystallized from ether to give 5.3 g. (77%) of III, m.p. 95-97°. An analytical specimen prepared from a mixture of ether and petroleum ether exhibited m.p. 95-97°; λ max (ethanol) 228 mμ (ε, 23,070), 274 (18,900), 308 (8,750); NMR, δ 3.12 (s, 2, $COCH_2$), 3.65, 3.70 (s, 4, CH_2NCH_2), 3.79, 3.81 (s, 6, 2 OCH_3), 6.48 (s, 2, C_6-H, C_8-H), 7.33 (s, 5, phenyl).

Anal. calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44. Found: C, 72.55; H, 6.63.

2-Benzyl-2,3-dihydro-5-hydroxy-7-methoxy-4(1*H*)-isoquinolone (IV).

A solution of 4.3 g. (14.5 mmoles) of III in 45 ml. of 48%

hydrobromic acid was stirred and refluxed for 2 hours, cooled and 20 ml. of water added. The resulting precipitate was collected, suspended in water, adjusted to *p*H 10 with 5% sodium hydroxide and extracted with benzene. The extract was evaporated to leave a crystalline residue of 2.9 g. (71%) of IV, m.p. 102-104°. An analytical specimen prepared from a mixture of ether and petroleum ether exhibited m.p. 102-104°; λ max (ethanol) 227 mμ (infl.) (ε, 12,000), 279 (15,900), 315 (6,280); λ max (in ethanol saturated with sodium acetate) 228 mμ (ε, 12,250), 280 (15,920), 315 (6,240); λ max (in 0.002 *M* sodium ethoxide) 245 mμ (ε, 16,550), 279 (12,600), 355 (7,900); NMR δ 3.36 (s, 2, $COCH_2$), 3.71 (s, 4, CH_2NCH_2), 3.81 (s, 1, OCH_3), 6.39 (s, 2, C_6-H, C_8-H), 7.33 (m, 5, phenyl), 12.00 (s, 1, OH).

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05. Found: C, 72.35; H, 6.07.

7-Methoxy-1,2,3,4-tetrahydro-5-isoquinolinol (V).

A mixture of 800 mg. (2.8 mmoles) of IV and 1 ml. of 20% ethanolic hydrogen chloride in 100 ml. of acetic acid was hydrogenated in the presence of 500 mg. of 10% palladium on carbon at 33 atmospheres and 120° for 2 hours. The catalyst was filtered and the colorless filtrate evaporated under reduced pressure. The residue was dissolved in water, rendered alkaline with ammonium hydroxide and the resulting precipitate collected to give 310 mg. (61%) of V, m.p. 237-239°. An analytical specimen prepared from a mixture of methanol and ether exhibited m.p. 238-240°; λ max (ethanol) 225 mμ (infl.) (ε, 10,800), 280 (infl.) (2,100), 286 (2,150); 97.5% pure by GLC (180 cm. x 2 mm. ID glass column, 10% OV-17 on Gaschrom Q 100-200 mesh, 200°, 28 ml. of nitrogen/minute gave a retention time of 15 minutes).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 67.25; H, 7.38.

The hydrobromide of V exhibited m.p. 253-255° (from methanol-ether); λ max (ethanol) 227 mμ (infl.) (ε, 9,200), 280 (infl.) (2,500), 286 (2,580); NMR δ 2.82, 3.45 (t, 4, J = 6 Hz, CH_2CH_2), 3.67 (s, 3, OCH_3), 4.16 (s, 2, CH_2N), 6.26, 6.36 (AB, 2, J meta = 2Hz, C_6-H, C_8-H), 9.03 (s, 2, $\overset{+}{N}H_2$), 9.65 (s, 1, OH).

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot HBr$: C, 46.17; H, 5.42. Found: C, 46.21; H, 5.68.

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(6) All melting points (corrected) were taken in open capillary tubes with a Thomas-Hoover melting apparatus. Ultraviolet spectra were determined with a Cary Model 14 spectrophotomer and the apparent pK_a's estimated from spectral data at various *p*H's. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 or HA-100 spectrometer using tetramethylsilane as internal standard and DMSO-d_6 as solvent. Gas liquid chromatography was done on a Barber-Colman Model 5000 instrument. All organic extracts were washed with water and dried over anhydrous sodium sulfate prior to evaporation.

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