

Monophenolic 1,2,3,4-Tetrahydroisoquinolines and Their Methyl Ethers

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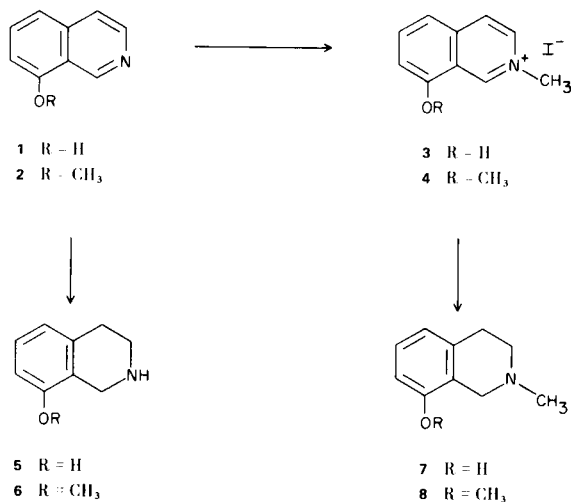
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In connection with our studies in the field of cactus alkaloids (1) we have accumulated considerable spectral data on the monophenolic tetrahydroisoquinolines and their *O*- and *N*-methyl derivatives. These spectra, particularly the nmr data which we have compiled in Table I can provide valuable information pertinent to the structural elucidation of the isoquinoline alkaloids.

The 5- and 8-substituted derivatives can be distinguished from their 6- and 7-substituted isomers by the multiplicity of the signals of the aromatic protons. The 5- and 8-oxygenated compounds show a triplet ($J_0 = 7-8$ Hz) and two doublets ($J_0 = 7-8$ Hz) whereas the 6- and 7-oxygenated derivatives give rise to a doublet of doublets ($J_0 = 8-9$ and $J_m = 2.5$ Hz) and two doublets ($J_0 = 8$ and $J_m = 2.5$ Hz). The aromatic substitution patterns are further distinguished by the magnitude of the difference between the chemical shifts of the methylene groups at positions 1 and 4. The observed differences in the chemical shifts with the 5- (or 7) substituted isomers are substantially larger than those observed with their 8 (or 6) isomers. It is evident from these results that a detailed nmr analysis is a good method for determining the position of a substituent in the aromatic moiety of a tetrahydroisoquinoline.

The various tetrahydroisoquinolines were prepared as described in the literature or by new syntheses which followed well-established routes (2). The relatively rare 8-substituted tetrahydroisoquinolines were synthesized as below.



EXPERIMENTAL (3)

8-Hydroxy-2-methylisoquinolinium Iodide (3).

A solution of 3.63 g. (25 mmoles) of 8-isoquinolinol (1) (4,5,6) and 4 ml. (64 mmoles) of methyl iodide in 50 ml. of ethanol was stirred at reflux temperature for 8 hours, cooled and filtered to give 5.6 g. of yellow crystals, m.p. 221-224°. An additional 0.8 g. of product (m.p. 218-222°) was obtained from the mother liquors. This increased the total yield of **3** to 6.3 g. (89%). The m.p. of the analytical sample after recrystallization from ethanol-ethyl acetate was 220-221° [Lit. (7): m.p. 217-219°]; λ max in 2-propanol $m\mu$ (ϵ): 250 (30,500), 314 (2,000), 381 (5,300); ν max (potassium bromide): 3540, 3440, 1647 cm^{-1} .

Anal. Calcd. for C₁₀H₁₀INO: C, 41.83; H, 3.51; N, 4.88. Found: C, 41.59; H, 3.71; N, 4.69.

8-Methoxy-2-methylisoquinolinium Iodide (4).

A solution of 2.0 g. (13.8 mmoles) of **1**, (4,5,6), 754.6 mg. (13.8 mmoles) of sodium methoxide, and 3.5 ml. of freshly distilled methyl iodide in 50 ml. of ethanol was treated and worked up as in the preceding experiment to give 2.97 g. (71%) of **4**, m.p. 231-232°, λ max in 2-propanol $m\mu$ (ϵ): 249 (27,700), 280 (2,100), 309 (1,650), 341 (5,900).

Anal. Calcd. for C₁₁H₁₂INO: C, 43.87; H, 4.02; N, 4.65. Found: C, 43.58; H, 3.80; N, 4.65.

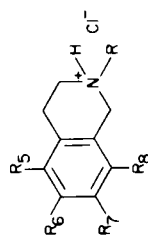
2-Methyl-1,2,3,4-tetrahydro-8-isoquinolinol (7).

To a stirred solution of 11.8 g. (41.1 mmoles) of **3** in 100 ml. of warm water was added 6 g. (158 mmoles) of sodium borohydride. The reaction mixture was allowed to stand overnight at room temperature and was filtered to give 5.9 g. of free base **7**. An additional 0.53 g. of free base was obtained by saturating the mother liquors with ammonium chloride and extracting three times with 400 ml. portions of methylene chloride. Reaction of the free base (6.43 g.) with ethanolic hydrogen chloride afforded 7.1 g. (87%) of **7**-hydrochloride, m.p. 241.5-243°. A sample from another experiment was recrystallized from ethanol to give white crystals, m.p. 243-244°, which were submitted for analysis, λ max in 2-propanol $m\mu$ (ϵ): 218 (6,390), 275 (2,110), 280 s (2,050); λ max in 0.1 N potassium hydroxide $m\mu$ (ϵ): 242 (8,780), 288 (3,300); ν max (potassium bromide): 3,180, 2700-2400 cm^{-1} .

Anal. Calcd. for C₁₀H₁₃NO·HCl: C, 60.15; H, 7.07; N, 7.02. Found: C, 60.16; H, 7.37; N, 6.87.

A solution of 1.07 g. (5.36 mmoles) of **7**-hydrochloride in water was adjusted to pH 9 with solid sodium carbonate and extracted with methylene chloride. After work-up the residue was sublimed and crystallized from acetone-pentane to give 598 mg. (68%) of **7**, m.p. 174-175°, *in vacuo*. A portion of this material (106 mg.) was sublimed to give 105 mg. of pure **7**, m.p. 175.5-176° [Lit. (6): m.p. 177-178°], *in vacuo*, which was submitted to analysis; λ max in 2-propanol $m\mu$ (ϵ): 274 (1,830), 280 (1,800);

TABLE I
Nmr Spectral Data



No.	Ref.	Compound				M.p. °C	Chemical Shifts (δ) and Coupling Constants (Hz)										NCH ₃
		R ₅	R ₆	R ₇	R ₈		R	CH ₂ -1	CH ₂ -3	CH ₂ -4	CH-5	CH-6	CH-7	CH-8	OH	NH	
9	(a)	OH	H	H	H	275-277	4.11, s	3.27, t	2.79, t	H	6.59, d J _o = 7	7.00, t	6.80, d J _o = 7.5	9.71, b	9.71, b		
10	(b)	H	OH	H	H	190.5	4.06, s	3.24, t	2.89, t	H	6.60, bs	6.64, dd J _m = 2.5	6.97, d J _o = 8	9.48, s	9.67, b		
11	(g)	H	H	OH	H	254-255	4.10, s	3.25, t	2.87, t	H	6.68, dd J _m = 2.5	6.72, d J _o = 7	6.60, bs	9.61, b	9.61, b		
5		H	H	H	OH	271-272	4.00, s	3.27, m	2.94, m	H	6.78, d J _o = 7.5	6.72, d J _o = 7	9.96, b	9.96, b	9.72, b		
12	(a)	OH	H	H	CH ₃	183-185	4.25, s	3.39, m	2.87, m	CH ₃	6.56, d J _o = 7	7.03, t	6.81, d J _o = 7.5	9.80, b	11.35, b		2.81, s
13	(c)	H	OH	H	H	177-178	4.18, s	3.37, t	2.81, t	CH ₃	6.63, bs	6.68, dd J _m = 2.5	6.94, d J _o = 8	9.59, s	11.33, b		2.80, s
14	(h,j)	H	H	OH	H	250-254	4.21, s	3.37, m	2.95, m	CH ₃	6.70, dd	6.63, d J _o = 7	6.55, d	9.51, s	11.34, b		2.81, s
7		H	H	H	OH	243-244	4.11, s	3.37, m	3.08, m	CH ₃	6.79, d J _o = 7.5	6.63, d J _o = 7	10.05, s	10.05, s	11.33, b		2.86, s
15	(a)	OCH ₃	H	H	H	233-234	4.14, s	3.25, t	2.81, t	H	6.76, d J _o = 8	7.18, t	6.84, d J _o = 8	9.86, b	9.86, b		3.76, s
16	(d)	H	OCH ₃	H	H	238-239	4.09, s	3.24, t	2.96, t	H	6.73, bs	6.77, dd J _m = 2.5	7.09, d J _o = 9	9.84, b	9.84, b		3.70, s
17	(f)	H	H	OCH ₃	H	231-232	4.13, s	3.24, t	2.90, t	H	6.78, dd J _m = 2.5	6.77, d J _o = 8	6.77, d	9.84, b	9.84, b		3.69, s
6		H	H	H	OCH ₃	261-262	4.00, s	3.24, t	2.96, t	H	6.84, d J _o = 8	6.77, d J _o = 8	9.85, b	9.85, b		3.78, s	
18	(a)	OCH ₃	H	H	CH ₃	222	4.26, s	3.38, m	2.90, m	CH ₃	6.71, d J _o = 8	7.20, t	6.85, d J _o = 8	11.75, b	11.75, b		3.76, s
19	(e)	H	OCH ₃	H	CH ₃	165-168	4.12, b	3.40, b	3.05, b	CH ₃	6.80, dd J _m = 2.5	6.80, dd J _m = 2.5	7.07, d J _o = 9	11.71, b	11.71, b		3.72, s

20	(f,h)	H	H	OCH ₃	H	CH ₃	208-210	4.27, s	3.39, m	3.02, m	7.12, d J _o = 9	6.83, dd J _m = 2.5	6.73, d	11.80, b	3.71, s	2.82, s
8		H	H	H	OCH ₃	CH ₃	215-216	4.13, s	3.36, m	3.09, m	6.86, d J _o = 8	7.23, t J _o = 8	6.80, d	11.77, b	3.79, s	2.85, s
21	(i)	H	H	H	H	H	197-198	4.18, s	3.27, t	3.00, t	7.20, s	7.20, s	7.20, s	9.85, b		
22	(j)	H	H	H	CH ₃	CH ₃	221-222	4.31, s	3.41, m	3.12, m	7.20, s	7.20, s	7.20, s	11.90, b		2.83, s
23	(i)		Tetralin				liquid	CH ₂ -1,4: CH ₂ -2,3:	2.67, m 1.70, m		7.00, s	7.00, s	7.00, s			

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λ max in 0.1 *N* potassium hydroxide $m\mu$ (ϵ): 241 (8,690), 388 (3,350).

Anal. Calcd. for C₁₀H₁₃NO: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.72; H, 7.96; N, 8.40.

8-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**8**-hydrochloride).

A solution containing 2 g. (6.64 mmoles) of **4** in ethanol was hydrogenated over platinum oxide at room temperature and at 50 psi pressure. The catalyst was removed by filtration, and the filtrate was evaporated to dryness to give 1.88 g. of crude hydroiodide salt. This material was dissolved in 25 ml. of 1 *N* sodium hydroxide and the solution was extracted three times with 75 ml. portions of methylene chloride. The organic layers were washed twice with 25 ml. portions of water, dried with sodium sulfate, and evaporated under reduced pressure to give 1.09 g. of crude oil. An ethanolic solution of this material was treated with hydrogen chloride in ethanol, and then evaporated to dryness. The residue was crystallized from ethanol-ether to give 1.13 g. (80%) of **8**-hydrochloride, m.p. 215-216°, *in vacuo*; λ max in 2-propanol $m\mu$ (ϵ): 218 (7,050), 271 (1,720), 278 (1,790).

Anal. Calcd. for C₁₁H₁₅NO·HCl: C, 61.82; H, 7.55; N, 6.56. Found: C, 61.56; H, 7.53; N, 6.42.

1,2,3,4-Tetrahydro-8-isoquinolinol (**5**).

A solution of 18 g. (0.1 mole) of the hydrochloride of 8-isoquinolinol (**1**) (4,5,6) in 1.2 liters of ethanol was hydrogenated with platinum oxide catalyst at room temperature and 50 psi initial pressure. The catalyst was removed by filtration and the solution evaporated to dryness. Recrystallization of the residue from 1 *N* hydrochloric acid-concentrated hydrochloric acid (2:1) yielded 15 g. (81%) of **5**-hydrochloride, m.p. 271-272°, dec. *in vacuo*; λ max in 2-propanol $m\mu$ (ϵ): 216 (6,970), 275 (2,390), 281 (2,320); λ max in 0.1 *N* potassium hydroxide $m\mu$ (ϵ): 242 (9,060), 288 (3,350).

Anal. Calcd. for C₉H₁₁NO·HCl: C, 58.22; H, 6.52; N, 7.54. Found: C, 58.07; H, 6.38; N, 7.52.

The free base **5** was obtained by treatment of a methanolic solution of **5**-hydrochloride with one equivalent of sodium methoxide. The solution was evaporated to dryness and the residue extracted three times with 50 ml. of methylene chloride. Evaporation of the organic extracts gave a yellowish solid which was sublimed twice in high vacuum at 140° to give white crystals of **5**, m.p. 181-181.5°, *in vacuo*; λ max in 2-propanol $m\mu$ (ϵ): 220 (sh) (7,500), 274 (1,810), 281 (1,800).

Anal. Calcd. for C₉H₁₁NO: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.23; H, 7.73; N, 9.44.

8-Methoxyisoquinoline (**2**).

To a solution of 29 g. (0.2 mole) of 8-isoquinolinol (**1**) (4,5,6) and 11.35 g. (0.21 mole) of sodium methylate in 175 ml. of methanol, 36.1 g. (0.21 mole) of phenyltrimethylammonium chloride were added, and the mixture was stirred for 1 hour, filtered from the precipitated salt, and then evaporated under reduced pressure. The dark oily residue was dissolved in 150 ml. of DMF and the solution was heated at reflux for two hours, cooled, and then evaporated. The residue was dissolved in 250 ml. of methylene chloride and the solution was extracted three times with 60 ml. portions of 1 *N* sodium hydroxide. The aqueous layers were extracted twice with 250 ml. portions of methylene chloride. The organic layers were then washed three times with 50 ml. portions of water, dried with sodium sulfate, treated with charcoal, and evaporated to dryness to give 43.2 g. of dark oil. Dimethylaniline (16 g., 66% of theory) was removed

from this material by distillation at 58-89°/17-18 mm, and the distillation residue (26.1 g. of dark oil) was filtered through a column of 10 g. of alumina "Woelm" activity II (20 mm long x 30 mm wide). The column was eluted with three 125 ml. portions of ether, and after evaporation of the eluate 25.8 g. (81%) of light brown liquid was obtained. Crystallization from ether-pentane gave 20.6 g. (65%) of pure **2**, m.p. 48-51°. From the mother liquor an additional 1.2 g. (4%) of **2**, m.p. 50-51.5°, was obtained. For analysis a sample of a previous run was recrystallized from ether-pentane, m.p. 50.5-51.5°; λ max in 2-propanol $m\mu$ (ϵ): 233 (20,200), 261 (sh) (1,850), 285 (sh) (3,100), 298 (3,400), 326 (5,300); λ max in 0.1 N hydrochloride $m\mu$ (ϵ): 243 (23,100), 279 (sh) (1,000), 306 (1,550), 368 (5,900).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.54; H, 5.58; N, 8.79.

The hydrochloride of **2** was prepared as follows. A solution of **2** in methanol was acidified with ethanolic hydrogen chloride and evaporated to dryness. The residue was crystallized from methylene chloride-ether to give pure **2**-hydrochloride, m.p. 170-170.5°, dec.

Anal. Calcd. for $C_{10}H_9NO \cdot HCl$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.02; H, 5.03; N, 7.09.

8-Methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**6**-hydrochloride).

A solution of 26.8 g. (0.137 mole) of **2**-hydrochloride was hydrogenated and worked up as described for compound **5** to give 22.9 g. (84%) of **6**-hydrochloride, m.p. 261-262.5°, after recrystallization from methanol-ether; λ max in 2-propanol $m\mu$ (ϵ): 218 (7,490), 272 (1,750), 278 (1,840).

Anal. Calcd. for $C_{10}H_{13}NO \cdot HCl$: C, 60.15; H, 7.07; N, 7.02. Found: C, 60.20; H, 6.97; N, 7.00.

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