Preferential Cleavage of Trimethoxy-substituted 1,2,3,4-Tetrahydroisoquinoline Alkaloids†

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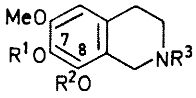
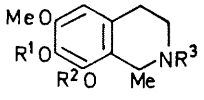
Summary Controlled *O*-demethylation of vicinal trimethoxy-substituted 1,2,3,4-tetrahydroisoquinolines with 20% hydrochloric acid cleaves certain substrates to afford a diphenol, together with the expected monophenol.

THE preferential cleavage of the middle of three neighbouring aromatic methoxy-groups by mineral acid has been explained by steric interactions[1] and has recently been applied in the ready synthesis of phenethylamines,[2] 3,4-dihydroisoquinolines,[3] homoberbines,[4] and homoapomorphines.[5] We have extended these studies to the 6,7,8-trimethoxy-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids anhalinine[6] (**1**), (±)-*O*-methylanhalonidine[7] (**7**), and the corresponding tertiary amines *O*-methylanhalidine[8] (**5**) and (±)-*O*-methylpellotine[6] (**11**). The 5,6,7-trimethoxy-substituted 1,2,3,4-tetrahydroisoquinoline (±)-thalifendlerine[9] (**13**) has also been included.

The progress of the selective *O*-demethylation of the substrate in 10—15 volumes of 20% HCl was followed by t.l.c. and the reaction temperature and time optimized (reflux for 2 to 3 h) to favour the formation of a minimum of products. The reaction mixtures were separated into their components by selective extraction and the isomeric monophenols, when formed, were separated by fractional crystallization.



(1)–(6)



(7)–(10)

	R^1	R^2	R^3
(**1**), (**7**)	Me	Me	H
(**2**), (**8**)	H	Me	H
(**3**), (**9**)	Me	H	H
(**4**), (**10**)	H	H	H
(**5**), (**11**)	Me	Me	Me
(**6**), (**12**)	H	Me	Me

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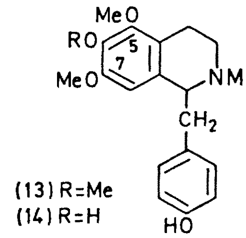
† Presented in part by one of us (A.B.) at the 13th Symposium on the Chemistry of Natural Products, Sapporo, Japan, September 25—27, 1969, Symposium Papers, pp. 177—186.

Treatment of (**1**), HCl[6] afforded 4% of the 7,8-diphenolic tetrahydroisoquinoline (**4**), HCl‡: m.p. 275—277°; n.m.r. $[(CD_3)_2SO]$ δ 2·88, 3·25 (m, 4H, CH_2CH_2), 3·77 (s, 3H, CH_3O), 4·00 (s, 2H, CH_2), 6·32 (s, 1H, aromatic), 8·53, 8·88 (br, 2H, 2 O*H*), 9·50 (br, 2H, N*H*·HCl); u.v. λ_{max} (EtOH) 206 nm (38,500), 271(905), infl 227(7000), infl 280(720), 21% of the 7-monophenol [(**2**), HCl],[10] 4% of the 8-monophenol anhalamine hydrochloride[11] [(**3**), HCl], and 60% of starting material. Similarly, (**7**), HCl[7] yielded 6% of the 7,8-diphenol (**10**), HCl‡: m.p. 263—265°, n.m.r. $[(CD_3)_2SO]$ δ 1·53 (d, 3H, *J* 7Hz CH_3), 2·70—3·50 (CH_2CH_2), 3·74 (s, 3H, CH_3O), 4·47 (q, 1H, *J* 7Hz, C*H*), 6·31 (s, 1H, aromatic), 8·90 (br, 4H, 2 O*H* + N*H*,HCl); u.v. λ_{max} (EtOH) 207 nm (43,540), 272(850), infl 230(7530), infl 281(640), 20% of the 7-monophenol (**8**),[3] 5% of the 8-monophenol (±)-anhalonidine[11] (**9**), and 48% of unchanged (**7**).

The formation of mixtures of phenolic products could not be avoided. The diphenols (**4**) and (**10**) were also obtained by further hydrolysis of their monophenolic pairs (**2**), (**3**) and (**8**), (**9**), respectively. This finding has been utilized for a ready synthesis of the rare 7,8-methylenedioxy-substituted alkaloids (−)-anhalonine and (−)-lophophorine.§

In contrast, the corresponding tertiary amines (**5**)[8] and (**11**)[6] and the 5,6,7-trimethoxy-substituted tetrahydroisoquinoline (**13**), HCl[9] under similar conditions were *O*-demethylated at the middle methoxy-group to afford (**6**), HCl¶ (81%), (**12**), HCl[3] (72%), and the 6-demethyltetrahydroisoquinoline (**14**), HCl[12] (38%), respectively.



(13) R=Me
(14) R=H

We thank Professor S. M. Kupchan, University of Virginia, for providing us with an authentic sample of (**14**), and Messrs. J. O'Brien and J. Van Burik for technical assistance.

(*Received, August 3rd*, 1970; *Com.* 1275.)

‡ Correct analyses for carbon, hydrogen, and nitrogen were obtained.

§ Forthcoming publication.

¶ M.p. 216—217°; identical with an authentic sample obtained by reductive condensation of (**2**) and formaldehyde in the presence of Raney nickel.

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