

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

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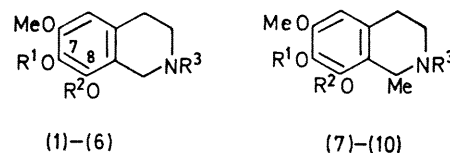
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**Summary** Controlled *O*-demethylation of vicinal trimethoxy-substituted 1,2,3,4-tetrahydroisoquinolines with 20% hydrochloric acid cleaves certain substrates to afford a diphenol, together with the expected monophenol.

(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

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



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
(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

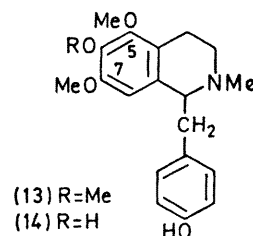
monophenols, when formed, were separated by fractional crystallization.

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Treatment of (1),  $\text{HCl}^6$  afforded 4% of the 7,8-diphenolic tetrahydroisoquinoline (4),  $\text{HCl}^\dagger$ : m.p. 275—277°; n.m.r.  $[(\text{CD}_3)_2\text{SO}]$   $\delta$  2.88, 3.25 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 3.77 (s, 3H,  $\text{CH}_3\text{O}$ ), 4.00 (s, 2H,  $\text{CH}_2$ ), 6.32 (s, 1H, aromatic), 8.53, 8.88 (br, 2H, 2 OH), 9.50 (br, 2H,  $\text{NH}\cdot\text{HCl}$ ); u.v.  $\lambda_{\text{max}}$  (EtOH) 206 nm (38,500), 271(905), inf 227(7000), inf 280(720), 21% of the 7-monophenol [(2),  $\text{HCl}$ ],<sup>10</sup> 4% of the 8-monophenol anhalamine hydrochloride<sup>11</sup> [(3),  $\text{HCl}$ ], and 60% of starting material. Similarly, (7),  $\text{HCl}^7$  yielded 6% of the 7,8-diphenol (10),  $\text{HCl}^\dagger$ : m.p. 263—265°, n.m.r.  $[(\text{CD}_3)_2\text{SO}]$   $\delta$  1.53 (d, 3H,  $J$  7Hz  $\text{CH}_3$ ), 2.70—3.50 ( $\text{CH}_2\text{CH}_2$ ), 3.74 (s, 3H,  $\text{CH}_3\text{O}$ ), 4.47 (q, 1H,  $J$  7Hz, CH), 6.31 (s, 1H, aromatic), 8.90 (br, 4H, 2 OH +  $\text{NH}\cdot\text{HCl}$ ); u.v.  $\lambda_{\text{max}}$  (EtOH) 207 nm (43,540), 272(850), inf 230(7530), inf 281(640), 20% of the 7-monophenol (8),<sup>3</sup> 5% of the 8-monophenol ( $\pm$ )-anhalonidine<sup>11</sup> (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-methylene-dioxy-substituted alkaloids (—)-anhalonine and (—)-lophophorine.§

In contrast, the corresponding tertiary amines (5)<sup>8</sup> and (11)<sup>6</sup> and the 5,6,7-trimethoxy-substituted tetrahydroisoquinoline (13),  $\text{HCl}^9$  under similar conditions were *O*-demethylated at the middle methoxy-group to afford (6),  $\text{HCl}^\ddagger$  (81%), (12),  $\text{HCl}^3$  (72%), and the 6-demethyltetrahydroisoquinoline (14),  $\text{HCl}^{12}$  (38%), respectively.



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† 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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