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THE STRUCTURE AND TOTAL SYNTHESIS OF TAKATONINE

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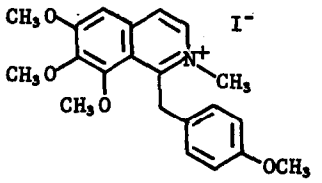
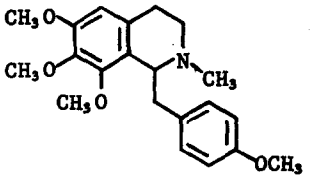
Takatonine is a quaternary alkaloid isolated from Thalictrum minus in the form of its iodide salt. The structure of the alkaloid was tentatively postulated as 1-(4'-methoxybenzyl)-2-methyl-6,7,8-trimethoxyisoquinoline iodide (I) (1).

In the course of an investigation of the structure of the cytotoxic alkaloid, cissampareine (2,3), it was found that the thin layer chromatographic behavior and infrared and N.M.R. spectra of tetrahydrotakatonine differed from those of 1-(4'-methoxybenzyl)-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (II) (4). This observation and the conversion of tetrahydrotakatonine to 3,4,5-trimethoxyphthalic anhydride (1) led to the postulation that takatonine iodide should be assigned structure III, and tetrahydrotakatonine, structure IV. Confirmation of the latter assignments by total synthesis of takatonine iodide and tetrahydrotakatonine by an unequivocal route is reported herewith. Takatonine and thalifendlerine (5) appear to be the first benzylisoquinoline alkaloids recognized to contain a substituent at C-5.

Condensation of 2,3,4-trimethoxybenzaldehyde (V) (6) with nitromethane gave 2,3,4-trimethoxy-β-nitrostyrene (VI), $C_{11}H_{13}O_5N$ (Found: C, 55.18; H, 5.47; N, 6.09), m.p. 77-78°. Reduction of β-nitrostyrene V with lithium aluminum hydride gave 2,3,4-tri-



(I)



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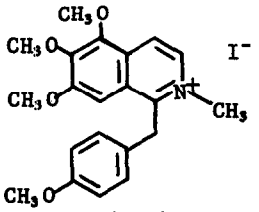

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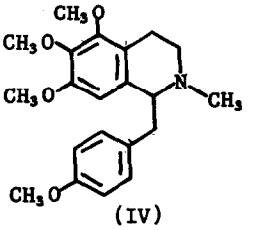
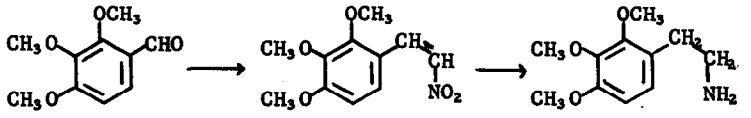


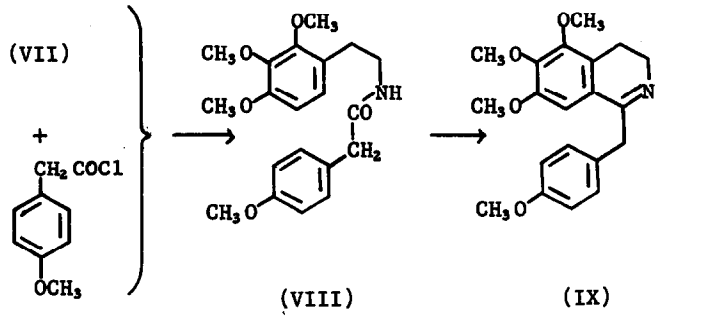
(IV)

methoxyphenethylamine (VII), analyzed as picrate, $C_{17}H_{20}O_{10}N_4$ (Found: C, 46.49; H, 4.80; N, 12.19), m.p. 139-140°. The reaction of amine VII with 4-methoxyphenylacetyl chloride afforded N-(2,3,4-trimethoxyphenethyl)-4'-methoxyphenyl acetamide (VIII), $C_{20}H_{25}O_5N$ (Found: C, 67.21; H, 7.20; N, 4.19), m.p. 77-78°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655, 3420 (-CO-NH-). Cyclization of VIII by phosphorus oxychloride gave 1-(4'-methoxybenzyl)-5,6,7-trimethoxy-3,4-dihydroisoquinoline (IX); as hydrochloride, m.p. 146.5-149.5°, λ_{max}^{MeOH} mμ (log ε): 272 (3.96), 315 (3.43), and picrate, $C_{26}H_{26}O_{11}N_4$ (Found: C, 54.74; H, 4.44; N, 9.70), m.p. 170-172°. Reduction of the dihydroisoquinoline IX with sodium borohydride in methanol afforded 1-(4'-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (X); hydrochloride, $C_{20}H_{26}O_4NCl$ (Found: C, 63.08; H, 7.37; N, 3.32), m.p. 181-185°, λ_{max}^{MeOH} mμ (log ε): 278 (3.54), 284 (3.51); picrate, $C_{26}H_{29}O_{11}N_4$ (Found: C, 54.72; H, 4.95; N, 9.68), m.p. 180.5-182.5°.

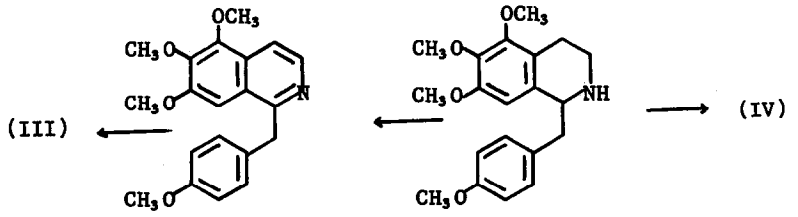
1-(4'-Methoxybenzyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV) was obtained from the tetrahydroisoquinoline X by N-methylation with 38% formalin and sodium borohydride reduction; hydrochloride, $C_{21}H_{28}O_4NCl$ (Found: C, 64.08; H, 7.26; N, 3.56), m.p. 188-192°, λ_{max}^{MeOH} 281 mμ (log ε



(V) (VI) (VII)



(VII) (VIII) (IX)



(III) (XI) (X) (IV)

3.51); picrate, $C_{27}H_{30}O_4N_{11}$ (Found: C, 55.51; H, 5.38; N, 9.42), m.p. 143-145°; free base IV, N.M.R. $^{CDCl_3}\tau$: 6.15 (6H, $OC\underline{H}_3$), 6.22 (3H, $OC\underline{H}_3$), 6.43 (3H, $OC\underline{H}_3$), 7.48 (3H, $NC\underline{H}_3$). Comparison of I.R. spectra, N.M.R. spectra and Rf values upon thin layer chromatography on alumina showed tetrahydrotakatonine to be identical with the synthetic 1,2,3,4-tetrahydroisoquinoline IV. The identity was also confirmed by I.R. spectral comparison and mixed melting point determinations of the hydrochlorides and picrates.

The tetrahydroisoquinoline X was dehydrogenated to 1-(4'-methoxybenzyl)-5,6,7-trimethoxyisoquinoline (XI) by treating with palladium in decalin at 180-240° under nitrogen; hydrochloride, $C_{20}H_{23}O_4NCl\cdot H_2O$ (Found: C, 60.26; H, 6.39; N, 3.33), m.p. 100-105°, λ_{max}^{MeOH} mμ (log ε): 241.5 (4.67), 278 (3.70), 325-329 (3.52), 337 (3.60). The isoquinoline XI was refluxed with methyl iodide under nitrogen to give yellow crystals of the methiodide III, $C_{21}H_{24}O_4NI$ (Found: C, 52.41; H, 5.26; N, 2.77), m.p. 181-182°, λ_{max}^{MeOH} mμ (log ε); 265 (4.61), 318 (3.69), N.M.R. $^{CDCl_3}\tau$: 6.24 (3H, $OC\underline{H}_3$), 5.97 (3H, $OC\underline{H}_3$), 5.91 (3H, $OC\underline{H}_3$), 5.87 (3H, $OC\underline{H}_3$), 5.38 (3H, $\overset{+}{N}C\underline{H}_3$). The melting point was not depressed on admixture with an authentic sample of takatonine iodide. The I.R., U.V., and N.M.R. spectra were identical with those of the authentic sample of takatonine iodide.

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