The Structure of Capaurimine

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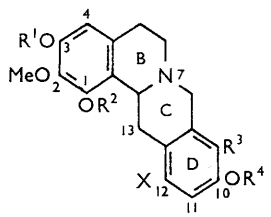
5,6,13,13a-Tetrahydro-1,9-dihydroxy-2,3,10-trimethoxy-8*H*-dibenzo[*a*, *g*]quinolizine (I), formerly thought to be capaurimine, has been synthesized, but was not identical with natural capaurimine. The 3,9-dihydroxy-1,2,10-trimethoxy-isomer (II) was also synthesized but was not identical with natural capaurimine. The previous assignment of the position of the substituents in capaurimine is therefore incorrect.

CAPAURIMINE, $C_{20}H_{23}NO_5$, has been found only in *Corydalis montana* [1] and *C. pallida*.[2] It crystallises from chloroform–methanol in stout prisms, m.p. 212°, $[\alpha]_D^{24}$ −287° (in chloroform). It has two phenolic hydroxys and three methoxys and on methylation with diazomethane yields di-*O*-methylcapaurimine which is identical with methylcapaurine (III). On ethylation with diazoethane it yielded a di-*O*-ethyl ether which on complete oxidation with potassium permanganate gave a mixture of 3-ethoxy-4,5-dimethoxy- and 3-ethoxy-4-methoxyphthalic acid; both specimens were identified as their *N*-methylimides. Therefore, capaurimine was assigned as (I).[3] To confirm this assignment, we have synthesized



(I) $R^1 = R^4 = Me$, $R^2 = X = H$, $R^3 = OH$
(II) $R^1 = X = H$, $R^2 = R^4 = Me$, $R^3 = OH$
(III) $R^1 = R^2 = R^4 = Me$, $R^3 = OMe$, $X = H$
(XII) $R^1 = R^4 = Me$, $R^2 = H$, $R^3 = OH$, $X = Br$
(XIII) $R^1 = H$, $R^2 = R^4 = Me$, $R^3 = OH$, $X = Br$

compound (I) by application of earlier methods,[4,5] but have found it to be different from natural capaurimine.

Condensation of the amine (IV) [6] with ester (V) [7] by heating afforded the amide (VI), whose cyclization by a Bischler–Napieralski reaction gave a mixture of the 3,4-dihydroisoquinoline derivatives (VIIa) and (VIIb). Since the two products could not be separated, the mixture was reduced with sodium borohydride to give a mixture of the 1,2,3,4-tetrahydroisoquinoline derivatives (VIII) and (IX), which were converted into their oxalates. The oxalate of (VIII) crystallised out, and the filtrate was evaporated under reduced pressure to give a residue which was made basic and treated as usual to give a syrup (IX) which was characterized as its hydrochloride.

Debenzylation of the hydrochloride of (IX) with ethanol–concentrated hydrochloric acid afforded the 8-hydroxy-derivative (X), whose n.m.r. spectrum showed one aromatic proton, 5-H, at 6·22 p.p.m. The same treatment of the crystalline oxalate gave the 6-hydroxy-derivative (XI), whose n.m.r. spectrum showed one aromatic proton, 5-H, at 6·40 p.p.m. The assignment of the structures of (X) and (XI) from their n.m.r. spectra is by analogy with results obtained in our synthesis of so-called corpaverine;[4,8,9] in 6,7,8-trisubstituted isoquinolines, the signal for 5-H was at higher field when the hydroxy-group was in the 8-position than when it was in the 6-position.

Mannich reaction of (X) with formalin afforded the expected 9-hydroxy-derivative (XII),[5] whose i.r. spectrum showed the characteristic Bohlmann bands at 2850–2700 cm.$^{-1}$. The n.m.r. spectrum of (XII) showed three methoxy-groups at 3·85 (3H) and 3·80 p.p.m. (6H), one aromatic proton (4-H) at 6·22 p.p.m., and the other aromatic proton (11-H) at 6·92 p.p.m. Debromination of (XII) with zinc powder and alkali afforded the expected

[1] R. H. F. Manske, *Canad. J. Res.*, 1942, **20** *B*, 49.
[2] R. H. F. Manske, *Canad. J. Res.*, 1940, **18** *B*, 80.
[3] R. H. F. Manske, *J. Amer. Chem. Soc.*, 1947, **69**, 1800.
[4] T. Kametani and T. Kikuchi, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 879.
[5] T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), 1967, 530.
[6] Y. Inubushi and K. Fujitani, *J. Pharm. Soc. Japan*, 1958, **78**, 486.
[7] K. W. Gopianath, T. R. Govindachari, and N. Viswanathan, *Chem. Ber.*, 1959, **92**, 1659.
[8] T. Kametani, K. Ohkubo, and I. Noguchi, *J. Chem. Soc.* (*C*), 1966, 715.
[9] T. Kametani and K. Ohkubo, *Chem. and Pharm. Bull.* (*Japan*), in the press.

compound (I), whose i.r. and n.m.r. spectra were not identical with those of natural capaurimine.

Since the i.r. spectrum of natural capaurimine showed the characteristic Bohlmann bands at 2850—2700 cm.$^{-1}$, it has a *trans*-quinolizidine skeleton, *i.e.* it is a protoberberine-type compound. When the n.m.r. spectra of our synthetic specimen (I) and natural capaurimine are compared, the pattern of the three methoxy-groups of (I) is closely similar to that of the natural compound, but the signal of the aromatic proton at C-4 in our sample (I) is at 6·24 p.p.m. whereas that in natural capaurimine is at 6·35 p.p.m. This suggests, by the argument above, that the hydroxy-group in the A ring of capaurimine is at the 3-position, not the 1-position, *i.e.* capaurimine is (II). This theory was, however, disproved by the synthesis of (II).

Debenzylation of the di-*O*-benzyl derivative (VIII), followed by Mannich reaction with formalin, afforded the 3,9-dihydroxy-derivative (XIII), which was debrominated to give the compound (II). The i.r. and n.m.r. spectra of this compound (II) were also different from those of natural capaurimine.

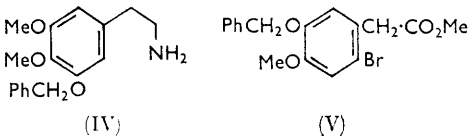
Methylation of our synthetic specimens (I) and (II) with diazomethane gave the same 1,2,3,9,10-pentamethoxyprotoberberine (III), whose i.r. and n.m.r. spectra were also not identical with those of di-*O*-methylcapaurimine, whose i.r. spectrum was the same as that of *O*-methylcapaurine.

Therefore, the suggested structures of capaurimine and capaurine are not correct, perhaps at the positions of substituents, and we are now investigating the structures of capaurimine and capaurine synthetically.

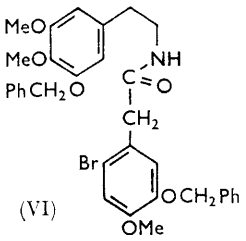
EXPERIMENTAL

N-(3-Benzyloxy-4,5-dimethoxyphenethyl)-5-benzyloxy-2-bromo-4-methoxyphenylacetamide (VI).—A mixture of 3-benzyloxy-4,5-dimethoxyphenethylamine (IV) [6] (2·8 g.) and methyl 5-benzyloxy-2-bromo-4-methoxyphenylacetate (V) [7] (3·6 g.) was heated in an oil-bath at 170—180° for 9 hr. After the reaction, recrystallisation from ethanol afforded the *amide* (VI) (5 g.) as colourless needles, m.p. 142—143° (Found: C, 63·95; H, 5·4; N, 2·5. $C_{33}H_{34}BrNO_6$ requires C, 63·85; H, 5·5; N, 2·25%), $\nu_{max.}$ ($CHCl_3$) 3380 (NH) and 1670 cm.$^{-1}$ (C=O).

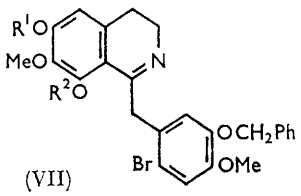
Mixture of 8-Benzyloxy-6,7-dimethoxy- (VIIa) *and 6-Benzyloxy-7,8-dimethoxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-3,4-dihydroisoquinoline* (VIIb).—A mixture of the above amide (VI) (5 g.), phosphoryl chloride (10 ml.), and dry benzene (50 ml.) was heated on a water-bath for 3 hr.,



(IV) (V)

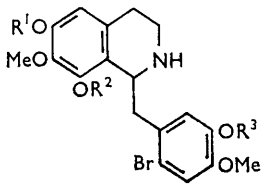


(VI)



(VII)

a; R^1 = Me, R^2 = CH_2Ph
b, R^1 = CH_2Ph, R^2 = Me



(VIII) R^1 = R^3 = CH_2Ph, R^2 = Me
(IX) R^1 = Me, R^2 = R^3 = CH_2Ph
(X) R^1 = Me, R^2 = R^3 = H
(XI) R^1 = R^3 = H, R^2 = Me

and an excess of n-hexane was added to the reaction mixture. After being allowed to stand overnight, the syrup precipitated was separated by decantation and washed with n-hexane several times. A solution of the above syrup in a small amount of methanol was poured into a cooled concentrated ammonium hydroxide solution and the oil that separated was extracted with ether. The extract was washed with water, dried (K_2CO_3), and evaporated to give the 3,4-dihydroisoquinoline derivatives (VIIa) and (VIIb) (4 g.) as an oily mixture, which could not be crystallised or separated; $\nu_{max.}$ ($CHCl_3$) 1620 cm.$^{-1}$ (C=N). It was therefore used in the following reaction without further purification.

6-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-7,8-dimethoxyisoquinoline (VIII) *and 8-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline* (IX).—To a solution of the preceding isoquinolines (VIIa) and (VIIb) (4 g.) in methanol containing 5 drops of concentrated hydrochloric acid was added portionwise sodium borohydride (4 g.) at room temperature and the mixture was refluxed with stirring on a water-bath for 1·5 hr. After the solvent had been distilled under reduced pressure, the residue was made basic with 5% sodium hydroxide solution and the alkaline mixture was extracted with ether to remove the precipitate. The extract was washed with water, dried (K_2CO_3), and evaporated to give a syrup, whose oxalate was recrystallised from ethanol to give the *oxalate* (2 g.) of

(VIII) as colourless prisms, m.p. 203—205° (Found: C, 60·0; H, 5·6; N, 2·25. $C_{33}H_{35}BrNO_5,C_2H_2O_4$ requires C, 60·45; H, 5·35; N, 2·0%).

The filtrate from the above preparation of the oxalate was evaporated under reduced pressure, and the residue was basified with 5% sodium hydrogen carbonate solution and extracted with ether. The extract was washed with water, dried (K_2CO_3), and evaporated to give a syrup, whose hydrochloride was recrystallised from methanol–ether to give the *hydrochloride* (2 g.) of (IX) as colourless needles, m.p. 172—174° (Found: C, 60·85; H, 5·9; N, 2·5. $C_{33}H_{35}BrNO_5$,HCl,1/2H_2O requires C, 60·95; H, 5·5; N, 2·15%).

1-(2-*Bromo*-5-*hydroxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-8-*hydroxy*-6,7-*dimethoxyisoquinoline* (X).—A mixture of (IX) (2 g.) and ethanol–concentrated hydrochloric acid (1 : 1) (50 ml.) was heated on a water-bath for 2 hr. After the reaction, the usual work-up afforded the phenolic base, whose recrystallisation from methanol afforded the 1,2,3,4-*tetrahydroisoquinoline* (X) (800 mg.) as colourless needles, m.p. 203—205° (Found: C, 53·45; H, 5·55; N, 3·05. $C_{19}H_{22}BrNO_5$ requires C, 53·8; H, 5·25; N, 3·3%), δ ($CDCl_3$) 3·82 and 3·80 (6H, two singlets, 2OCH_3) and 6·22 (1H, singlet, 5-*H*) p.p.m.

12-*Bromo*-5,6,13,13a-*tetrahydro*-1,9-*dihydroxy*-2,3,10-*trimethoxy*-8H-*dibenzo*[a,g]*quinolizine* (XII).—A mixture of the above phenolic base (X) (500 mg.), 37% formalin (15 ml.), a few drops of concentrated hydrochloric acid, and water (15 ml.) was heated on a water-bath for 3 hr. The cooled reaction mixture was made basic with ammonia and extracted with ethyl acetate. The extract was washed with water, dried(K_2CO_3), and evaporated to give a syrup, which was recrystallised from methanol to give the 1,9-*dihydroxy-derivative* (XII) (300 mg.) as colourless needles, m.p. 141—143° (Found: C, 53·0; H, 5·55; N, 2·9. $C_{20}H_{22}BrNO_5,H_2O$ requires C, 52·85; H, 5·3; N, 3·1%), δ ($CDCl_3$) 6·92 (1H, singlet, 11-*H*), 6·22 (1H, singlet, 4-*H*), 3·85 (3H, singlet, OCH_3), and 3·80 (6H, singlet, 2OCH_3) p.p.m.

5,6,13,13a-*Tetrahydro*-1,9-*dihydroxy*-2,3,10-*trimethoxy*-8H-*dibenzo*[a,g]*quinolizine* (I).—A mixture of the above bromo-compound (XII) (200 mg.), 10% sodium hydroxide solution (5 ml.), and zinc powder (200 mg.) was heated in an oil-bath at 130—140° for 3 hr. After cooling, an insoluble substance was filtered off, and an excess of crystalline ammonium chloride was added to the filtrate. The resultant ammoniacal solution was extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give a solid, which was recrystallised from methanol to afford *so-called capaurimine* (I) (80 mg.) as colourless needles, m.p. 190—191° (Found: C, 66·95; H, 6·55; N, 4·4. $C_{20}H_{23}NO_5$ requires C, 67·2; H, 6·5; N, 3·9%), $\nu_{max.}$ ($CHCl_3$) 3505 cm.$^{-1}$ (OH), δ [$(CD_3)_2SO$] 6·73 (1H, doublet, *J* 8·0 c./sec.), 6·46 (1H, doublet, *J* 8·0 c./sec.), 6·24 (1H, singlet, 4-*H*), 3·72 (6H, singlet, 2OCH_3), and 3·65 (3H, singlet, OCH_3) p.p.m.

1-(2-*Bromo*-5-*hydroxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-6-*hydroxy*-7,8-*dimethoxyisoquinoline* (XI).—A mixture of the compound (VIII) (2 g.) and ethanol–concentrated hydrochloric acid (1 : 1) (50 ml.) was heated for 2 hr. and the reaction mixture was treated according to the same procedure as for the debenzylation of (IX). The n.m.r. spectrum of the resultant phenolic syrup (XI) showed the protons of three methoxy-groups at 3·90, 3·80, and 3·78 p.p.m. and one aromatic proton (5-H) at 6·40 p.p.m. Recrystallisation of the hydrochloride from methanol–ether afforded the *hydrochloride* (800 mg.) of (XI) as colourless needles, m.p. 173—175° (Found: C, 47·35; H, 5·35; N, 3·1. $C_{19}H_{22}BrNO_5$,HCl,H_2O requires C, 47·65; H, 5·25; N, 2·9%).

12-*Bromo*-5,6,13,13a-*tetrahydro*-3,9-*dihydroxy*-1,2,10-*trimethoxy*-8H-*dibenzo*[a,g]*quinolizine* (XIII).—A mixture of the hydrochloride (1 g.) of (XI), water (30 ml.), and 37% formalin (30 ml.) was heated on a water-bath for 3 hr. The reaction mixture was made basic with ammonia and extracted with ethyl acetate. The extract was washed with water, dried (K_2CO_3), and evaporated to give a syrup, whose recrystallisation from methanol afforded the 3,9-dihydroxyprotoberberine (XIII) (500 mg.) as colourless needles, m.p. 110—112° (Found: C, 51·45; H, 5·2; N, 3·4. $C_{20}H_{22}BrNO_5$,1·5H_2O requires C, 51·85; H, 5·45; N, 3·0%), $\nu_{max.}$ ($CHCl_3$) 2770—2860 cm.$^{-1}$ (Bohlmann bands), δ ($CDCl_3$) 7·03 (1H, singlet, 11-*H*), 6·55 (1H, singlet, 4-*H*), 3·85 (6H, singlet, 2OCH_3), and 3·82 (3H, singlet, OCH_3) p.p.m.

5,6,13,13a-*Tetrahydro*-3,9-*dihydroxy*-1,2,10-*trimethoxy*-8H-*dibenzo*[a,g]*quinolizine* (II).—A mixture of the preceding bromo-compound (XIII) (500 mg.), 10% sodium hydroxide solution (5 ml.), and zinc powder (500 mg.) was heated under reflux at 130—140° for 3 hr. After the reaction mixture had been filtered to remove the precipitate, an excess of crystalline ammonium chloride was added to the filtrate and the resultant ammoniacal solution was extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give a syrup, whose recrystallisation from methanol afforded 3,9-*dihydroxyprotoberberine* (II) (100 mg.) as colourless needles, m.p. 208—210° (Found: C, 67·25; H, 6·45; N, 4·3. $C_{20}H_{23}NO_5$ requires C, 67·2; H, 6·5; N, 3·9%), $\nu_{max.}$ ($CHCl_3$) 3560 cm.$^{-1}$ (OH), δ [$(CD_3)_2SO$] 6·78 (1H, doublet, *J* 8·0 c./sec.), 6·5 (1H, doublet, *J* 8·0 c./sec.), 6·37 (1H, singlet, 4-H), 3·79 (3H, singlet, OCH_3), 3·77 (3H, singlet, OCH_3), and 3·75 (3H, singlet, OCH_3).

We thank Dr. R. H. F. Manske, Uniroyal Ltd., Research Laboratories, Guelph, Ontario, Canada, for the gift of natural capaurimine and capaurine, Miss Y. Tadano, Pharmaceutical Institute, School of Medicine, Tohoku University, for n.m.r. spectral determinations, and the Analytical Centre of Tokyo College of Pharmacy and the Pharmaceutical Institute, Tohoku University, for micro-analyses.

[7/1568 *Received, November 29th,* 1967]