The Structure of the Alkaloid Protostemonine

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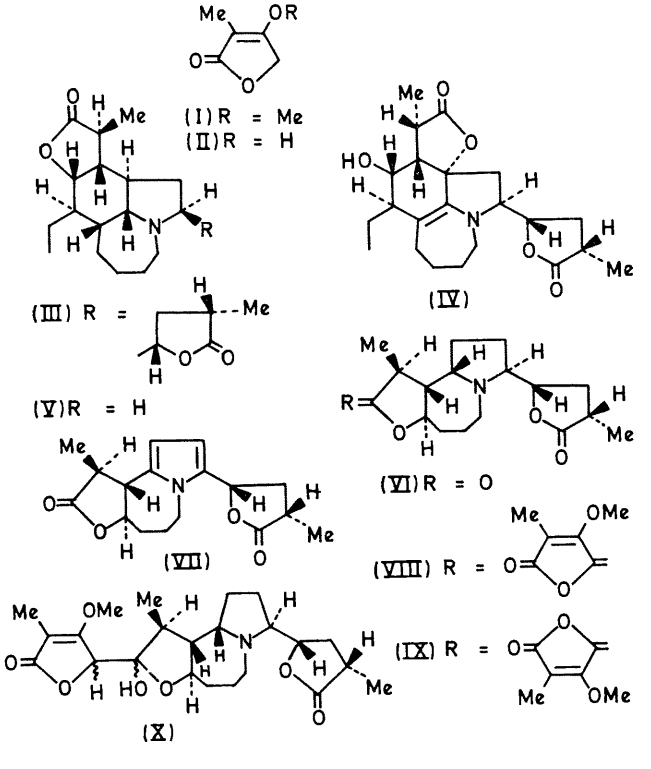
Summary Protostemonine, an alkaloid from *Stemona japonica*, is formulated as (VIII) or (IX).

PROTOSTEMONINE, an alkaloid from the roots of *Stemona japonica*, appeared of structural interest because Kondo and Satomi[1] reported that it was converted into stemonine,[2] $C_{17}H_{25}NO_4$, by treatment with hydrochloric acid through



an intermediate "stemonium chloride", $C_{17}H_{26}ClNO_4$. Re-investigation has shown that protostemonine corresponds more precisely to $C_{23}H_{31}NO_6$ (M^+ 417) rather than $C_{20}H_{29}NO_5$ as previously assigned and its spectral properties, λ_{max} (EtOH) 305 nm (ϵ 23,000); ν_{max} (KBr disc) 1770, 1740, 1679, and 1618 cm^{-1}; n.m.r. ($CDCl_3$) τ 5·87 (s, 3H), 7·94 (s, 3H), 8·66 (d, 3H), and 8·75 (d, 3H) indicate that the alkaloid contains one OMe, two secondary Me, one olefinic Me, one γ-lactone and a conjugated dienone system in which all carbon atoms are tetrasubstituted (there are no olefinic protons in the n.m.r. spectrum).

We have found that "stemonium chloride" which was obtained by treatment of protostemonine with hydrogen chloride in benzene followed by crystallisation of the resulting gummy precipitate from acetone in a manner previously described[1] is to be assigned a revised formula, $C_{23}H_{33}NO_7,HCl,H_2O$ based on the combustion analysis and mass spectrum (M^+ 435) and it is hence preferable to rename it protostemonine hydrate hydrochloride. The hydrochloride [λ_{max} (EtOH) 233 nm (ϵ 10,500); ν_{max} (KBr disc) 1777(γ-lactone), 1757($\alpha\beta$-unsaturated γ-lactone), and 1656(C=C) cm^{-1}] gave, on stirring with 3% aqueous potassium carbonate and benzene at room temperature for 24 hr., stemonine along with a neutral oil which was characterised as 4-hydroxy-3-methoxy-2-methylcrotonolactone (I) λ_{max} (EtOH) 232·5 nm (ϵ 39,000); ν_{max} ($CHCl_3$) 1750 and 1670 cm^{-1}; n.m.r. ($CDCl_3$) τ 5·36 (q, 2H, J 1 Hz), 6·00 (s, 3H), 8·16 (t, 3H, J 1 Hz), giving on hydrolysis with hydrochloric acid 3,4-dihydroxy-2-methylcrotonolactone (II), m.p. 186—189°, identical with an authentic specimen.[3] Pyrolysis of protostemonine hydrate hydrochloride in a high vacuum at 215—220° gave also the lactone (I) and stemonine hydrochloride.

Spectral data of stemonine, λ_{max} (EtOH) 210 nm (end-absorption); ν_{max} (KBr disc) 1765 cm^{-1}; n.m.r. ($CDCl_3$) τ 5·50—6·02 (m, 2H), 8·78 (d, 3H, J 6 Hz), 8·80 (d, 3H, J 6·5 Hz) show the presence of two secondary methyls, but neither an OH nor an NH group is observed. The mass spectrum of stemonine exhibits a base peak at m/e 208 (M^+ — 99) which is characteristic of a γ-lactone moiety attached to the α-position of a pyrrolidine ring, as is the case in tuberostemonine (III)[4] and oxotuberostemonine (IV).[5] The remaining two oxygen atoms in the molecule

of stemonine are to be assigned also to a γ-lactone grouping, since stemonine is neither an aldehyde nor a ketone because of the absence of any Cotton effect at about 300 nm in the o.r.d. curve; and its dehydrogenation product, bisdehydrostomonine, $C_{17}H_{21}NO_4$, m.p. 172—175° obtained by treatment of stemonine with activated manganese dioxide in tetrahydrofuran at room temperature for 48 hr. exhibits two carbonyl bands at 1765sh and 1750 cm^{-1} in the i.r. spectrum. Bisdehydrostemonine gives a positive Ehrlich test, indicating the presence of a pyrrole ring in the molecule and exhibits only an AB-type quartet at τ 3·86 (d, 1H, J 4 Hz) and 4·08 (d, 1H, J 4 Hz) in the olefinic proton region corresponding to the β- and β'-hydrogen atoms in the pyrrole ring. This finding shows that there is no substituent at the β- or β'-position in the pyrrolidine moiety of stemonine while both α- and α'-positions are substituted. Considering the results thus obtained and the established structures of tuberostemonine (III) and related alkaloids such as oxotuberostemonine (IV) and stenine (V),[6] the most plausible structure of stemonine is represented by formula (VI), and bisdehydrostemonine is formulated as (VII). Dr. Koyama and his associate[7] have confirmed the structure and elucidated the stereochemistry and absolute configuration of stemonine by determining the crystal structure of stemonine hydrobromide hemihydrate by crystallographic X-ray analysis. With the establishment of the structure of stemonine we now suggest for protostemonine either structure (VIII) or (IX) on the basis of our inference that protostemonine hydrate, which is assigned structure (X), undergoes a retro-aldol-type cleavage on treatment with alkali, giving stemonine (VI) and the lactone (I).

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[1] H. Kondo and M. Satomi, *J. Pharm. Soc. Japan*, 1947, **67**, 182, 185, 188.
[2] K. Suzuki, *J. Pharm. Soc. Japan*, 1911, **31**, 349; 1929, **49**, 457; 1931, **51**, 419; 1934, **54**, 561.
[3] L. Wolff, *Annalen*, 1895, **288**, 1.
[4] H. Harada, H. Irie, N. Masaki, K. Osaki, and S. Uyeo, *Chem. Comm.*, 1967, 460, and references therein.
[5] C. P. Huber, S. R. Hall, and E. N. Maslen, *Tetrahedron Letters*, 1968, 4081.
[6] S. Uyeo, H. Irie, and H. Harada, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 768.
[7] H. Koyama and K. Oda, *J. Chem. Soc.* (*B*), in the press.