The Structure of Sewarine, an Indole Alkaloid from *Rhazya stricta*

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Summary Sewarine, a phenolic indole alkaloid from *Rhazya stricta*, is shown to be 10-hydroxyakuammicine (I).

SEWARINE, a new alkaloid from *Rhazya stricta*, has been shown[1] to be a $C_{20}H_{22}N_2O_3$ compound on the basis of analyses and mass spectra. We now present new data which show that sewarine is a phenolic 2-methyleneindoline alkaloid of the akuammicine type, and has structure (I).

Sewarine, m.p. 245° (decomp.), gave a monohydrochloride salt, m.p. 210° (decomp.), $[\alpha]_D^{32}$ −724° (EtOH), λ_{max} (MeOH) 220, 311, 340 nm (ϵ 10,800, 14,400, 11,900) ν_{max} (Nujol) 3280 (N–H), 1675 ($\alpha\beta$-unsaturated ester –C=O), 1600, 1572 cm.$^{-1}$ (exocyclic and aromatic –C=C–). Electrometric titration† indicated one basic pK'_a of 7·7 (66% Me_2N·CHO) with A.M.W. 370 (calc., 374). These data, together with the strikingly high negative specific rotation, suggest the presence of an akuammicine (II) skeleton.[2–5] The mass spectrum further corroborates this assignment, since prominent peaks were observed at *m/e* 92, 107, and 121, as for akuammicine itself.[6] The n.m.r. spectrum of sewarine hydrochloride in CD_3OD showed the presence of only three aromatic protons in a 1,2,4-pattern. Other signals revealed the presence of a methoxycarbonyl group (3H, s, τ 6·31) and an ethylidene group (1H,q, τ 4·20, J 6Hz, and 3H, d, τ 8·60, J 6Hz). These data correspond to those for these functional groups in other akuammicine alkaloids. The lack of a fourth aromatic proton is due to the presence of a phenolic hydroxyl group, which was demonstrated in several ways. First, the u.v. spectrum of sewarine undergoes a bathochromic shift in alkaline solution [to λ_{max} 324, 363 nm (ϵ 12,200, 9500)]. Secondly, the methiodide[1] (III) of sewarine revealed on electrometric titration only one acidic pK'_a of 12·1 (Ar–OH) (A.M.W. 512; calc. for $C_{21}H_{25}IN_2O_3$·CH_3OH, 512). With MeI–MeONa sewarine gave the *ON*-dimethyl quaternary iodide (IV), $C_{22}H_{27}N_2O_3I$, m.p. 243—244° (decomp.), whose n.m.r. spectrum (CD_3OD) showed 3H singlets at τ 6·17 and 6·35 from the new *O*-and *N*-methyl groups, respectively. The *N*- methyl signal in the salt (III) was at τ 6·55. The methoxycarbonyl group of sewarine, as in other akuammicine alkaloids, was lost on treatment with HCl (sealed tube), giving desmethoxycarbonylsewarine (V), $C_{18}H_{20}N_2O$, m.p. 206° (decomp.).

The C-10 position for the phenolic hydroxyl in sewarine

† Precipitation of the compound at pH 12 did not permit determination of the acidic pK'_a, and required the use of the quaternary salt (III) for this determination.

was revealed by comparison of the chemical shifts of the aromatic protons of vindoline (VI), ibogaine, (VII), and sewarine (I; $R^2 = H_B$) hydrochloride (see below). These

Chemical shifts of aromatic protons (τ units)

	H_A	J_{AB}	H_B	J_{BC}	H_C	Solvent
Vindoline	3·09	8Hz	3·70	2Hz	3·92	$CDCl_3$
Ibogaine	3·05	2Hz	3·25	9Hz	2·92	$CDCl_3$
Sewarine hydrochloride ..	3·02	2Hz	3·30	7Hz	3·17	CD_3OD

data are also in accord with those of Witkop and his co-workers[7,8] for other hydroxylated indole derivatives. Further corroboration is given by the magnitude of the bathochromic shift of the u.v. spectrum of sewarine in alkaline solution, which is much closer to that of *p*-hydroxyaniline [λ_{max} (EtOH, neutral) 232, 300 nm (ϵ 7450, 2320)→ λ_{max} (EtOH, alkaline) 248, 314 nm (ϵ 10,800, 2240)] than to that of *m*-hydroxyaniline [λ_{max} (EtOH, neutral) 234, 285 nm (ϵ 6130, 2160) → λ_{max} (EtOH, alkaline) 240, 293 nm (ϵ 7000, 3090)]. In addition, the mass spectrum of sewarine (I) showed no significant peaks due to the loss of OH or H_2O, whereas that of the aliphatic hydroxyakuammicine mossambine (VIII)[9] showed an M — 17 peak at *m/e* 321, ascribable to the loss of OH. High resolution mass spectrometry of sewarine disclosed a small peak at *m/e* 146·06487 (calc. for C_9H_8ON: 146·06059), which is assigned to the fragment (IX).

Treatment of sewarine with $NaBH_4$ in aqueous acid solution gave the 2,16-dihydro-compound (X), $C_{20}H_{24}N_2O_3$, m.p. 202° (decomp.), [ν_{max} (Nujol) 1735 cm.$^{-1}$ (saturated ester –C=O)], whose mass spectrum was closely analogous to that of 2,16-dihydroakuammicine, (XI)[6] except for the displacement by 16 mass units of characteristic fragments incorporating the indole nucleus at *m/e* 144 and 251 in (XI) to *m/e* 160 and 267 respectively in (X). Other fragments at *m/e* 130, 139, and 194, arising from the aliphatic portions of the molecules, were common to both spectra.

Our results thus indicate that sewarine is 10-hydroxyakuammicine (I). The 11-hydroxyakuammicine structure (XII) has recently been assigned to vinervine, which occurs with its methyl ether vinervinine (XIII) in *Vinca erecta*.[10,11]

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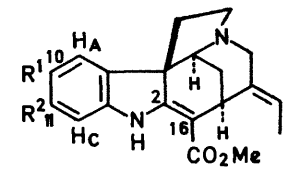
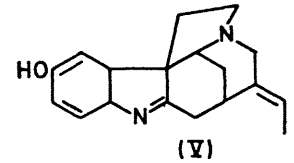
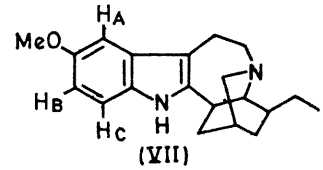


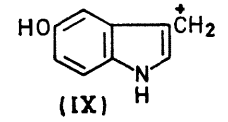
(I) $R^1 = OH; R^2 = H$
(II) $R^1 = R^2 = H$
(XII) $R^1 = H; R^2 = OH$
(XIII) $R^1 = H; R^2 = OMe$



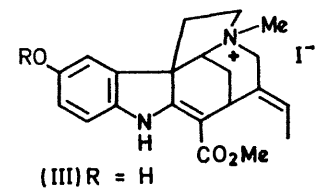
(V)



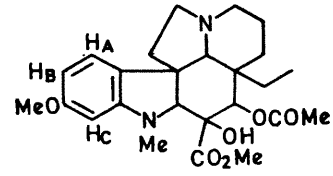
(VII)



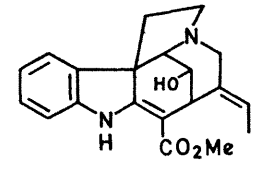
(IX)



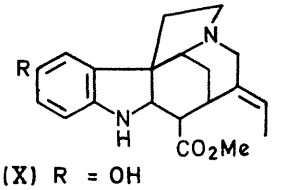
(III) R = H
(IV) R = Me



(VI)



(VIII)



(X) R = OH
(XI) R = H

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[1] S. Siddiqui, Y. Ahmad, and M. I. Baig, *Pakistan J. Sci. Indust. Res.*, 1966, **9**, 97.
[2] K. Aghoramurthy and R. Robinson, *Tetrahedron*, 1957, **1**, 172.
[3] K. Bernauer, W. Arnold, C. Weissmann, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1960, **43**, 717.
[4] P. N. Edwards and G. F. Smith, *J. Chem. Soc.*, 1961, 152.
[5] J. Lévy, J. Le Men, and M.-M. Janot, *Bull. Soc. chim. France*, 1960, 979.
[6] H. Budzikiewicz, J. M. Wilson, C. Djerassi, J. Lévy, J. Le Men, and M.-M. Janot, *Tetrahedron*, 1963, **19**, 1265.
[7] F. Märki, A. B. Robertson, and B. Witkop, *J. Amer. Chem. Soc.*, 1961, **83**, 3341.
[8] J. W. Daly and B. Witkop, *J. Amer. Chem. Soc.*, 1967, **89**, 1032.
[9] X. Monseur, R. Goutarel, J. Le Men, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Bull. Soc. chim. France*, 1962, 1088.
[10] P. Kh. Yuldashev, U. Ubaev, M. A. Kuchenkova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1965, **1**, 34.
[11] N. Abdurakhimova, P. Kh. Yuldashev, and S. Yu. Yunusov, *Dokl. Akad. Nauk S.S.S.R.*, 1967, **173** (1), 87.