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THE STRUCTURES OF LYTHRANINE, LYTHRANIDINE, AND LYTHRAMINE, NOVEL ALKALOIDS FROM LYTHRUM ANCEPS MAKINO

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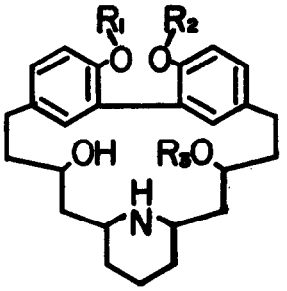
Several alkaloids have recently been isolated[1~4] from the American Lythraceous family, and their structures have been elucidated.[5~9] The X-ray analyses with O-methyllythrine hydrobromide[10], vertaline hydrobromide[11], and lythridine methiodide[12] have been useful for establishing the absolute configuration of the original alkaloids.

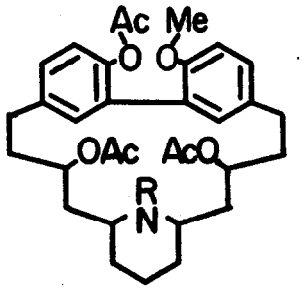
This communication deals with the assignment of the structures Ia, Ib, and IVa to three new alkaloids, lythranine, lythranidine, and lythramine, respectively, isolated from Lythrum anceps Makino (Japanese name: Misohagi).

Lythranine has not yet been crystallized, but the molecular formula was found to be $C_{28}H_{37}NO_5$ on the basis of the elemental analyses and mass spectral data of some derivatives. Lythranine hydrochloride[13] showed the N.M.R. proton signals[14] at 1.89 (3H, singlet, $OCOC\underline{H}_3$), 3.90 (3H, singlet, $OC\underline{H}_3$), 3.92 (1H, broad, $>C\underline{H}OH$), 5.13 (1H, broad, $>C\underline{H}OAc$), and 6.8-7.7(6H, aromatic protons). The presence of a phenolic hydroxy-group in lythranine was assumed from the U.V. maximum at 289 mμ which shifted to 313 mμ on addition of the aq. sodium hydroxide. The hydrochloride of the alkaloid, on acetylation with acetic anhydride and pyridine, afforded an O,O-diacetate(IIa) as a major product, which was crystallized as a hydrochloride, $C_{32}H_{41}NO_7 \cdot HCl$, m.p. 180-218°(decomp.), $[\alpha]_D^{25}$-33°, and an amorphous O,O,N-triacetate(IIb) as a minor product. The I. R. spectrum of the latter revealed the presence of an amide function(1640 cm^{-1}).

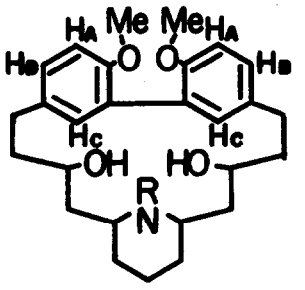
Lythranine(Ia), on basic hydrolysis, gave an oily deacetyl derivative(Ib), whose I.R. spectrum was superimposable with that of lythranidine, a minor alkaloid.



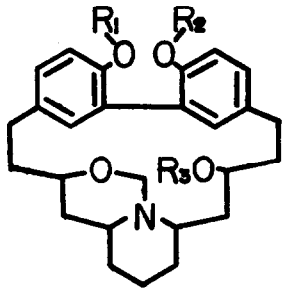
(Ia) R_1=H, R_2=Me, R_3=Ac
or R_1=Me, R_2=H, R_3=Ac
(Ib) R_1=R_3=H, R_2=Me



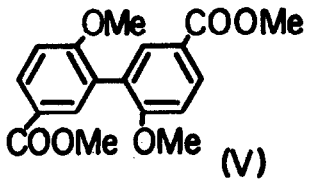
(IIa) R=H
(IIb) R=Ac



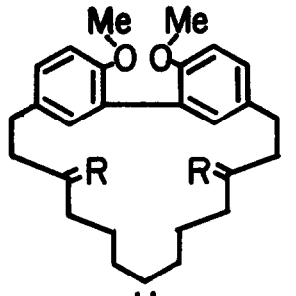
(IIIa) R=H
(IIIb) R=Me



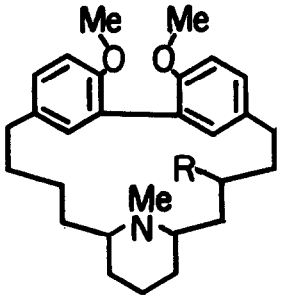
(IVa) R_1=H, R_2=Me, R_3=Ac
or R_1=Me, R_2=H, R_3=Ac
(IVb) R_1=R_2=Me, R_3=H



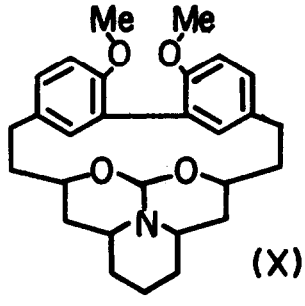
(V)



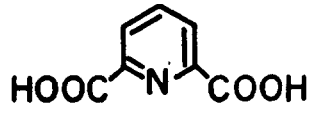
(VIa) R=<H, OH (VIb) R=O



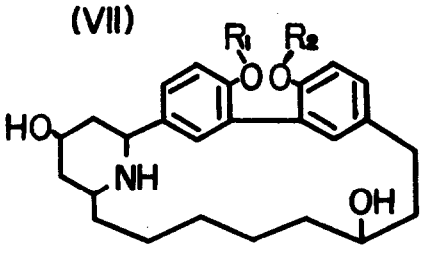
(VIII) R=Cl
(IX) R=H



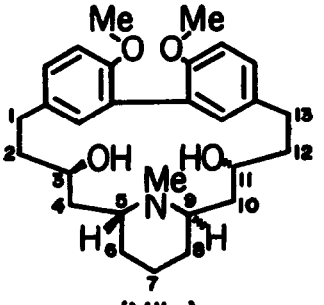
(X)



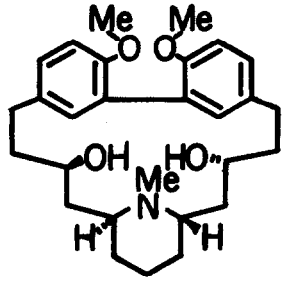
(VII)



(XI) R_1=H, R_2=Me
or R_1=Me, R_2=H



(XIIa)



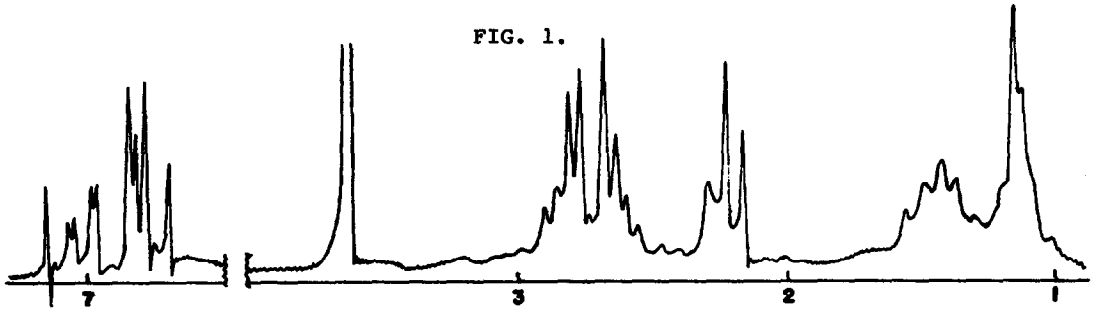
(XIIb)

Acetylation of lythranidine hydrochloride yielded an O,O,O-triacetate(IIa) as a major product, whose hydrochloride, $C_{32}H_{41}NO_7 \cdot HCl$, m.p. 180-217°(decomp.), $[\alpha]_D^{25}$ -27°, was shown to be identical with the hydrochloride of lythranine O,O-diacetate by the I.R. comparison and thin layer chromatographic behaviors. Thus, the relationship in which lythranidine corresponds to deacetyllythranine was established.

Methylation of deacetyllythranine(=lythranidine)(Ib) with diazomethane afforded an oily deacetyl-O-methyllythranine(=O-methyllythranidine)(IIIa)[N.M.R. : 3.76(6H, singlet, $OC\underline{H}_3 \times 2$), 4.69(3H, broad, disappeared with D_2O, $O\underline{H} \times 2$, $N\underline{H}$), 6.82(2H, doublet, J_{AB}= 8 c.p.s., $\underline{H}_A \times 2$), 7.10(2H, doublets of doublet, J_{AB}= 8, J_{BC}= 2 c.p.s., $\underline{H}_B \times 2$), and 7.39(2H, doublet, J_{BC}= 2 c.p.s., $\underline{H}_C \times 2$)] as a major product and deacetyl-O,N-dimethyllythranine(IIIb), $C_{28}H_{39}NO_4$, m.p. 167-169°, as a minor product. Oxidation of IIIa with potassium permanganate gave 2,2'-dimethoxydiphenyl-5,5'-dicarboxylic acid[15] characterized as the dimethyl ester V.

The double Hofmann degradations ——— provided that each of the Hofmann degradation was followed by hydrogenation ——— yielded a neutral alcohol VIa, $C_{27}H_{38}O_4$, m.p. 132.5-134°, which was oxidized with the chromic acid-pyridine complex to a diketone VIb, $C_{27}H_{34}O_4$, m.p. 116-118°. The N.M.R. spectrum(Fig. 1.) of VIb taken at 100 Mc.[16] revealed the signals at 3.64(3H, singlet, $OC\underline{H}_3$) and 2.23(2H, triplet, J = 7 c.p.s., $CH_2C\underline{H}_2CO$). The latter triplet turned into a singlet on irradiation at 1.42. A typical A_2B_2-type centered at 2.74($ArC\underline{H}_2C\underline{H}_2CO$) and a characteristic pattern of the aromatic protons on a 1,2,4-trisubstituted benzene ring also appeared. It was ascertained by mass spectrum (M^+: 422) that the apparent number shown above should be doubled because of the completely symmetric character of this ketone.

FIG. 1.



The ketone, on oxidation with potassium permanganate, gave a mixture of carboxylic acids, which was methylated with diazomethane and analyzed by the vapor phase chromatography[17]. In addition to V, several straight chain dicarboxylic acids having the carbon atoms from six(adipic acid) to nine (azelaic acid) were detected, giving a strong support for the structure VIb.

Lythranine(Ia), on dehydrogenation with Pd-black followed by oxidation with potassium permanganate, yielded dipicolinic acid VII, characterized as the dimethyl ester. Thus, the presence of a piperidine ring in lythranine was confirmed.

Lythramine(IVa), $C_{29}H_{37}NO_5$, was crystallized with 1/2 mole of the solvent when crystallized from acetone, which was confirmed by its N.M.R. spectrum and elemental analysis. The presence of one acetoxy-, one methoxy-, and one phenolic hydroxy-groups and of the six aromatic protons was deduced from the spectral data. A characteristic signal of an AB type(J=11 c.p.s.) centered at 4.57 in the N.M.R. spectrum of lythramine was assigned to the geminal protons on the carbon atom bearing O- and N-functions. Subsequently, lythramine was proved to be identical with a product(IVa) formed by a reaction of lythranine(Ia) with formaldehyde. The presence of a methylene bridge between a hydroxy- and an imino-groups was confirmed through the transformation of deacetyl-O-methyllythramine(IVb), $C_{28}H_{37}NO_4 \cdot CH_3OH$,[18] m.p. 118-121°, into the foregoing deacetyl-O,N-dimethyllythranine (=O,N-dimethyllythranidine)(IIIb) by hydrogenolysis with $LiAlH_4$. Six-membered ring character of the ring bearing oxygen and nitrogen atoms was deduced from the geminal protons' coupling constant value[19] of IVa.

Deacetyl-O,N-dimethyllythranine(IIIb) was treated with phosphorous oxychloride in pyridine at room temperature overnight. The subsequent catalytic reduction using Adams' catalyst afforded a monochloro-derivative(VIII), $C_{28}H_{38}NO_2Cl$, m.p. 168.5-170°, which on reduction with sodium and isopropylalcohol gave bisdeoxy-O,N-dimethyllythranidine(IX), $C_{28}H_{39}NO_2$, m.p. 127-129°. The latter showed no signal but two methoxy-methyl protons' in the region between 3.0 and 6.0 in its N.M.R. spectrum. Moreover, deacetyl-O-methyllythranine (IIIa), on refluxing in ethyl orthoformate in the presence of p-toluenesulfonic acid, gave an amidoacetal(X), $C_{28}H_{35}NO_4$, m.p. 227-229°[N.M.R. 3.79(3H, singlet, $OC\underline{H}_3$), 3.82(3H, singlet, $OC\underline{H}_3$), 5.26(1H, singlet, $\overset{O}{\underset{O}{>}}C\underline{H}$-N), 6.81(1H, doublet,

J_{AB}= 8 c.p.s., 6.83(1H, doublet, J_{AB}= 8 c.p.s., 7.07(2H, doublets of doublet, J_{AB}= 8, J_{BC}= 2 c.p.s.), 7.36(1H, doublet, J_{BC}= 2 c.p.s.), 7.95(1H, doublet, J_{BC}= 2 c.p.s.)]. These facts make an alternative structure XI for lythranidine very unlikely[20].

Finally, a consideration on the stereochemistry of the alkaloids based on the optical rotation is presented.

TABLE I.

Compounds	$[\alpha]_D^{25}$
Deacetyl-O,N-dimethyllythranine(IIIb) (= O,N-dimethyllythranidine)	-51°(c = 1.00) in $CHCl_3$
Alcohol VIa	-14°(c = 2.26) in dioxane
Ketone VIb	± 0°(c = 1.13) in dioxane
Bisdeoxy-O,N-dimethyllythranidine(IX)	-73°(c = 0.50) in $CHCl_3$
Amidoacetal X	-123°(c = 0.85) in $CHCl_3$

As shown in Table I, both VIa and IX are optically active. Thus, the absolute configurations at C-3 and C-11 must be the same, and those at C-5 and C-9 must be also the same. Hence, the stereochemistry of IIIb may be represented by either of XIIa or XIIb or one of their enantiomers. The investigation of the detailed stereochemistry of the alkaloids by O.R.D. determination is in progress.

We are indebted to Nippon Shinyaku Co. Ltd. for preparing the methanolic extract of the material plant.

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13 The substance is hygroscopic, so it does not give a constant melting point and the definite analytical data.

14 The N.M.R. spectra were taken in $CDCl_3$ at 60 Mc., and the chemical shifts are expressed as δ-value from TMS as an internal standard. We express our thanks to Dr. T. Shingu for measuring.

15 The authentic samples were kindly supplied by Dr. L. R. Row and Dr. K. P. Mathai in India.

16 We are grateful to Research Laboratory of Takeda Chemical Industries for measuring.

17 Column size: 183 cm. × 0.3 cm. ; Column packing: 5% Versamide on 60-80 mesh Chromosolb W ; N_2 flow-rate: 35 ml. per min. ; Instrument: Shimazu Model GC-1C.

18 This compound has not been well crystallized from any other solvent but MeOH.

19 R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, Tetrahedron Suppl. No. 7, 355 (1966).

20 It is impossible without a large steric strain to construct an amidoacetal based on the formula XI using a stereomodel.