Lythraceous Alkaloids. Part VII.[1] The Absolute Configurations of Lythrancines-I—IV and Lythrancepines-I—III[2]

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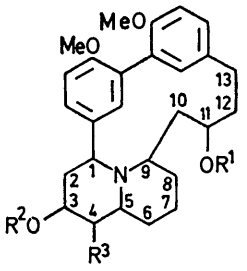
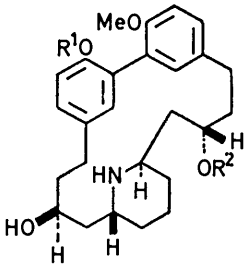
An n.m.r. investigation of lythrancine-IV provided evidence for a *cis*-relationship among 1-, 3-, and 4-H, and of a *cis*-ring-juncture of the quinolizidine ring. The chemical conversion of lythrancepine-II (VIa) into compound (XVI), which was proved to be the antipode of (XVII) derived from lythranidine (IX), established the absolute configuration of C-5, -9, and -11. Consideration of this result together with the relative stereochemistry of C-1-, -3, and -4 led to two possible stereostructures (A) and (B). Use of a stereomodel showed a preference for (A). *X*-Ray analysis of lythrancine-II-*O*-brosylate rigorously confirmed (A). The absolute stereochemistry of the seven new bases was established as (Ib)—(VIIb).

In the preceding paper,[1] we reported the structure of seven new alkaloids, lythrancine-I (Ia), -II (IIa), -III (IIIa), -IV (IVa), and lythrancepine-I (Va), -II (VIa), and -III (VIIa), isolated from *Lythrum anceps* Makino. These alkaloids have a quinolizidine ring in the molecule and have in common a structure in which a new bond is formed between the secondary amine and a benzyl carbon atom of lythranine (VIII).[3] In this paper, the

[1] Part VI, E. Fujita and Y. Saeki, *J.C.S. Perkin I*, 1972, 2141.
[2] Preliminary communication, E. Fujita and Y. Saeki, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 1515.
[3] E. Fujita and K. Fuji, *J. Chem. Soc.* (*C*), 1971, 1651.

stereochemistry and absolute configuration of these alkaloids are discussed.





(Ia) $R^1 = R^2 = H$, $R^3 = OH$
(IIa) $R^1 = Ac$, $R^2 = H$, $R^3 = OH$
(IIIa) $R^1 = R^2 = Ac$, $R^3 = OH$
(IVa) $R^1 = R^2 = Ac$, $R^3 = OAc$
(Va) $R^1 = R^2 = R^3 = H$
(VIa) $R^1 = Ac$, $R^2 = R^3 = H$
(VIIa) $R^1 = R^2 = Ac$, $R^3 = H$

(VIII) $R^1 = H$, $R^2 = Ac$
(IX) $R^1 = R^2 = H$
(X) $R^1 = Me$, $R^2 = H$

First, the n.m.r. spectrum (Figure 1) of lythrancine-IV (IVa) was effective in establishing the stereochemistry

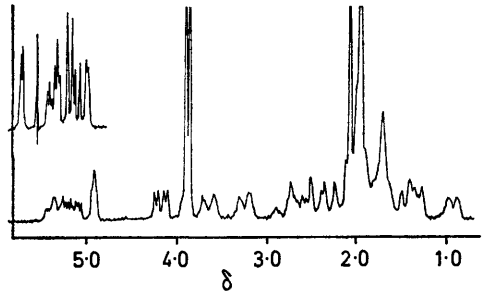


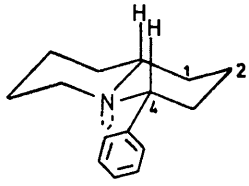
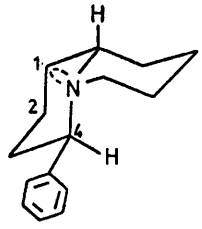
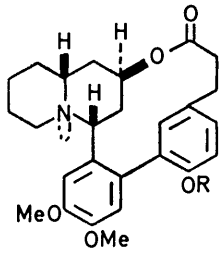
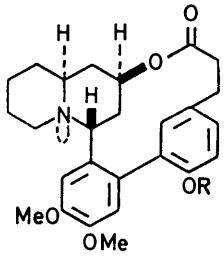
FIGURE 1 The 100 MHz n.m.r. spectrum of lythrancine-IV

of C-1, -3, and -4 among the six asymmetric centres. The 1-H signal was observed at δ 4·17 as a double doublet (*J* 11 and 4 Hz), which suggested that 1-H had an axial conformation given the usual chair–chair conformation of quinolizidine. An octet for the 3-H signal at δ 5·15 (*J* 3, 6, and 11·5 Hz) suggested an axial conformation, while a narrow triplet (*J* 3 Hz) at δ 4·91 due to 4-H implied an equatorial conformation. Thus, 1- and 3-H have a *cis*-diaxial relationship, and 3- and 4-H must be also *cis* to each other. Hence, the *cis*-relationship of the two acetoxy-groups at C-3 and -4 in lythrancine-IV (IVa) is confirmed, and this is supported by easy formation of a five-membered ring carbonate [1] by reaction of phosgene with lythrancine-II (IIa).*

9-H is known to be *trans* to 5-H, because methyl *trans*-6-methoxycarbonyl-2-piperidylacetate is obtained on oxidation of lythrancine-II (IIa) and subsequent esterification.[1]

Generally, a signal due to a proton attached to a carbon atom between a nitrogen and a phenyl group was observed at δ *ca.* 4 in the *cis*-quinolizidine derivatives and at δ *ca.* 3 in the *trans*-quinolizidine derivatives [4,5] (Table). As mentioned above, the 1-H signal of lythrancine-IV was observed at δ 4·17. Thus, the quinolizidine ring-juncture of this alkaloid was deduced to be *cis*. The absence of the Bohlmann absorption band [6] in the i.r. spectrum of this alkaloid also suggested a *cis*-ring-juncture.

Chemical shift of 4-H [δ (p.p.m.) from tetramethylsilane] for some 4-phenylquinolizidines

Compound		Chemical shift	Ref.
		2·7	5
		3·83	5
	R = Me	3·14	4
	R = Ac	3·14	4
	R = Me	4·07	4
	R = Ac	4·00	4

Jones oxidation [7] of lythrancepine-II (VIa) gave an oxo-product (XI), which was subjected to a retro-Michael type reaction by treatment with silica gel. The product gave two spots on t.l.c. Attempted separation of the two compounds by column chromatography resulted in ready isomerisation of the more polar substance into another less polar compound.† This

* Lythrancine-IV is identical with *OO*-diacetyl-lythrancine-II.[1]

† The less polar substance proved to be (XII), because catalytic hydrogenation of the isomerisation product gave the ketone (XIV). The more polar substance must be the desired compound (XIII).

[4] J. P. Ferris, C. B. Boyce, R. C. Briner, B. Douglas, J. L. Kirkpatrick, and J. A. Weisbach, *Tetrahedron Letters*, 1966, 3641.

[5] F. Bohlmann, D. Shumann, and C. Arndt, *Tetrahedron Letters*, 1965, 2705.

[6] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.

[7] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

isomerisation also occurred on allowing a solution of the mixture to stand in chloroform. Then the original

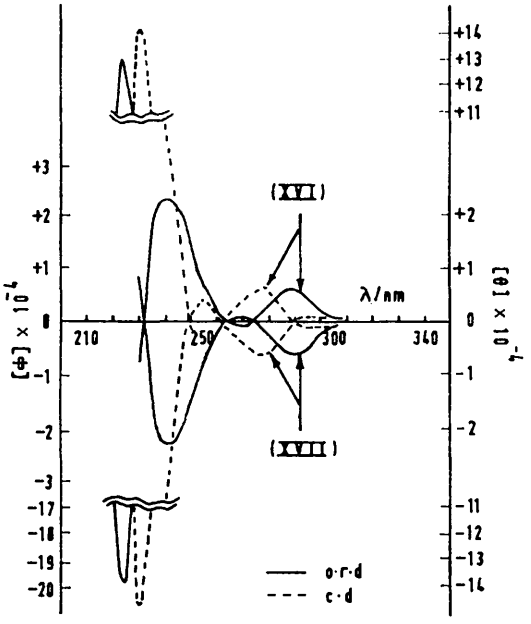
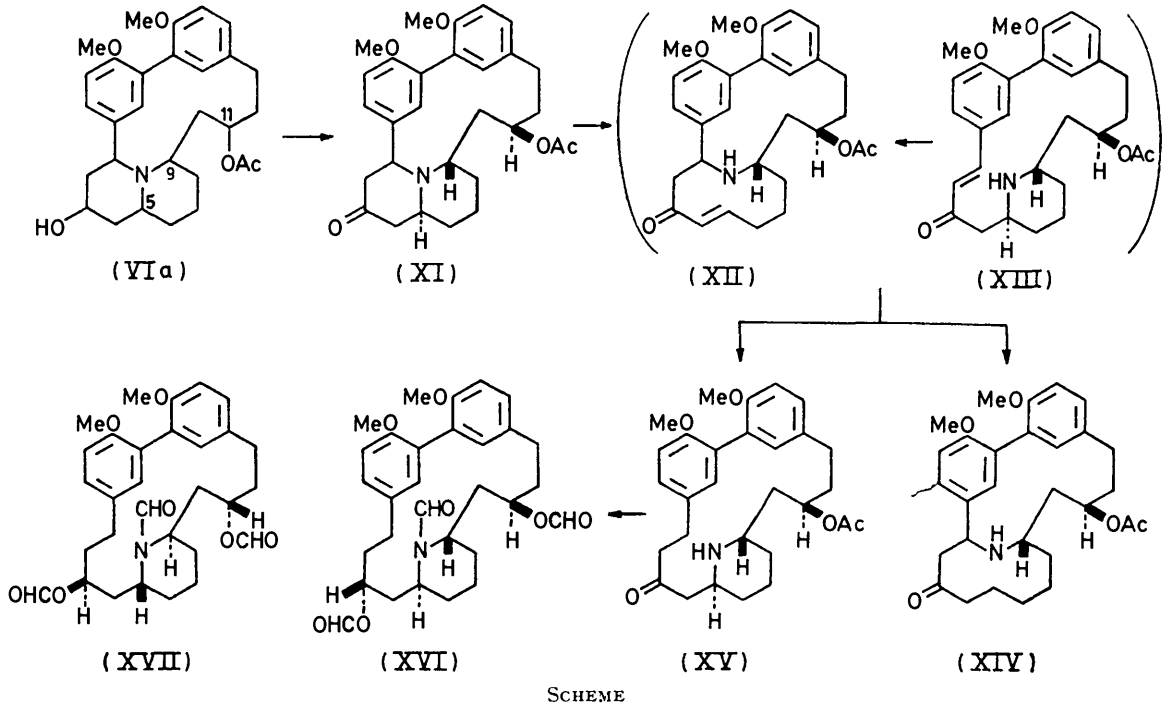


FIGURE 2 The o.r.d. and c.d. spectra of compounds (XVI) and (XVII)

mixture was directly subjected to catalytic hydrogenation to give a mixture of products, from which two ketones (XIV) and (XV) were isolated by column chromatography on the neutral silica gel.[8] Ketone (XIV), m.p. 81—82°, showed a characteristic double doublet (J 4 and 8 Hz) at δ 3·80 attributed to 1-H. The desired ketone (XV), m.p. 89—90°, showed no methine proton signal in the region δ 3·5—4·5.

Ketone (XV) on lithium aluminium hydride reduction in anhydrous tetrahydrofuran gave a mixture which revealed two spots on t.l.c. The R_F value of the less polar product coincided with that of *O*-methyllythranidine (X).[9] The sodium borohydride reduction of ketone (XV) in methanol occurred stereoselectively, and, after hydrolysis, the desired product, whose R_F value coincided with that of *O*-methyl-lythranidine (X), was formed in over 80% yield. This stereoselective hydride attack is reasonably explained by consideration of the stereomodel of (XV). The diol, without purification, was subjected to formylation with formic acid and acetic anhydride to yield a crystalline *NOO*-triformate, m.p. 211—212°, $[\alpha]_D$ +70°. Lythranidine (IX), the absolute configuration of which had been established,[3] was methylated by diazomethane and then formylated as usual to yield a crystalline *NOO*-triformate (XVII), m.p. 211—212°, $[\alpha]_D$ −70°. The m.p.s, t.l.c., i.r., n.m.r., and mass spectra of the foregoing triformate and (XVII) were proved to be completely identical, but they showed rotations of opposite sign with the same absolute value. The o.r.d. and c.d. spectra of both triformates are shown in Figure 2. Thus, the triformates were proved to be antipodes, and the former was shown to be



SCHEME

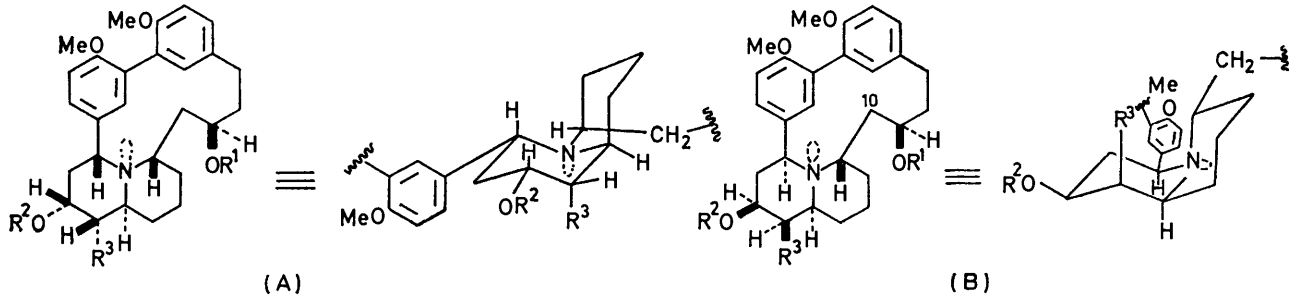
(XVI). Hence, the absolute configuration of (I)—(VII), at C-5, -9, and -11, was established as *S*, *S*, and *R*,

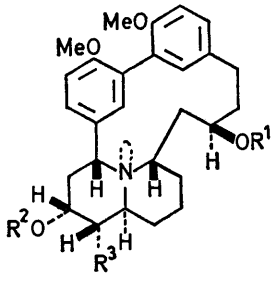
[8] J. G. Buchanan and J. C. P. Schwarz, *J. Chem. Soc.*, 1962, 4770.

[9] E. Fujita, K. Fuji, K. Bessho, and S. Nakamura, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 2393.

respectively. Consideration of the result of this chemical conversion together with the relative stereochemistry among C-1, -3, and -4 led to only two possible formulae, (A) and (B), for (I)—(VII). Use of a stereomodel showed a preference for (A), because (B) has large interactions between the 10-methylene group and the aromatic hydrogen atom and the thirteen-membered ring is highly strained.

Finally, *X*-ray analysis of lythrancine-II-*O*-brosylate carried out by Sim *et al.** rigorously confirmed the stereochemistry (A). In conclusion, the absolute stereochemistry of the seven new bases has been established as (Ib)—(VIIb). The occurrence of two related groups of alkaloids possessing antipodal stereochemistry in a same plant is biosynthetically interesting.





(Ib) $R^1 = R^2 = H$, $R^3 = OH$
(IIb) $R^1 = Ac$, $R^2 = H$, $R^3 = OH$
(IIIb) $R^1 = R^2 = Ac$, $R^3 = OH$
(IVb) $R^1 = R^2 = Ac$, $R^3 = OAc$
(Vb) $R^1 = R^2 = R^3 = H$
(VIb) $R^1 = Ac$, $R^2 = R^3 = H$
(VIIb) $R^1 = R^2 = Ac$, $R^3 = H$

EXPERIMENTAL

General details are given in ref. 1. O.r.d. and c.d. spectra were measured on a JASCO ORD/UV-5 spectrometer for solutions in dioxan at room temperature.

Jones Oxidation of Lythrancepine-II (VI).—To a stirred solution of lythrancepine-II (VI) (540 mg) in ice-cooled acetone (30 ml) was added dropwise Jones reagent (1 ml) and the mixture was stirred at room temperature for 1 h. After decomposition of the excess of reagent with methanol (1 ml), the solvent was evaporated, the residue was dissolved in water, made alkaline with aqueous sodium carbonate solution, and extracted with dichloromethane. The extract was dried (Na_2SO_4) and evaporated. The residue (540 mg) in dichloromethane was chromatographed on neutral silica gel † (10 g). Elution with dichloromethane gave a crystalline mass, which was recrystallized from methanol to give a *dehydro-derivative* (XI) of lythrancepine-II (370 mg), m.p. 219—220°, $\nu_{max.}$ 1718 cm^{-1}, δ 2·00 (3H, s, OCOMe), 3·86 (3H, s, OMe), 3·88 (3H, s, OMe), 4·33 (1H, dd, *J* 5·5 and 10 Hz, 1-H), and 5·40 (1H, m, 11-H) (Found: C, 72·1; H, 7·4; N, 2·9%; M^+, 477·2522. $C_{29}H_{35}NO_5$ requires C, 72·15; H, 7·4; N, 2·95%; *M*, 477·2515).

Ketones (XIV) *and* (XV).—A solution of ketone (XI) (370 mg) in dichloromethane (10 ml) was adsorbed on a column of silica gel (20 g) and left at room temperature for 5 h. Elution with dichloromethane–methanol (3%) gave an oil (345 mg), which consisted of enones (XII) and (XIII). The mixture (289 mg) in ethyl acetate (30 ml) was hydrogenated over platinum oxide (10 mg) at room temperature under atmospheric pressure. The catalyst was filtered off and the solution was evaporated *in vacuo* to give an oil (272 mg), which was purified by chromatography on neutral silica gel † (20 g). The major compound, *ketone* (XIV) (148 mg) was eluted with dichloromethane–methanol (1%) and crystallized from methanol, m.p. 81—82°, $\nu_{max.}$ 1713 cm^{-1}, δ 1·81 (3H, s, OCOMe), 3·71 (6H, s, 2 × OMe), 3·80 (1H, dd, *J* 4 and 8 Hz, 1-H), and 5·00 (1H, m, 11-H) (Found: C, 69·85; H, 8·0; N, 2·7%; M^+, 479·2693. $C_{29}H_{37}NO_5,H_2O$ requires C, 70·0; H, 7·9; N, 2·8%; *M*, 479·2672). The desired *ketone* (XV) (69 mg) was eluted with dichloromethane–methanol (3%) and crystallized from ether, m.p. 89—90°, $\nu_{max.}$ 1715 cm^{-1}, δ 1·81 (3H, s, OCOMe), 3·71 (3H, s, OMe), 3·73 (3H, s, OMe), and 5·00 (1H, m, 11-H) (Found: M^+, 479·2657. $C_{29}H_{37}NO_5$ requires *M*, 479·2672).

Triformate (XVI).—A solution of ketone (XV) (110 mg) and sodium borohydride (100 mg) in ice-cooled methanol (20 ml) was stirred for 1 h, followed by an additional 1 h at room temperature. The mixture was concentrated *in vacuo* to *ca.* 5 ml, diluted with water (50 ml), and stirred at room temperature for 3 h. The products, obtained by the usual work-up, showed two spots on t.l.c. [silica gel G developed by dichloromethane–methanol (30%)], and the major spot had the same R_F value as that of *O*-methyl-lythranidine (X).[9] Without purification, the mixture (63 mg) was treated with acetic anhydride (3 ml) and 100% formic acid (2 ml) at room temperature for 20 h. The mixture was evaporated *in vacuo* to dryness. The residue (70 mg) in dichloromethane was chromatographed on neutral silica gel. Elution with dichloromethane afforded a crystalline mass, which was recrystallized from methanol to give the

* To be published elsewhere.

† A suspension of Kieselgel (0·05—0·2 mm; Merck; 500 g) in 20% aqueous ammonia (2 l) was left to stand for 1 h and filtered. After sufficient washing with water, it was dried and activated by heating at 110° for 2 h.[8]

triformate (XVI) (36 mg), m.p. 211—212°, $[\alpha]_D$ +70° (*c* 0·20), $\nu_{max.}$ 1718 and 1643 cm^{-1}, δ 3·73 (3H, s, OMe), 3·80 (3H, s, OMe), 4·70—5·50 (2H, m, 3- and 11-H), 7·80 (2H, s, 2 × CHO), and 8·15 (1H, s, CHO) (Found: C, 69·05; H, 7·4; N, 2·55%; M^+, 523·2572. $C_{30}H_{37}NO_7$ requires C, 68·8; H, 7·1; N, 2·7%; *M*, 523·2570).

Triformate (XVII).—This compound was prepared from *O*-methyl-lythranidine (X) [9] by reaction with acetic anhydride–100% formic acid (1 : 1; 6 ml). It was obtained as *crystals* from methanol, m.p. 211—212°, $[\alpha]_D$ −70° (*c* 0·20) (Found: C, 68·75; H, 6·9; N, 2·55%; M^+, 523·2574). The i.r., n.m.r., and mass spectra were superimposable on those of (XVI). Behaviour on t.l.c. was also identical with that of (XVI).

We thank Mr. T. Takakuwa, Japan Spectroscopic Co., for o.r.d. and c.d. spectra and Miss Y. Mano, Kyoto University, for elemental analyses. Thanks are also due to Mrs. Y. Watanabe and Miss H. Shimomi of this Institute for mass and n.m.r. spectra.

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