Lythraceous Alkaloids. Part VI.[1] The Structures of Lythrancine-I, -II, -III, and -IV and Lythrancepine-I, -II, and -III [2]

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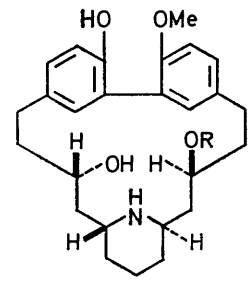
Chemical and spectroscopic investigation of seven new *Lythrum* alkaloids led to elucidation of their structures. All were shown to have a common basic structure of 4-(biphenyl-3-yl)perhydroquinolizine with a butane bridge between the 3'-position of the biphenyl group and the 6-position of the quinolizine nucleus. Lythrancine-I, -II, -III, and -IV and lythrancepine-I, -II, and -III are represented by formulae (XIV)—(XX), respectively.

In previous publications,[1,3-6] the isolation of three bases, lythranine (I), lythranidine (II), and lythramine (III) from *Lythrum anceps* Makino (Lythraceae) and their structural elucidation were reported. Recently, seven new alkaloids, lythracine-I, -II, -III, and -IV and lythrancepine-I, -II, and -III were isolated from the same plant source.[1] The Table indicates some of their physical constants and molecular formulae. This paper describes their structure elucidation.

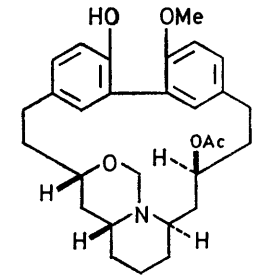
Alkaloid	M.p.(°)	$[\alpha]_D^{20}$(°)	Molecular formulae
Lythrancine-I	*a*	+65	$C_{27}H_{35}NO_5$
Lythrancine-II	274—275	+125	$C_{29}H_{37}NO_6$
Lythrancine-III	134—136	+38	$C_{31}H_{39}NO_7$
Lythrancine-IV	237—238	+27	$C_{33}H_{41}NO_8$
Lythrancepine-I	149—151	+59	$C_{27}H_{35}NO_4$
Lythrancepine-II	187—189	+44	$C_{29}H_{37}NO_5$
Lythrancepine-III	175—177	+7	$C_{31}H_{39}NO_6$

[a] A powder.

Acetylation of lythrancine-II with acetic anhydride in pyridine at room temperature furnished lythrancine-II *O*-acetate, whereas the same reaction at 110° for 3 h gave lythrancine-II *OO*-diacetate. These products were identical with lythrancine-III and lythrancine-IV, respectively. Hydrolysis of lythrancine-II with 1% methanolic potassium hydroxide yielded lythrancine-I. That lythrancine-I has no acetoxy-group was shown by its i.r. and n.m.r. spectra. Lythrancine-II was identified as the monoacetate of lythrancine-I by a comparison of their molecular formulae. Thus, lythrancine-III and -IV correspond to lythrancine-I diacetate and triacetate, respectively. Both lythrancepine-I and lythrancepine-II, on acetylation with acetic anhydride in pyridine, gave lythrancepine-III. Lythrancepine-I has no acetate group. The identity of lythrancepine-II and -III with lythrancepine-I monoacetate and diacetate, respectively, was similarly clarified. It was proved that the lythrancepine series were the deoxy-derivatives of the lythrancine series as follows. Lythrancine-III was converted into the *O*-tosylate, which



(I) R = Ac
(II) R = H



(III)

was reduced with lithium aluminium hydride and then acetylated to afford lythrancepine-III accompanied by an epimer.† Thus, these seven alkaloids have a common skeleton and a tertiary nitrogen atom.

Lythrancine-II showed absorptions at 3480 (O–H) and 1720 cm^{-1} (C=O) in its i.r. spectrum. Its n.m.r. spectrum showed an acetoxy-methyl signal at δ 2·01 p.p.m. together with a one-proton multiplet (H_a) at δ 5·35 p.p.m. [C*H*(OAc)]. Thus, a carbonyl group must be present as a secondary acetate. Furthermore, a six-proton singlet at δ 3·87 p.p.m. (two methoxy-groups)

† This compound was later proved to be the C-3 epimer of lythrancepine-III.

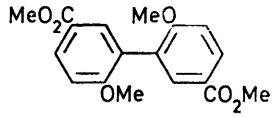
[1] Part V, E. Fujita, K. Bessho, Y. Saeki, M. Ochiai, and K. Fuji, *Lloydia*, 1971, **34**, 306.
[2] Preliminary communication, E. Fujita and Y. Saeki, *Chem. Comm.*, 1971, 368.
[3] E. Fujita, K. Bessho, K. Fuji, and A. Sumi, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2216.
[4] E. Fujita, K. Fuji, K. Bessho, and S. Nakamura, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2393.
[5] E. Fujita, K. Fuji, and K. Tanaka, *J. Chem. Soc. (C)*, 1971, 205.
[6] E. Fujita and K. Fuji, *J. Chem. Soc. (C)*, 1971, 1651.

and a double doublet (J 4 and 10·5 Hz) at δ 4·08 p.p.m. (ArCH_c·N) [7] were observed.

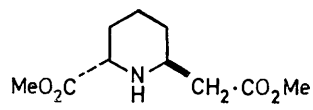
The n.m.r. spectrum of lythrancine-II *OO*-diacetate (*i.e.* lythrancine-IV) showed three acetoxy-groups, and also signals for protons attached to acetoxylated carbon atoms (see Experimental section). Lythrancine-II, therefore, has two secondary hydroxy-groups. All the oxygen atoms and nitrogen are thus accounted for.

Treatment of lythrancine-II with phosgene in toluene–pyridine readily gave a crystalline product,* which showed a characteristic absorption of a five-membered cyclic carbonate at 1798 cm^{-1} in its i.r. spectrum. Thus, the two secondary hydroxy-groups are present as a *cis*-diol.

Lythrancine-II was oxidized to yield acidic products, which were methylated and fractionated into neutral and basic fractions. The neutral fraction was chromatographed to give a crystalline product, which was identical with an authentic sample of dimethyl 6,6′-dimethoxybiphenyl-3,3′-dicarboxylate (IV).[8] The basic fraction was distilled under reduced pressure to give a colourless oil, whose molecular formula, $C_{10}H_{17}NO_4$, was determined by high-resolution mass spectrometry. The i.r. spectrum showed the presence of an ester and an imino-group. The imino-group was established chemically by the formation of an *N*-methyl derivative when treated with formic acid and formaldehyde under reflux. In the n.m.r. spectrum of this *N*-methyl derivative, an ABX-type signal was observed. The AB part appeared as two quartets with coupling constants of 14·5 (J_{AB}), 8·5 (J_{AX}), and 5 Hz (J_{BX}) at δ 2·29 and 2·66 p.p.m., which were assignable to the methylene protons adjacent to a methoxycarbonyl group. The X part resonated at δ 3·50 p.p.m. as a multiplet, which was assignable to a methine proton adjacent to the nitrogen. The rest of the spectrum (see Experimental section) was consonant with the formulation of the base as methyl *trans*-6-methoxycarbonyl-2-piperidylacetate (V).



(IV)

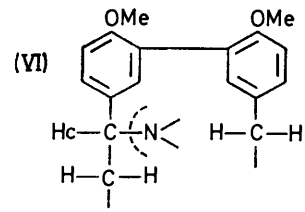


(V)

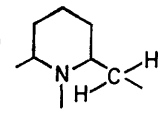
Oxidation of lythrancine-II with chromic anhydride in acetic acid gave a dihydroxy-ketone, with the glycol portion unchanged. Its i.r. and u.v. spectra suggested a benzoyl carbonyl group.† Consequently, lythrancine-II contains the partial structures (VI)—(IX). Hence, lythrancine-III contains (VI), (VII), (IX), and (X), and lythrancine-IV (VI), (VII), (IX), and (XI). Unlike lythrancine-IV, lythrancine-III did not exhibit any signal for H_x at δ *ca.* 4·9 p.p.m. in the n.m.r. spectrum.

Jones oxidation of lythrancine-III gave a monoketone and a diketone. Reduction of the former with sodium borohydride in methanol afforded lythrancine-II and its epimer which on acetylation with acetic anhydride–pyridine gave an epimer of lythrancine-IV.‡

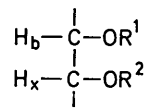
(VI)



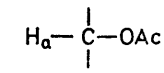
(VII)



(VIII) $R^1 = R^2 = H$
(X) $R^1 = H$, $R^2 = Ac$
or $R^1 = Ac$, $R^2 = H$
(XI) $R^1 = R^2 = Ac$

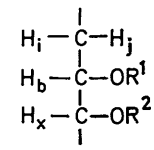


(IX)



In the n.m.r. spectrum of the monoketone, a double doublet signal of proton H_b appeared at δ 5·55 p.p.m. (J 7 and 14 Hz). This means that H_b must be adjacent to a methylene group. Thus, the partial structures (VIII), (X), and (XI) can be extended to (XII).

(XII)



Periodate cleavage of the *cis*-diol of lythrancine-II and Hofmann degradation of lythrancine-II, -III, and -IV were tried, but all attempts were unsuccessful.

The spectra of the diketone were investigated in detail. The u.v. and i.r. spectra suggested the presence of a benzoyl group, indicating the second oxidation at a benzylic position. The n.m.r. spectrum (see Figure) exhibited an ABX-type signal, *i.e.* a double doublet (H_e) (J 10 and 14·5 Hz) at δ 2·61, a doublet (H_f) (J 14·5 Hz) at 3·25, and a multiplet (H_a) at 5·81 p.p.m. The double doublet of the A part (H_e) collapsed into a doublet (J 14·5 Hz) on irradiation at δ 5·81 p.p.m. (H_a: the X part). The value of the coupling constant between H_e and H_f suggested a geminal coupling and the chemical shifts of H_e and H_f were in agreement with those of methylene protons adjacent to a carbonyl group. By a simultaneous irradiation at δ 3·17, where a broad doublet (H_g) (J 11 Hz) was present, and at 5·81 p.p.m. (H_a), an octet (H_k) (J 3, 6, and 15 Hz) at δ 1·47 p.p.m. split into a doublet with a geminal coupling of 15 Hz. The chemical shift of H_g suggested it to be a methine proton adjacent to the nitrogen atom.[9]

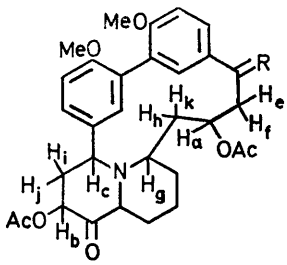
Double irradiation of the double doublets at δ 4·53 (H_c) and 5·58 (H_b) p.p.m. gave an AB quartet (H_iH_j)

* This compound was later shown to be (XXI).
† This compound was later shown to be (XXIII).
‡ This compound was later shown to be the C-4 epimer of lythrancine-IV.

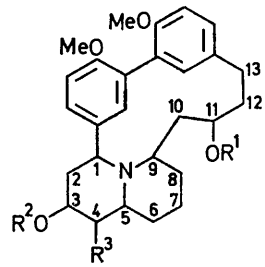
[7] W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.*, 1961, **83**, 4816; M. Uskokovíc, H. Bruderer, C. von Plantan, T. Williams, and A. Brossi, *ibid.*, 1964, **86**, 3364.
[8] K. V. J. Rao and L. R. Row, *J. Org. Chem.*, 1960, **25**, 981.
[9] H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Letters*, 1964, 2553.

with a geminal coupling constant of 13 Hz at δ 1·95 and 2·35 p.p.m.

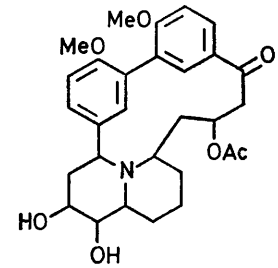
On the basis of the foregoing results, structure (XIIIb) was assigned to the diketone; hence, the monoketone is



(XIIIa) R = H_2
(XIIIb) R = O



lythrancine — I (XIV) R^1 = R^2 = H, R^3 = OH
lythrancine — II (XV) R^1 = Ac, R^2 = H, R^3 = OH
lythrancine — III (XVI) R^1 = R^2 = Ac, R^3 = OH
lythrancine — IV (XVII) R^1 = R^2 = Ac, R^3 = OAc
lythrancepine — I (XVIII) R^1 = R^2 = R^3 = H
lythrancepine — II (XIX) R^1 = Ac, R^2 = R^3 = H
lythrancepine — III (XX) R^1 = R^2 = Ac, R^3 = H
(XXI) R^1 = Ac, R^2 R^3 = —CO—O—
(XXII) R^1 = R^3 = H, R^2 = Ac



(XXIII)

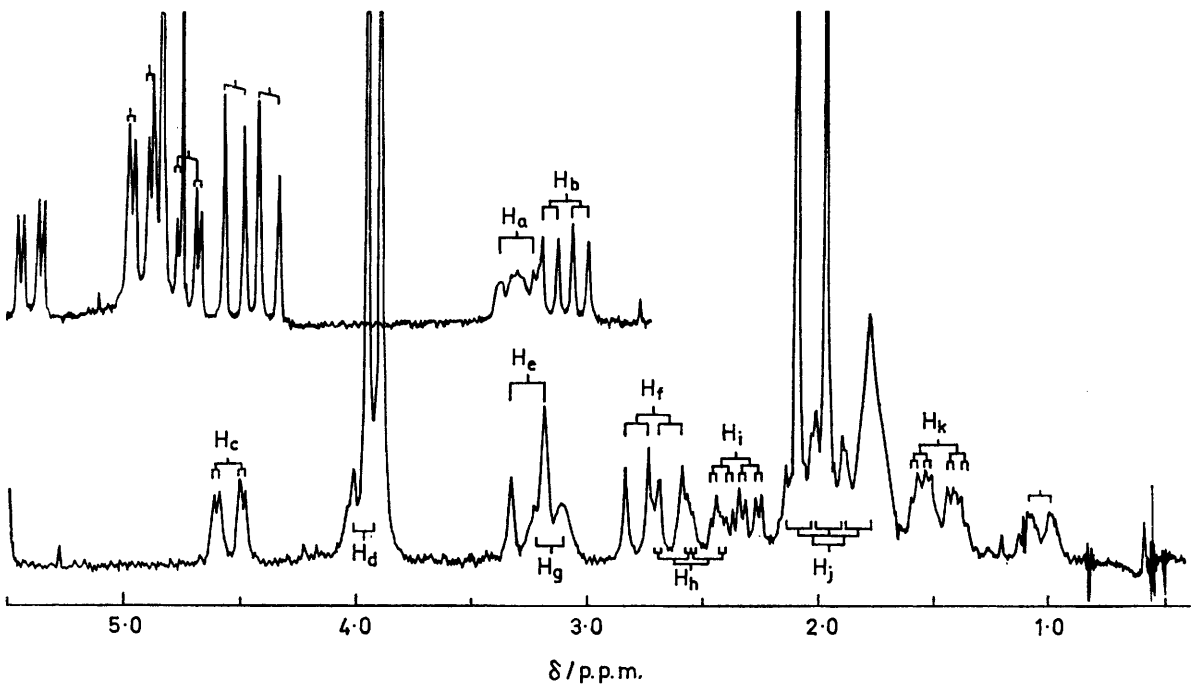


FIGURE The 100 MHz n.m.r. spectrum of the diketone (XIIIb)

(XIIIa), and the original base, lythrancine-III, must be (XVI). Thus, the structures of the seven alkaloids were established as (XIV)—(XX). Another possible structure (XXII) for lythrancepine-II was rejected on the following observation. In the n.m.r. spectrum of lythrancepine-II, a multiplet of the proton on the acetoxylated carbon atom was recognized at δ 5·33 p.p.m. The 11-H signal was always observed at δ 5·34 ± 0·01 for the 11-acetates, while 3-H in the 3-acetates resonated at somewhat higher field, δ 4·99—5·15 p.p.m.

EXPERIMENTAL

M.p.s were taken on a micro hot-stage and are uncorrected. I.r. spectra were recorded on a Hitachi model EPI-S_2 spectrometer. U.v. spectra were determined on a Hitachi model EPS-3 spectrophotometer for 95% ethanol solutions. Rotations were measured on a JASCO DIP-180 automatic polarimeter for chloroform solutions at room

temperature. The n.m.r. spectra were recorded with a Varian A-60 or HA-100 spectrometer in deuteriochloroform; signals are reported in p.p.m. from tetramethylsilane as internal standard. The mass spectra were determined on a JMS-OISG double-focusing mass spectrometer. Merck standardized alumina grade I or Kieselgel 0·05—0·2 mm (Merck) was used for chromatography. Identity of compounds was established by mixed m.p. and i.r. spectra (see the Table for some physical constants).

Lythrancine-I (XIV).—Lythrancine-I (XIV) was isolated as a powder, $[\alpha]_D$ +65° (*c* 0·96), $\nu_{max.}$ ($CHCl_3$) 3400 cm^{-1} (OH), δ 3·82 (6H, s, 2 × OMe) (Found: M^+, 453·2539. $C_{27}H_{35}NO_5$ requires *M*, 453·2515).

Lythrancine-II (XV).—Lythrancine-II (XV) was isolated as needles from methanol–n-hexane, m.p. 274—275° $[\alpha]_D$ +125° (*c* 0·726), $\nu_{max.}$ ($CHCl_3$) 3480 and 1720 cm^{-1}, $\lambda_{max.}$ 289 nm (ε 8000), δ 2·01 (3H, s, OAc), 3·87 (6H, s, 2 × OMe), 4·08 (1H, dd, *J* 4 and 10·5 Hz, 1-H), and 5·35 (1H, m, 11-H) (Found: C, 70·25; H, 7·75; N, 2·8%; M^+, 495·2610. $C_{29}H_{37}NO_6$ requires C, 70·3; H, 7·55; N, 2·85%; *M*, 495·2621).

Lythrancine-III (XVI).—Lythrancine-III (XVI) had m.p. 134—136° (from methanol), $[\alpha]_D$ +38° (*c* 1·1), $\nu_{max.}$ ($CHCl_3$) 3480 and 1723 cm^{-1}, $\lambda_{max.}$ 290 nm (ε 6200), δ 2·00 (3H, s, OAc), 2·03 (3H, s, OAc), 3·85 (6H, s, 2 × OMe), 4·17 (1H, t, *J* 7 Hz, 1-H), 4·99 (1H, sept, *J* 2, 7, and 10 Hz, 3-H), and 5·35 (1H, m, 11-H), *m/e* 537·2707 (M^+) ($C_{31}H_{39}NO_7$ requires 537·2727) (Found: C, 67·95; H, 7·15; N, 2·6. $C_{31}H_{39}NO_7$,0·5H_2O requires C, 68·1; H, 7·4; N, 2·55%).

Lythrancine-IV (XVII).—Lythrancine-IV (XVII) had m.p. 237—238° (from methanol), $[\alpha]_D$ +27° (*c* 1·1), $\nu_{max.}$ (KBr) 1735 cm^{-1}, $\lambda_{max.}$ 290 nm (ε 5800), δ 1·94 (6H, s, 2 × OAc), 2·06 (3H, s, OAc), 3·83 (3H, s, OMe), 3·88 (3H, s, OMe), 4·17 (1H, dd, *J* 4 and 11 Hz, 1-H), 4·91 [1H, narrow triplet, *J* 3 Hz, 4-H (H_x)], 5·15 (1H, octet, *J* 3, 6, and 11·5 Hz, 3-H), 5·35 (1H, m, 11-H) (Found: C, 68·15; H, 7·15; N, 2·2%; M^+, 579·2836. $C_{33}H_{41}NO_8$ requires C, 68·35; H, 7·15; N, 2·4%; *M*, 579·2832).

Lythrancepine-I (XVIII).—Lythrancepine-I (XVIII) had m.p. 149—151° (from ether), $[\alpha]_D$ +59° (*c* 0·98), $\nu_{max.}$ ($CHCl_3$) 3550 and 3380 cm^{-1}, $\lambda_{max.}$ 290 nm (ε 6300), δ 3·84 (6H, s, 2 × OMe), *m/e* 437·2565 (M^+) ($C_{27}H_{35}NO_4$ requires 437·2566) (Found: C, 70·15; H, 8·4; N, 2·95. $C_{27}H_{35}NO_4$,0·5H_2O requires C, 69·8; H, 8·25; N, 3·0%).

Lythrancepine-II (XIX).—Lythrancepine-II (XIX) had m.p. 187—189° (from chloroform–ether), $[\alpha]_D$ +44° (*c* 1·0), $\nu_{max.}$ (KBr) 3550 and 1725 cm^{-1}, $\lambda_{max.}$ 290 nm (ε 6000), δ 1·95 (3H, s, OAc), 3·84 (3H, s, OMe), 3·86 (3H, s, OMe), 4·02 (1H, dd, *J* 3 and 11 Hz, 1-H), and 5·33 (1H, m, 11-H) (Found: C, 72·0; H, 8·05; N, 2·6%; M^+, 479·2662. $C_{29}H_{37}NO_5$ requires C, 72·6; H, 7·8; N, 2·9%; *M*, 479·2672).

Lythrancepine-III (XX).—Lythrancepine-III (XX) had m.p. 175—177° (from ethanol), $[\alpha]_D$ +7° (*c* 0·23), $\nu_{max.}$ (KBr) 1730 cm^{-1}, $\lambda_{max.}$ 290 nm (ε 6800), δ 1·95 (3H, s, OAc), 1·98 (3H, s, OAc), 3·86 (3H, s, OMe), 3·88 (3H, s, OMe), 4·10 (1H, dd, *J* 2·5 and 11 Hz, 1-H), 5·05 (1H, m, 3-H), and 5·33 (1H, m, 11-H) (Found: C, 71·6; H, 8·0; N, 2·6%; M^+, 521·2801. $C_{31}H_{39}NO_6$ requires C, 71·35; H, 7·55; N, 2·7%; *M*, 521·2777).

Acetylation of Lythrancine-II.—(*a*) A solution of lythrancine-II (XV) (1·0 g) in acetic anhydride (10 ml) and pyridine (30 ml) was kept at room temperature for 2 h. After removal of the solvent *in vacuo*, the residue was chromatographed on silicic acid, and elution with dichloromethane afforded a crystalline mass (970 mg) of pure *O*-acetyl derivative, as needles, m.p. 133—135° (from methanol), which was identical with lythrancine-III (XVI).

(*b*) The compound (300 mg) in acetic anhydride–pyridine (1 : 5, 20 ml) was heated at 110° in an oil-bath for 3 h, cooled, and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and extracted with 5% hydrochloric acid. The aqueous acid solution was made alkaline with ammonium hydroxide, and extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4), and evaporated to afford the *OO*-diacetate as needles (270 mg), m.p. 232—233° (from methanol), which was identical with lythrancine-IV (XVII).

Hydrolysis of Lythrancine-II.—Lythrancine-II (XV) (50 mg) was dissolved in 1% methanolic potassium hydroxide (5 ml) and stirred for 2 h at room temperature. The mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to yield an oil (35 mg), identical with lythrancine-I (XIV) (t.l.c., i.r., and n.m.r.).

Acetylation of Lythrancepine-I.—To the solution of lythrancepine-I (XVIII) (50 mg) in pyridine (1 ml) a drop of acetic anhydride was added, and the mixture was left at room temperature for 5 h. After evaporation to dryness *in vacuo*, the residue was dissolved in benzene and extracted with 5% hydrochloric acid. The aqueous acid layer was made alkaline with ammonia and extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give viscous oil, which was crystallized from ethanol to give lythrancepine-I *OO*-diacetate (38 mg), m.p. 174—176° (from ethanol), identical with lythrancepine-III (XX).

Acetylation of Lythrancepine-II.—Acetylation of lythrancepine-II (XIX) (50 mg) by the foregoing procedure afforded lythrancepine-II *O*-acetate (37 mg), m.p. 174—178°, identical with lythrancepine-III (XX).

Hydrolyses of Lythrancepine-II and -III.—Lythrancepine-II (50 mg) was hydrolysed as described for lythrancine-II to afford lythrancepine-I (31 mg), m.p. 148—150° (from ether). Hydrolysis of lythrancepine-III (50 mg) in the same way gave lythrancepine-I (30 mg), m.p. 148—149°.

Tosylation of Lythrancine-III.—To a solution of lythrancine-III (XVI) (500 mg) in pyridine (2 ml) was added dropwise a solution of toluene-*p*-sulphonyl chloride (500 mg) in pyridine (3 ml). The mixture was stirred overnight at room temperature. The solvent was evaporated *in vacuo*, and the residue was dissolved in benzene and then extracted with 1% hydrochloric acid. The extract was made alkaline with ammonia and extracted with dichloromethane. After the extract was washed with water and dried (Na_2SO_4), the solvent was evaporated to afford lythrancine-III *O*-tosylate (420 mg) as prisms, m.p. 192—194° (from methanol), $\nu_{max.}$ ($CHCl_3$) 1732 and 1180 cm^{-1}, δ 1·68 (3H, s, OAc), 2·03 (3H, s, OAc), 2·40 (3H, s, ArMe), 3·86 (3H, s, OMe), 3·90 (3H, s, OMe), 4·12 (1H, dd, *J* 4 and 10 Hz, 1-H), 4·58 (1H, br s, 4-H), 5·02 (1H, m, 3-H), and 5·45 (1H, m, 11-H) (Found: C, 65·65; H, 6·75; N, 2·05. $C_{38}H_{45}NO_9S$ requires C, 65·95; H, 6·55; N, 2·05%).

Conversion of Lythrancine-III O-Tosylate into Lythrancepine-III (XX) *and its C-3 Epimer.*—To a solution of lithium aluminium hydride (500 mg) in dry tetrahydrofuran (10 ml), lythrancine-III *O*-tosylate (500 mg) in dry tetrahydrofuran (10 ml) was added dropwise with stirring at room temperature. After stirring at room temperature

for 5 h, the mixture was heated under reflux for 1 h. Usual work-up yielded a viscous oily mass (417 mg). T.l.c. [silica gel G, Stahl (Merck); dichloromethane–ethyl acetate (1 : 1)] of this oil showed 2 spots; it was acetylated with acetic anhydride (3 ml) and pyridine (10 ml) at 110° for 3 h. The solvent was evaporated to dryness *in vacuo*, and the residue was chromatographed (alumina; benzene) to give a crystalline mass (130 mg) of lythrancepine-III (XX) (86 mg), m.p. 176—177° (from ethanol). Subsequent elution with benzene–dichloromethane (1 : 1) afforded an oily mass (227 mg), which was rechromatographed (silicic acid; dichloromethane) to give a crystalline mass of 3-*epi*-lythrancepine-III, m.p. 180—180·5° (from ether), $\nu_{max.}$ (KBr) 1730 cm^{-1}, δ 1·98 (3H, s, OAc), 2·10 (3H, s, OAc), 3·88 (6H, s, 2 × OMe), 4·23 (1H, dd, *J* 4 and 10 Hz, 1-H), 4·99 (1H, t, *J* 2·5 Hz, 3-H), and 5·33 (1H, m, 11-H) (Found: C, 71·2; H, 7·6; N, 2·55. $C_{31}H_{39}NO_6$ requires C, 71·35; H, 7·55; N, 2·7%).

Cyclic Carbonate (XXI) *of Lythrancine-II*.—To a solution of lythrancine-II (300 mg) in pyridine (20 ml), a solution of phosgene in toluene (*ca.* 10%, 10 ml) was added dropwise with cooling in an ice-bath and stirring. After stirring at room temperature overnight, the mixture was poured onto ice–water and the aqueous solution was made basic with ammonium hydroxide and extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a dark brown residue (270 mg). The residue in dichloromethane was chromatographed (silicic acid; dichloromethane) to give needles (192 mg), m.p. >300° (from methanol–chloroform), $\nu_{max.}$ ($CHCl_3$) 1798 and 1725 cm^{-1}, δ 2·03 (3H, s, OAc), 3·88 (6H, s, 2 × OMe), 4·33 (1H, d, *J* 6 Hz, 4-H), 4·73 (1H, septet, *J* 6, 6, and 10 Hz, 3-H), and 5·38 (1H, m, 11-H) (Found: C, 68·9; H, 6·85; N, 2·65. $C_{30}H_{35}NO_7$ requires C, 69·1; H, 6·75; N, 2·7%).

Oxidation of Lythrancine-II (XV).—To a solution of lythrancine-II (XV) (2·2 g) in acetone (100 ml) was added Jones reagent (20 ml) at 0° and stirred at room temperature for 10 h. After decomposition of the excess of reagent with methanol, the mixture was evaporated to dryness *in vacuo*. To the residue was added methanol (150 ml) and conc. sulphuric acid (1 ml) and heated under reflux for 3 h. The mixture was evaporated to dryness *in vacuo*. The residue was dissolved in water and extracted with ethyl acetate. The organic layer was washed with 5% aqueous sodium carbonate and dried (Na_2SO_4). The solvent was evaporated and the residue (705 mg) in benzene was chromatographed on alumina. Elution with benzene afforded prisms of dimethyl 6,6′-dimethoxybiphenyl-3,3′-dicarboxylate (IV) (502 mg), m.p. 174—175° (needles from methanol). The aqueous acidic layer was made alkaline with 5% aqueous sodium carbonate and extracted with dichloromethane. Evaporation of the solvent gave a brown oil (205 mg), which was distilled under reduced pressure to afford methyl *trans*-6-methoxycarbonyl-2-piperidylacetate (V), an oil (106 mg), b.p. 110° at 3 mmHg, $\nu_{max.}$ ($CHCl_3$) 3300 and 1725 cm^{-1}, δ 2·40 (2H, d, *J* 6·5 Hz, CH_2·CO_2Me), 2·66 (s, NH), 3·20 (1H, m, 6-H), 3·70 (3H, s, OMe), and 3·75 (3H, s, OMe) (Found: M^+, 215·1138. $C_{10}H_{17}NO_4$ requires *M*, 215·1157).

N-*Methylation of the Ester* (V).—The compound (100 mg) was heated with 100% formic acid (1 ml) and 40% aqueous formaldehyde (1 ml) at 100°. After 6 h, the mixture was poured into water, made alkaline with aqueous sodium carbonate, and extracted with dichloromethane. Usual work-up afforded an oil (94 mg), which was chromatographed (silicic acid; dichloromethane) to give the *N*-methyl derivative (72 mg), $[\alpha]_D$ −45° (*c* 0·37), $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}, δ 1·30—1·95 (6H, m), 2·29 [1H, dd (AB of ABX), *J* 8·5 and 14·5 Hz], 2·36 (3H, s, *N*-Me), 2·66 [1H, dd (AB of ABX), *J* 5 and 14·5 Hz], 3·39 (1H, t, *J* 5 Hz, CH), 3·50 [H, m (ABX)], 3·66 (3H, s, OMe), and 3·70 (3H, s, OMe).

Oxidation of Lythrancepine-II (XV) *with Chromic Anhydride–Acetic Acid*.—To a solution of lythrancine-II (XV) (2·35 g) in aqueous 50% acetic acid (120 ml) was added chromic anhydride (5 g) under stirring at room temperature. The mixture was stirred at room temperature for 13 h. The excess of the reagent was decomposed with ethanol, and the mixture was evaporated to dryness *in vacuo*. The residue was dissolved in water, made alkaline with ammonium hydroxide, and extracted with dichloromethane. The extract was dried (Na_2SO_4) and evaporated. The residue (1·3 g) was chromatographed [silicic acid; dichloromethane–methanol; (1—3%)] to give a crystalline mass which was recrystallized from methanol to give compound (XXIII) as prisms (728 mg), m.p. 235—236°, $\nu_{max.}$ ($CHCl_3$) 3450, 1725, and 1670 cm^{-1}, $\lambda_{max.}$ 286 (ε 17,300) and 245 nm (17,000), δ 2·10 (3H, s, OAc), 3·98 (3H, s, OMe), 4·07 (3H, s, OMe), 4·22 (1H, dd, *J* 3 and 12 Hz, 1-H), and 5·98 (1H, m, 11-H) (Found: C, 67·85; H, 7·0; N, 2·7. $C_{29}H_{35}NO_7$ requires C, 68·35; H, 6·9; N, 2·75%).

Jones Oxidation of Lythrancine-III (XVI).—To a solution of lythrancine-III (XVI) (276 mg) in acetone (5 ml) was added dropwise Jones reagent (1 ml) at 0° under stirring. The mixture was stirred at room temperature for 2·5 h. After decomposition of the excess of reagent with methanol, the mixture was evaporated *in vacuo*, diluted with water, made alkaline with ammonium hydroxide, and extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue (170 mg) was chromatographed (silicic acid; dichloromethane) to give a crystalline mass, which was recrystallized from ether to afford a monoketone (45 mg), m.p. 135—136°, $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}, δ 1·94 (3H, s, OAc), 2·08 (3H, s, OAc), 3·87 (6H, s, 2 × OMe), 4·47 (1H, dd, *J* 2 and 11·5 Hz, 1-H), 5·36 (1H, br t, *J* 5 Hz, 11-H), and 5·55 (1H, dd, *J* 7 and 14 Hz, 3-H) (Found: C, 69·2; H, 7·25; N, 2·5%; M^+, 535·2569. $C_{31}H_{37}NO_7$ requires C, 69·5; H, 6·95; N, 2·6%; M^+, 535·2570). Continued elution with the same solvent afforded the diketone (XIIIb) (63 mg), m.p. 161—162° (from ether), $\nu_{max.}$ ($CHCl_3$) 1730 and 1670 cm^{-1}, $\lambda_{max.}$ 285 (ε 17,000) and 245 nm (18,000), δ 1·96 (3H, s, OAc), 2·08 (3H, s, OAc), 3·89 (3H, s, OMe), 3·94 (3H, s, OMe), 4·53 (1H, dd, *J* 2·5 and 11 Hz, 1-H), 5·58 (1H, dd, *J* 6·5 and 13 Hz, 3-H), and 5·80 (1H, m, 11-H) (Found: C, 67·5; H, 6·5; N, 2·55. $C_{31}H_{35}NO_8$ requires C, 67·75; H, 6·4; N, 2·55%).

Reduction of Dehydrolythrancine-III with Sodium Borohydride.—Sodium borohydride (60 mg) was added to the solution of the monoketone (100 mg) in methanol (10 ml) at 0° and stirred for 1 h with cooling in an ice–water bath. Usual work-up afforded a viscous oil (97 mg), which was chromatographed on silicic acid. Elution with dichloromethane–methanol (1%) gave needles (11 mg), m.p. 274—275° (from methanol), which were identified as lythrancine-II (XV). Elution with dichloromethane–methanol (3%) afforded an oil (77 mg), $\nu_{max.}$ ($CHCl_3$) 3550, 3400, and 1725 cm^{-1}, δ 1·96 (3H, s, OAc), 3·85 (6H, s, 2 × OMe), 4·07 (1H, dd, *J* 2 and 12 Hz, 1-H), and 5·30 (1H, m, 11-H). This oil (70 mg) was dissolved in pyridine (3 ml) and acetic anhydride (10 drops) and left at room temperature for 40 h.

After evaporation *in vacuo*, the residue was crystallized from methanol. Recrystallization from methanol and ethyl acetate gave 4-*epi*-lythrancine-IV, m.p. 235—236°, $\nu_{max.}$ (KBr) 1735 cm^{-1}, δ 1·95 (3H, s, OAc), 2·01 (3H, s, OAc), 2·06 (3H, s, OAc), 3·88 (6H, s, 2 × OMe), 4·13 (1H, dd, J 3 and 12 Hz, 1-H), 4·95 (2H, m, 3- and 4-H), and 5·50 (1H, m, 11-H) (Found: C, 67·9; H, 7·25; N, 2·4. $C_{33}H_{41}NO_8$ requires C, 68·35; H, 7·15; N, 2·4%).

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