Lythraceous Alkaloids. Part 11.[1] Total Synthesis of (±)-Lythranidine[2]

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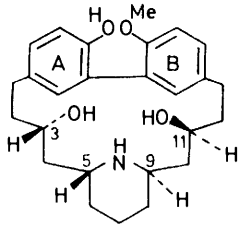
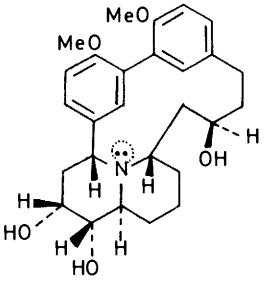
The total synthesis of (±)-lythranidine (1), a cyclophane alkaloid from *Lythrum anceps* Makino, has been achieved through a sequence of reactions including the following key steps: the Wittig reaction of an ylide (6) with a dialdehyde (3), epimerisation of a *cis*-2,6-disubstituted piperidine into the desired *trans*-isomer through the *N*-nitroso-derivative (11), amidoacetalisation of a mixture of stereoisomeric diols (12) to isolate the desired compound (13), and its partial demethylation followed by hydrolysis.

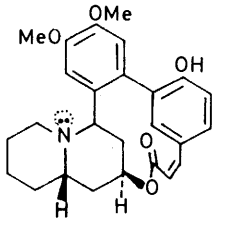
OVER forty alkaloids[3] have been isolated from the Lythraceae family of plants. They have been classified into five main structural types, A—E, representative alkaloids of which are shown in the Scheme.



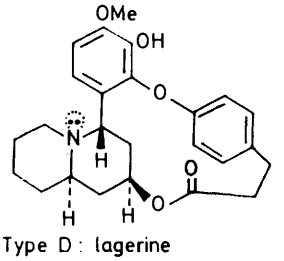
Type A : lythranidine (1)



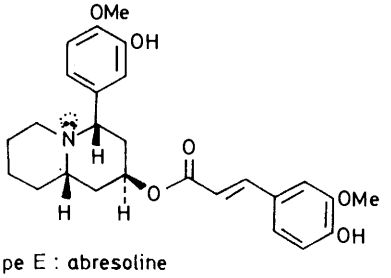
Type B : lythrancine - I



Type C: lythrine



Type D : lagerine



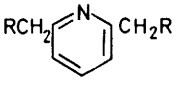
Type E : abresoline

SCHEME

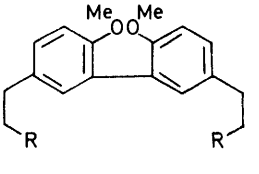
Although several alkaloids of types C—E have been synthesised,[4] no synthesis of a type A or B alkaloid has heretofore been reported.[5] We now describe the first total synthesis of the type A alkaloid, lythranidine (1). Lythranidine has previously been isolated from *Lythrum anceps* Makino (Japanese name ' Misohagi ') and its structure and absolute configuration elucidated.[6]

From a synthetic point of view, a total synthesis of the target molecule involves three interesting problems. These are the construction of the 17-membered ring, the formation of the *trans*-2,6-disubstituted piperidine ring, and the establishment of the correct relative stereochemistry at the four asymmetric centres in the mobile macrocyclic ring system. Consideration of the retrosynthesis of lythranidine (1) led to the conclusion that simultaneous formation of the bonds between C-3 and -4, and C-10 and -11 would be most pertinent for constructing the 17-membered ring. Thus, 2,6-bis(chloromethyl)pyridine (2) was adopted as a starting material for the lower part and 6,6'-dimethoxybiphenyl-3,3'-dipropionaldehyde (3) as that for the upper part of the molecule. The latter was obtained from the corresponding diol (4) [6b] by oxidation with chromic anhydride and pyridine in 76% yield.

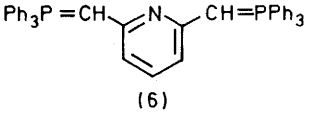
Treatment of 2,6-bis(chloromethyl)pyridine (2) with three equivalents of triphenylphosphine in refluxing



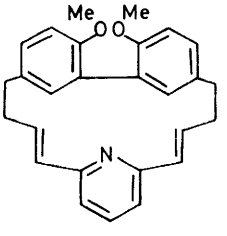
(2) R = Cl
(5) R = $\overset{+}{P}Ph_3$



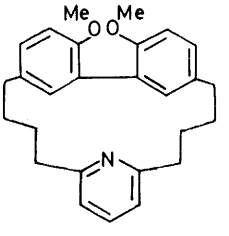
(3) R = CHO
(4) R = CH_2OH



(6)



(7)



(8)

dimethylformamide afforded the bisphosphonium salt (5), which on treatment with sodium hydride in dichloromethane gave the ylide (6). Wittig reaction of the dialdehyde (3) with (6) under high dilution conditions yielded the cyclophane (7) as fine crystals in 76% yield. On dehydrogenation over palladium–charcoal, compound

(7) afforded a tetrahydro-derivative (8), identical with an authentic specimen,[6b] thus accomplishing the synthesis of the 17-membered ring.

The observation of Fraser *et al.*[7] that *N*-nitroso-*trans*-2,6-disubstituted piperidine derivatives are thermodynamically more stable than the corresponding *cis*-isomers was effectively applied to solve the second problem. Thus, the diepoxide derived from reaction of (7) with *m*-chloroperbenzoic acid was hydrogenolysed over palladium–charcoal; subsequent acetylation with acetic anhydride–triethylamine gave (9) in 70% overall yield from (7). The pyridine derivative (9) on hydrogenation over Raney Ni under high pressure gave the *cis*-2,6-disubstituted piperidine derivative (10) in 98% yield. Its *N*-nitroso-derivative (11) on equilibration with potassium t-butoxide in dimethyl sulphoxide at 90 °C for 60 h under nitrogen, followed by denitrosation over Raney Ni[8] and hydrolysis, gave a mixture of stereoisomeric diols (12). An amorphous fraction having the same R_F value as *O*-methyl-lythranidine on t.l.c., collected by chromatography on an alumina column, was treated with toluene-*p*-sulphonic acid and ethyl orthoformate to give the racemic amidoacetal (13) in 14% overall yield from (10). Comparison of the i.r. and n.m.r. spectra and t.l.c. of the racemic amidoacetal (13) with those of the amidoacetal[6a] derived from natural lythranidine confirmed the correct stereochemistries at the four asymmetric carbons of the synthetic material. Thus, the foregoing second and third problems were solved.

Amidoacetalisation proved to be a remarkably useful method for isolating the compound with the correct stereochemistry from a complex mixture of stereoisomers. There are two possible stereoisomers * in the amidoacetal (13) involving either a *cis* or *trans* A–B ring junction. A Dreiding model revealed that the isomer having A–B *cis*-stereochemistry should be more stable than the corresponding *trans*-isomer, because all three 6-membered heterocyclic rings can exist in chair forms with both the bulky substituents at C-3 and -11 assuming equatorial positions. The total number of theoretically possible stereoisomers of (12) is sixteen. If one fixes the stereochemistry at C-3 as *S*, the possible stereoisomers are those shown schematically in the Figure.

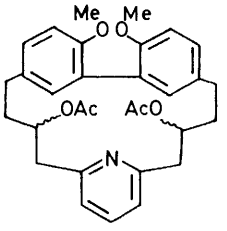
Isomer b is identical with isomer c and isomer e is identical with the mirror image of isomer h. Accordingly, four racemates (a, b, d, and e, and their enantiomers) and two *meso*-isomers can (f and g) exist. The piperidine derivative (10), derived from (9), is expected to be a mixture of isomers b, f, and g, but containing isomer b predominantly, since epoxidation of the symmetric compound (7) should be in favour of yielding the isomer in which two epoxide rings are *trans* to each other. The 5,9-*cis*-piperidine b should give the *trans*-isomers a and d by *cis*-trans isomerisation, while the *cis*-isomers f and g should give the *trans*-isomer e. Therefore, the relative amounts of isomers b, e, f, and g would be expected to be smaller than those of a and d.[7] In this step, a fraction having the same R_F value as *O*-methyl-lythranidine, the stereochemistry of which corresponded to d, was collected as described above. Close inspection of the Dreiding models of the corresponding amidoacetals derived from isomers a and d revealed that an amidoacetal with a *cis* A–B junction derived from d is the thermodynamically most stable one. As described earlier, the amidoacetal with a *cis* A—B junction derived from d is (13) itself. Thus, the reason why only the isomer having the correct stereochemistry was conveniently isolated from the complex mixture can be logically explained.

In the course of studies in our laboratory on the synthesis of C_{20}-gibberellins the ethanedithiol and boron trifluoride–ether system was found to be effective in cleaving aliphatic ethers.[9] This reagent system has also

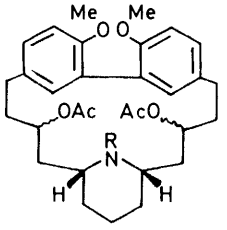
Position of carbon atoms

3 \ 5	11 \ 9	a	b	c	d*	e	f	g	h
		S \ S	S \ S	S \ S	S \ R	S \ R	S \ S	R \ S	R \ R
		S \ R	R \ S	R \ R	S \ S	S \ R	R \ S	R \ R	S \ S

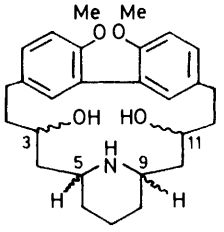
Possible stereoisomers of the diol (12) with *S*-configuration at C-3
* The stereochemistry of lythranidine.



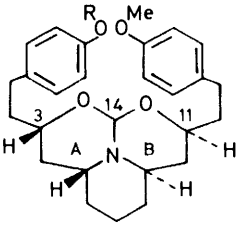
(9)



(10) R = H
(11) R = NO



(12)



(13) R = Me
(14) R = H

* The A–B *cis*-isomer having β-configuration at both 14-H and the lone pair on the nitrogen atom is the same compound as that having α-configuration at both centres. Similarly, the two possible isomers having A–B *trans*-junctions are the same.

been efficiently employed for the removal of benzyl protecting groups.[10] Changing the Lewis acid from boron trifluoride–ether to aluminium chloride or bromide affords a more effective reagent system which can cleave even aromatic methyl ethers.[11] Accordingly, the partial demethylation of the amidoacetal (13) was performed using aluminium chloride in ethanethiol under which conditions the reaction took place smoothly and afforded the desired product (14). Finally, compound (14), on hydrolysis with 20% hydrochloric acid followed by treatment with glacial acetic acid in benzene gave a crystalline material, m.p. 136—137°, in 45% overall yield from (13), the i.r. (in chloroform) and n.m.r. spectra of which were identical with those of the acetic acid salt of natural lythranidine.[12] The total synthesis of (±)-lythranidine was thus accomplished.

EXPERIMENTAL

M.p.s were taken on a Yanagimoto micro hot-stage. I.r. spectra were recorded on a Hitachi model EPI-S_2 spectrophotometer, n.m.r. spectra with a Varian A-60 or a JEOL JNM-FX 100 spectrometer, and mass spectra on a JEOL JMS-OISG double-focusing mass spectrometer. Merck Kieselgel (0.05—0.2 mm) or Woelm neutral aluminium oxide was used for column chromatography.

6,6′-Dimethoxybiphenyl-3,3′-dipropionaldehyde (3).—To a stirred mixture of pyridine (12 ml) and chromic anhydride (7.5 g) in dichloromethane (170 ml) was added a solution of 6,6′-dimethoxybiphenyl-3,3′-di(propan-3-ol) (4) [6b] (2.03 g) in one portion at 0 °C. After being stirred for 15 min, the solution was washed with 5% aqueous NaOH (× 3), 10% aqueous HCl (× 3), 5% aqueous $NaHCO_3$, and brine (× 3), then dried (Na_2SO_4) and evaporated. Column chromatography of the residue gave the *dialdehyde* (3) as an oil (1.52 g, 76%) (Found: C, 73.5; H, 6.8. $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.8%), $\nu_{max.}$ ($CHCl_3$) 1 724, 1 605, and 1 504 cm^{-1}; δ($CDCl_3$) 2.84 (8 H, m), 3.72 (6 H, s), 6.83—7.23 (6 H, m), and 9.83 (2 H, t, *J* 1.4 Hz).

The Bisphosphonium Salt (5).—A mixture of 2,6-bis-(chloromethyl)pyridine (2) (1.76 g) and triphenylphosphine (6.55 g) was heated under reflux in dimethylformamide for 10 h. The solvent was evaporated off under reduced pressure to give a crystalline residue which was recrystallised from chloroform–benzene to afford the bisphosphonium salt (5) (6.0 g, 98%), m.p. 280—282°, $\nu_{max.}$ ($CHCl_3$) 1 589, 1 488, and 1 439 cm^{-1}; δ($CDCl_3$) 5.45 (4 H, d, *J* 15 Hz), and 7.29—8.00 (33 H, m).

The Seventeen-membered Ring Compound (7).—To a stirred solution of the bisphosphonium salt (5) (43 mg) in anhydrous dichloromethane (5 ml) was added sodium hydride (50% dispersion in oil, 14 mg) under nitrogen and the mixture was heated under reflux for 30 min. After addition of further dichloromethane (40 ml), a solution of the dialdehyde (3) (20 mg) in anhydrous dichloromethane (5 ml) was added. The resulting solution, after refluxing for 8 h, was filtered, and the filtrate was evaporated to give an oil (50 mg), which was chromatographed (silica gel, benzene) to give *compound* (7) (21 mg, 76%), m.p. 230—232° (from CCl_4) (Found: C, 81.6; H, 6.9; N, 3.2. $C_{27}H_{27}NO_2$ requires C, 81.6; H, 6.9; N, 3.5%), $\nu_{max.}$ ($CHCl_3$) 1 650, 1 614, 1 561, and 1 499 cm^{-1}; δ($CDCl_4$) 2.30—3.10 (8 H, m), 3.71 (6 H, s), 6.28 (2 H, d, *J* 15 Hz), and 6.49—7.50 (11 H, m).

Hydrogenation of Compound (7).—Compound (7) (15 mg) was hydrogenated over 5% Pd–charcoal (5 mg) in methanol (5 ml). Column chromatography (silica gel, benzene–dichloromethane) gave (8) (9 mg, 60%), m.p. 155—156° (lit.,[6b] 154.5—156.5°).

The Amidoacetal (13).—Compound (7) (145 mg) was oxidised with *m*-chloroperbenzoic acid (251 mg) in dichloromethane. Usual work-up gave an oil (150 mg), which was hydrogenolysed over 5% Pd–charcoal (30 mg) in methanol (10 ml). The oily product (152 mg) was acetylated with acetic anhydride (1.5 ml) and triethylamine (1.5 mg) was acetylated with acetic anhydride (1.5 ml) and triethylamine (1.5 ml) at 80 °C for 6 h to afford the diacetate (9) as an oil (132 mg), $\nu_{max.}$ ($CHCl_3$) 1 724 cm^{-1}; *m/e* 575 (M^+).

The diacetate (9) (132 mg) was hydrogenated over PtO_2 (5 mg) and Raney Ni (W-2) in methanol (25 ml) at 60 °C under 20 atm overnight to give (10) as an oil (132 mg) which was treated with isopentyl nitrite (1 ml) in dichloromethane (2 ml) for 6 h at room temperature. Evaporation of the solvent followed by chromatography (silica gel, dichloromethane) afforded (11) as an oil (99 mg), $\nu_{max.}$ ($CHCl_3$) 1 730 and 1 450 cm^{-1}, *m/e* 610 (M^+).

A mixture of the nitroso-derivative (11) (82 mg) and Bu^tOK (90 mg) in dimethyl sulphoxide (1 ml) was stirred for 60 h at 90 °C under nitrogen. Work-up and chromatography over silica gel afforded an oil (54 mg). Denitrosation by hydrogenolysis of the oil in methanol (10 ml) over Raney Ni (W-2) under 30 atm overnight gave an oil which was hydrolysed by stirring in methanol–5% aqueous KOH (10 ml; 1 : 1 v/v) overnight. An oily product (40 mg) obtained after usual work-up was subjected to chromatography over alumina. Dichloromethane–methanol eluted a substance (14 mg) having the same R_F-value as *O*-methyl-lythranidine. A mixture of this substance (14 mg), ethyl orthoformate (2 ml), and toluene-*p*-sulphonic acid (4 mg) was heated under reflux for 4 h. After cooling, the reaction mixture was diluted with benzene (50 ml) and washed successively with 5% aqueous KOH (× 2) and brine (× 3), dried, and evaporated. Chromatography (silica gel, dichloromethane–methanol; 19 : 1 v/v) of the residue afforded the *amidoacetal* (13) (6 mg), m.p. 240—241.5° (from dichloromethane–methanol–isopropyl ether) (Found: C, 74.9; H, 7.9; N, 3.1. $C_{28}H_{35}O_4N$ requires C, 74.8; H, 7.9; N, 3.1%), $\nu_{max.}$ ($CHCl_3$) 1 610, 1 580, and 1 500 cm^{-1}; δ($CDCl_3$) 3.79 (3 H, s), 3.83 (3 H, s), 4.02br (2 H, m), 5.25 (1 H, s), and 6.70—7.59 (6 H, m). The spectroscopic data were identical with those of the amidoacetal derived from natural lythranidine.[6a]

Acetic Acid Salt of (±)-*Lythranidine*.—To a solution of ethanethiol (2 ml) and anhydrous aluminium chloride (26 mg) in dichloromethane (10 ml) was added a solution of the amidoacetal (13) (13 mg) in a small amount of dichloromethane at −10 °C and stirred for 10 min. Usual work-up gave compound (14) as a crude oil (11 mg), δ ($CDCl_3$) 3.93 (3 H, s) and 5.33 (1 H, s); *m/e* 435 (M^+).

To a methanolic solution of (14) (10 mg in 2 ml) was added 20% HCl (2 ml) and the mixture was heated at reflux for 6.5 h. The mixture was basified with aqueous Na_2CO_3, and extracted with dichloromethane. The organic layer was dried and evaporated to give an oil (9 mg) which was dissolved in benzene (5 ml). Addition of glacial acetic acid (5 drops) to the solution resulted in the formation of the acetic acid salt of (±)-lythranidine (1) (5 mg), m.p. 136—137° (from acetone), $\nu_{max.}$ ($CHCl_3$) 3 350, 1 586, and 1 501 cm^{-1}; δ ($CDCl_3$) 1.41 (3 H, s), 3.85 (3 H, s), 4.09 (2 H, m), and 6.63—7.74 (6 H, m). These spectroscopic data were

identical with those of the acetic acid salt of natural lythranidine.[12]

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