[Chem. Pharm. Bull. 32(1) 55—62 (1984)]

Lythraceous Alkaloids. XII.[1] Circular Dichroism Studies on Lythranine-Type Alkaloids

KAORU FUJI,*,[a] TOSHIHIDE YAMADA,[a] EIICHI FUJITA,[a]
KAORU KURIYAMA,*,[b] TATSUO IWATA,[b] MOTOO SHIRO[b]
and HIROSHI NAKAI[b]

Institute for Chemical Research, Kyoto University,[a] Uji, Kyoto 611, Japan
and Shionogi Research Laboratories, Shionogi & Co., Ltd.,[b]
Fukushima-ku, Osaka 553, Japan

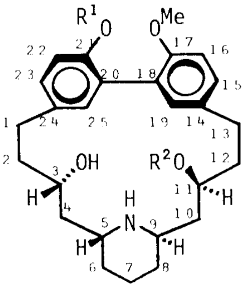
(Received May 16, 1983)

The circular dichroism (CD) spectra of Lythraceae alkaloids and their derivatives having a mobile biphenyl moiety were measured. The conformational chirality of the biphenyl system in these derivatives can be determined from the Cotton effects in the 200—240 nm region. The biphenyl system of *M* helicity showed a positive Cotton effect at long wavelength coupled with a negative Cotton effect at short wavelength, and *vice versa* for *P* helicity. Single crystal X-ray analyses of *O*-methyllythranidine *N,O,O*-triformate (**17**) and *O*-methyldeacetyl-lythranine (**20**) provided support for this conclusion.

Keywords—CD; Lythraceae; lythranine; piperidine alkaloid; biphenyl; cyclophane; atropisomerism; conformational chirality

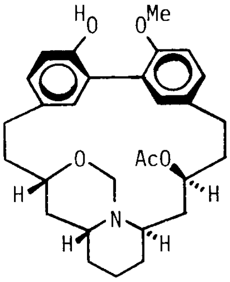
Over forty alkaloids have been isolated from Lythraceous plants in the past twenty years.[2] They can be divided into piperidine alkaloids (type A) and quinolizidine alkaloids (types B—E).[3] Only three alkaloids, lythranine (**1**), lythranidine (**2**), and lythramine (**3**), belong to the former group. The unique structure of type A alkaloids involving heteraphane[4] of *meta*, *meta*-biphenylene type, was determined more than ten years ago.[5] The biphenyl system in the type C alkaloids represented by lythridine (**4**) has been considered to be inherently dissymmetric[6] and the chirality has been determined by comparison of the circular dichroism (CD) curves with those of the dihydrothebaine derivatives **5** and **6**, in which the chirality of the biphenyl system had been conclusively determined by Berson.[7] The biphenyl moiety in type A alkaloids should exist as an equilibrium mixture of rotamers **7a** and **7b** in solution, since it is known that two methoxyl groups at the *ortho*-position of biphenyls are not bulky enough to allow the existence of each atropisomer.[8,9] The population of rotamers **7a** and **7b** must be somewhat biased because of the difference in their relative stability determined by the four asymmetric carbon atoms (C-3, C-5, C-9, and C-11) and the conformation of the macrocyclic ring. Consequently, the biphenyl system in these alkaloids acquires a chiral character (conformational chirality)[10] and causes chiroptical properties. In the present study, we undertook the measurement of the CD spectra of these alkaloids and their derivatives with the aim of obtaining an unambiguous correlation between the CD curve and the conformational chirality of the biphenyl group.

The hydrobromide ethanol solvate of bromolythranine (**8**) is a suitable reference compound because its absolute structure including the *M* helicity of the biphenyl group has been resolved by an X-ray analysis.[11] The CD curves of **8** in different solvents (Fig. 1) showed enormous changes in the region above 260 nm, because the pattern in this region is very sensitive to slight changes of torsional angle between the two benzene planes due to conformational change of the macrocyclic ring in the molecule. On the other hand, the spectra

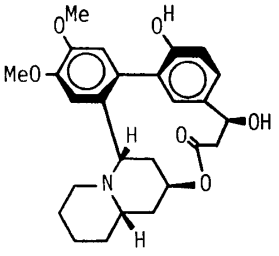


1: $R^1=H$, $R^2=Ac$

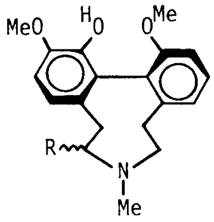
2: $R^1=R^2=H$



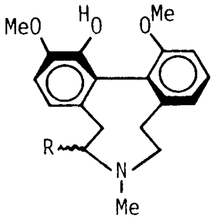
3



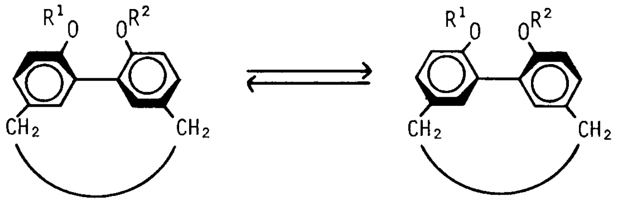
4



5: R = Me, Ph



6: R = Me, Ph

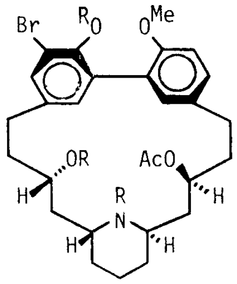


7a **7b**

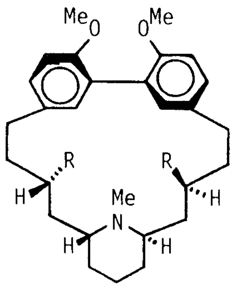
Chart 1

in the 200—240 nm region were essentially invariant, which means that the pattern in this region will not change unless the conformational chirality is reversed.[12] Thus, the spectrum in the 200—240 nm region is most reliable for determination of the chirality of a conformationally mobile biphenyl moiety. The CD curves of pertinent salts of lythranine (**1**), lythranidine (**2**), and lythramine (**3**) showed a positive Cotton effect at about 230 nm and a negative CD band at about 215 nm which corresponded to that of the standard compound **8** (see Experimental). Therefore, the favored chirality of the biphenyl group in these molecules was assigned as *R* (*M* helicity). The biphenyl group in compounds **9**—**16** has the same conformational chirality as in the natural alkaloids, because a similar type of CD pattern was observed with a slight change of intensity at each Cotton effect. Compounds **17** and **18** showed the completely opposite pattern of the CD curve between 200 and 240 nm, indicating *P* helicity of the biphenyl group in these molecules. A three dimensional single-crystal X-ray analysis[14] provided evidence that **17** has the biphenyl moiety with *P* helicity in the crystalline state, which coincides with the result obtained from the CD data. It was concluded that compounds **19** and **20** had the biphenyl group with *P* helicity because the CD curves showed the same trends as seen with **17** and **18** in the 200—240 nm region, though the negative band was slightly shifted to longer wavelength. An X-ray crystal structure determination of **20** supported this conclusion.[14]

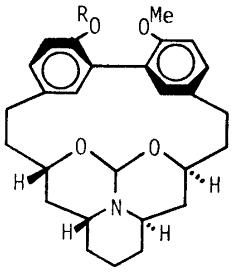
Compounds having an oxaquinolizidine ring (lythramine type) in the molecule have an *M* biphenyl moiety when the hydroxyl group at C-11 is acylated (**3**, **13**, **14**, and **15**), but a *P* biphenyl group when it is free (**19** and **20**). In the case of compounds having a piperidine ring, the biphenyl moiety has *P* helicity when both the hydroxyl groups at C-3 and C-11 are acylated (**17** and **18**), while *M* helicity is assigned to the biphenyl group when one or both of the substituents at C-3 and C-11 is a hydroxyl group (**1**, **2**, **8**, and **10**) or a group less bulky than the hydroxyl (**9**). The facts mentioned above indicate that the chirality of the biphenyl moiety can be easily reversed at room temperature by changing the substituents at the asymmetric carbon atoms. It is, therefore, concluded that the observed Cotton effects of these compounds are not attributable to atropisomerism due to restricted rotation of the biphenyl group, but are caused by the biased population of enantiomeric conformations of the



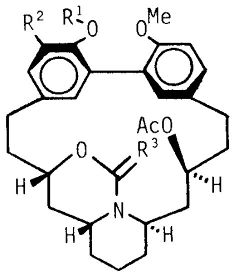
8 : R=H
22 : R=Ac



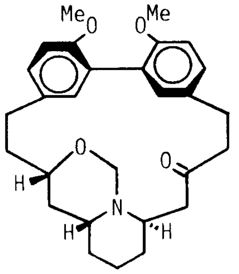
9 : R=H
10 : R=OH



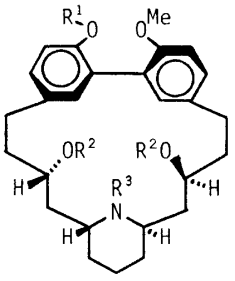
11 : R=Me
12 : R=H



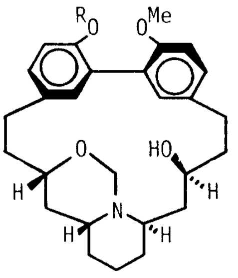
13 : R^1=Me, R^2=H, R^3=H_2
14 : R^1=H, R^2=Br, R^3=H_2
15 : R^1=R^2=H, R^3=O



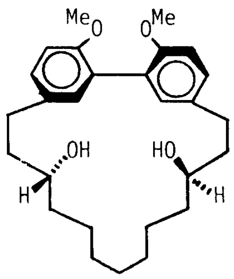
16



17 : R^1=Me, R^2=R^3=CHO
18 : R^1=R^2=Ac, R^3=H



19 : R=H
20 : R=Me



21

biphenyl group determined by other chiral centers in the mobile molecule.

Mislow *et al.*[15)] reported that the chirality of inherently dissymmetric biphenyls could be determined from the Cotton effect of the optically active transition (conjugation band) near 245 nm. The intensity of this Cotton effect is very sensitive to the torsional angle of biphenyls. In the case of biphenyls with a large torsional angle, it is quite difficult to determine the absolute sense of twist of the biphenyls because the Cotton effect in this region is accompanied by a Cotton effect of greater amplitude at shorter wavelength. The Cotton effect corresponding to the conjugation band was not observed in the CD curves of **9**, **10**, and **11** in EPA (a mixed solvent of ether, isopentane, and ethanol in the ratio of 5 : 5 : 2) at room temperature. However, such a band was clearly observed as the temperature was decreased (Figs. 2a—c), demonstrating *M* helicity of the biphenyl group, in accord with our conclusion. The macrocyclic compound **21** was assigned *P* helicity from the CD curve in the 200—230 nm region and *M* helicity from the sign of the conjugation CD band (Fig. 2d). The possibility of

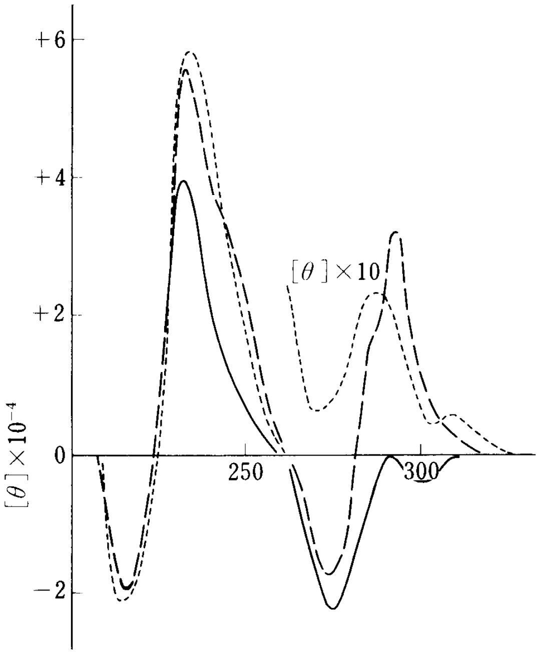


Fig. 1. CD Curves of the Hydrobromide of the Ethanol Solvate of 22-Bromolythranine (**8**)

——, methanol; ------, dioxane; –·–·–, acetonitrile.

the biphenyl group having a torsional angle of more than 90° in **21** cannot be excluded because **21** possesses a long ansa-chain in the molecule. These discrepancies remain to be resolved.

Assuming that compounds **9**, **10**, **11**, and **21** exist in two equilibrating conformations, **7a** and **7b**,16) the free energy difference between the conformations was calculated and the results are listed in Table I. It is clear that the most important factor deciding the conformational chirality of the biphenyl group is the existence of a piperidine ring, because the energy difference in **21**, where the piperidine ring is absent, is extremely small.

The CD curve of compound **22** in methanol was very similar to that of η-methyldihydrothebaine **6** (R = Me) perchlorate,6) and from this it can be concluded that the chirality of the biphenyl system in **22** is the same as that of **6** (R = Me), that is, *M* helicity. This is supported by the temperature change of the Cotton effect of the conjugation band (see Experimental). The CD band at *ca.* 250 nm in EPA is difficult to detect at room temperature but becomes large at −190 °C. The strong positive CD at low temperature indicates that the population of conformers with *M* helicity will increase on cooling of the solution, and the torsional angle between the benzene rings in the most stable conformation should not be large. This has been confirmed by X-ray crystallography. The crystal data are listed in Table II and a perspective view of **22** is shown in Fig. 3. The biphenyl moiety has *M* helicity, and the torsional angle between the mean planes of the benzene rings is 59.2°.

In conclusion, the biphenyl moiety in Lythraceae alkaloids of type A and their derivatives can be assigned on the basis of the Cotton effects in the 200—240 nm region and also the sign of the Cotton effect of the conjugation band at *ca.* 250 nm.

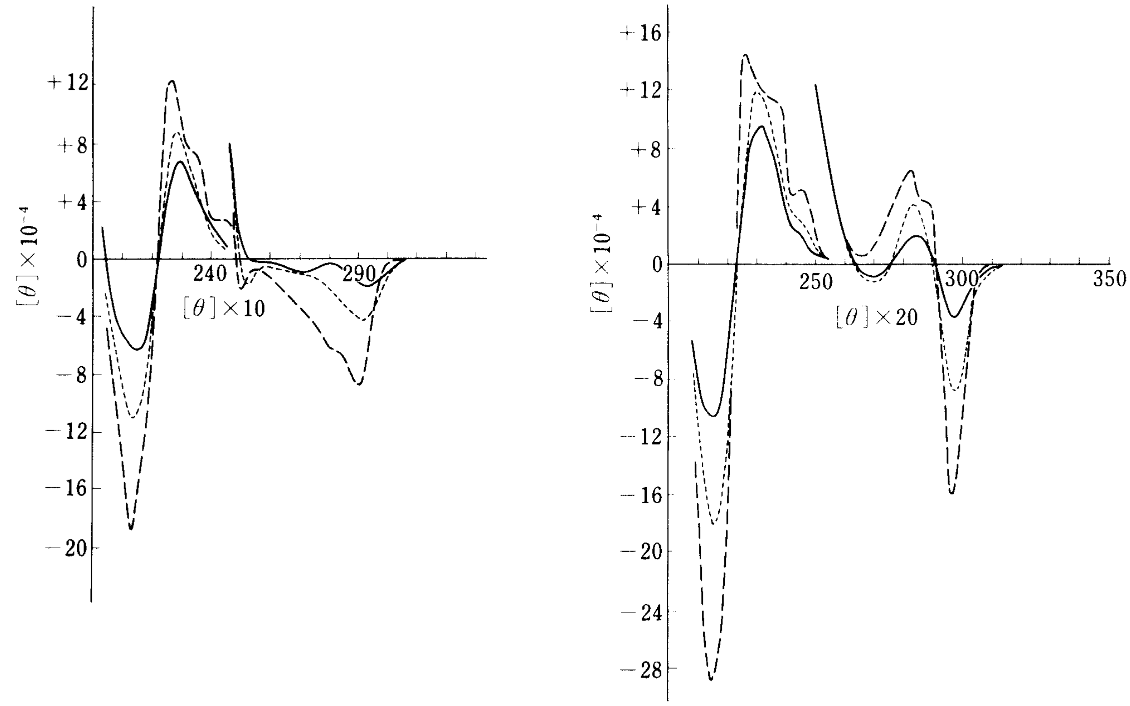
Experimental

Melting points are uncorrected. Infrared (IR) spectra were measured with a Hitachi EPI-S$_2$ spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Varian T-60 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane.

Compounds **9**—**13** and **16**—**21** have been reported elsewhere.17,18)

22-Bromolythramine (14)——A dilute solution of bromine in carbon tetrachloride was added to a solution of lythramine (**3**) (100 mg) in a mixture of carbon tetrachloride (5 ml) and chloroform (2 ml) at room temperature until

(a) bisdesoxy-*N*,*O*-dimethyllythranidine (**9**) (b) *N*,*O*-dimethyllythranidine (**10**)



(c) *O*-methyllythranidine amidoacetal (**11**) (d) diol **21**

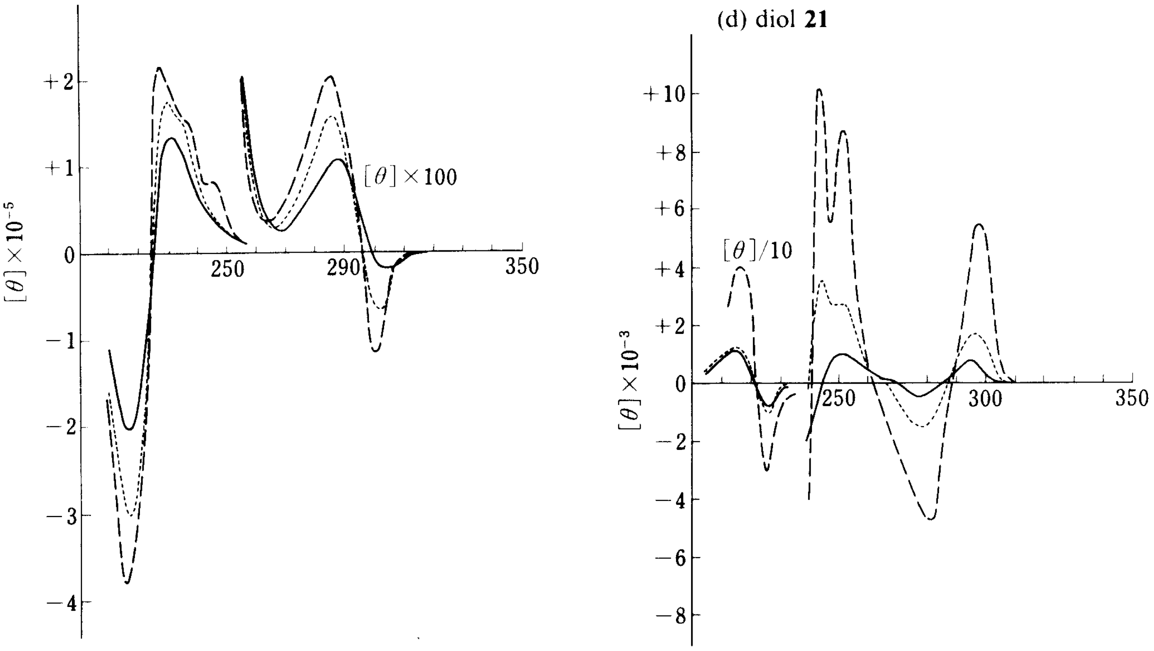


Fig. 2. Temperature-Dependent CD Spectra in EPA

——, +22 °C; ------, −68 °C; – – –, −190 °C.

an orange color persisted in the solution for a few minutes. Usual work-up gave **14** (70 mg), mp 184—186 °C (from acetone). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3300, 1730, 1505. *Anal.* Calcd for $C_{29}H_{36}BrNO_5$: C, 62.38; H, 6.50; N, 2.51. Found: C, 62.50; H, 6.57; N, 2.28.

Preparation of 15——A toluene solution of phosgene (10 ml) was added to a solution of lythranine (**1**) (300 mg) in pyridine (20 ml) under ice-cooling, and the mixture was stirred overnight at room temperature. Usual work-up and purification by column chromatography on silica gel afforded **15** (105 mg), mp 133—135 °C (from methanol). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3650, 1720, 1670, 1500. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, s), 3.87 (3H, s), 4.98 (1H, m), 6.85—7.30 (6H, m). *Anal.* Calcd for $C_{29}H_{35}NO_6$: C, 70.57; H, 7.15; N, 2.84. Found: C, 70.46; H, 7.15; N, 2.71.

Table I. Free Energy Differences between the Two Rotamers

Compound	ΔG^0 (kcal/mol)
9	0.7
10	0.8
11	1.0
21	0.2

Table II. Molecular Dimensions Relevant to the Biphenyl Moiety in 22-Bromolythranine *N,O,O*-Triacetate (**22**)

Dihedral angle between the mean planes of the benzene rings (°)	59.0
Torsion angle (°)	
C(19)–C(18)–C(20)–C(25)	−53.9
Interatomic distance (Å)	
C(18)–C(20)	1.480
Bond angle (°)	
C(17)–C(18)–C(20)	125.6
C(19)–C(18)–C(20)	115.6
C(17)–C(18)–C(19)	118.7
C(18)–C(20)–C(21)	124.7
C(18)–C(20)–C(25)	117.5
C(21)–C(21)–C(25)	117.3

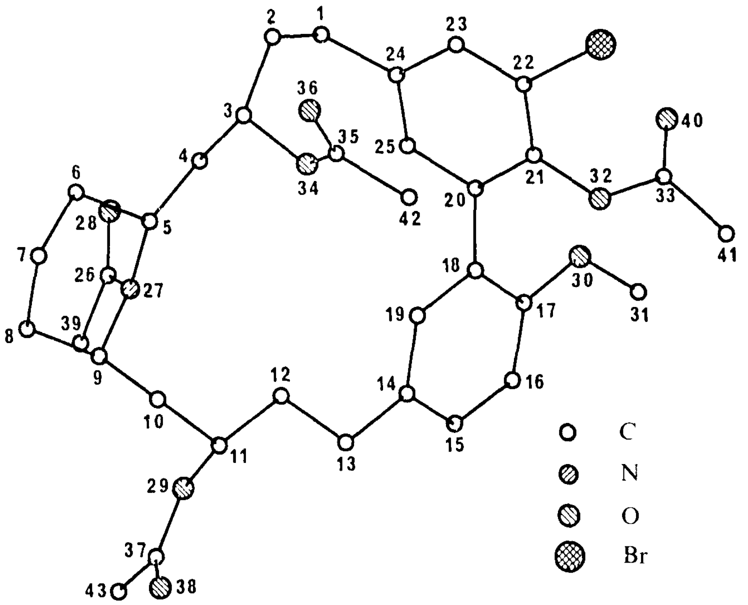


Fig. 3. Perspective View of **22**

CD Measurments——The CD spectra were obtained with a JASCO Model 6 recording spectropolarimeter (solvent as indicated, with $[\theta] \times 10^{-3}$ in parentheses after λ_{max} values).

Hydrochloride of Lythranine (**1**): methanol, 285 (+2.9), 228 (+52.8), 212 (−50.8); dioxane, 283 (+10.1), 231 (+152.1), 216 (−146.9).

Cinnamic Acid Salt of Lythranidine (**2**): methanol, 284 (+7.5), 229 (+74.3), 215 (−97.7); dioxane, 285 (+8.2), 234 (+102.3), 218 (−145.2).

Acetic Acid Salt of Lythranidine (**2**): methanol, 288 (+8.0), 230 (+84.8), 215 (−109.2).

Lythramine (**3**): methanol, 290 (−4.6), 249 (−1.5), 227 (+30.6); EPA, +25 °C, 290 (−4.6), 262 (−0.9), 244 (−7.8), 218 (+55.1); −68 °C, 289 (−10.1), 284.5 (−8.2), 231 (+64.4), 215 (−16.2); −190 °C, 289 (−12.4), 282 (−10.0), 229 (+106.4), 214 (−54.5).

Hydrochloride of Lythramine (**3**): methanol, 289.5 (−4.5), 267^{sh} (−1.4), 229 (+65.2), 213 (−67.2).

22-Bromolythranine (**8**) Hydrobromide Ethanol Solvate: methanol, 300 (−0.4), 275 (−2.1), 232 (+40.9), 210 (−16.2).

Bisdesoxy-*N,O*-dimethyllythranidine (**9**): methanol, 292 (−1.7), 265^{sh} (−0.4), 229 (+66.3), 213 (−76.2); EPA, +22 °C, 293 (−1.8), 270 (−1.0), 229 (+69.0), 214 (−63.0); −68 °C, 291 (−4.2), 252 (−1.7), 228 (+89.1), 214 (−110.0); −190 °C, 290 (−8.7), 250 (−2.1), 226 (+123.1), 213 (−190.1).

N,O-Dimethyllythranidine (**10**): methanol, 300 (−0.6), 289 (+0.2), 274 (−1.1), 230 (+72.6), 213 (−95.7); EPA,

+22 °C, 297 (−1.9), 285 (+1.0), 270 (−0.5), 231 (+97.0), 216 (−107.9); −68 °C, 297 (−4.4), 283 (+2.1), 272 (−0.9), 230 (+119.1), 216 (−182.2); −190 °C, 297 (−80.0), 282 (+3.3), 265 (+0.3), 226 (+150.2), 216 (−291.1).

O-Methyllythranidine Amidoacetal (**11**): methanol, 305 (−0.5), 286 (+6.7), 267 (+0.6), 232 (+127.1), 216 (−238.9); EPA, +22 °C, 303 (−1.1), 288 (+6.5), 268 (+1.5), 231 (+134.0), 217 (−205.9); −68 °C, 301 (−4.0), 286 (+9.5), 265 (+1.7), 230 (173.9), 217 (−302.0), −190 °C, 299 (−6.9), 285 (+12.3), 263 (+2.1), 227 (+213.8), 216 (−381.2).

Lythranidine Amidoacetal (**12**): methanol, 290 (+18.9), 250^{i} (+30.0), 234 (+60.7), 219 (−191.4); dioxane, 288 (+23.8), 250^{i} (+38.0), 237 (+82.5), 222 (−272.6).

O-Methyllythramine (**13**): methanol, 289 (−5.7), 249 (−0.8), 228 (+53.8), 211 (−15.8); dioxane, 288 (−4.1), 232 (+36.0), 213 (−19.5); EPA, +26 °C, 289 (−5.3), 247 (−2.0), 227 (+34.0); −68 °C, 289 (−10.5), 283 (−8.5), 246 (−4.7), 229 (45.5); −190 °C, 289 (−14.1), 282 (−11.8), 246 (−3.2), 228 (+89.4).

22-Bromolythramine (**14**): methanol, 288 (−5.5), 250 (−1.5), 220 (+35.0); dioxane, 286 (−5.0), 229 (+24.8).

26-Oxolythramine (**15**): methanol, 285 (+4.6), 230 (+62.4), 215 (−92.1); dioxane, 296 (+6.4), 233 (+59.4), 218 (−121.8).

O-Methyldeacetyl-11-dehydrolythramine (**16**): methanol, 300 (−0.8), 290 (+0.7), 273 (−3.5), 229 (+51.2), 213 (−65.0); dioxane, 273 (−9.3), 229 (+86.5), 213 (−129.7).

O-Methyllythranidine *N*,*O*,*O*-Triformate (**17**): methanol, 280 (−4.3), 256 (+0.5), 229 (−81.8), 213 (+82.8); dioxane, 296 (+1.1), 278 (−6.9), 254 (+3.7), 231 (−141.9), 218 (193.1).

Hydrochloride of *O*,*O*-Diacetyllythranine (**18**): methanol, 280 (−0.9), 228 (−18.2), 212 (+53.1); dioxane, 285 (−9.9), 233 (−27.4), 216 (+38.9).

Deacetyllythramine (**19**): methanol, 293 (−2.1), 237 (−9.6), 217 (+40.6); dioxane, 290 (−2.4), 237 (−10.2), 219 (+53.1); EPA, +26 °C, 294 (−2.8), 236 (−11.2), 218 (+51.5); −68 °C, 291 (−3.6), 237 (−21.8), 218 (+88.4); −190 °C, 301 (+0.5), 293 (−2.7), 286 (−3.1), 237 (−29.0), 216 (+81.8).

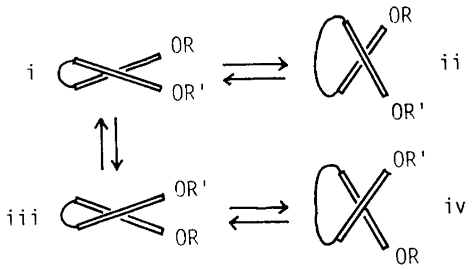
O-Methyldeacetyllythramine (**20**): methanol, 292 (−1.3), 278 (+0.5), 238 (−8.3), 219 (+27.7); dioxane, 290 (−1.1), 240 (−5.3), 221 (+18.2); EPA, +26 °C, 292 (−1.1), 273 (+0.3), 236 (−7.9), 218 (+32.7); −68 °C, 289 (−1.9), 237 (−29.7), 215 (+80.2); −190 °C, 299 (+0.3), 291 (−3.3), 282 (−2.6), 250 (+1.9), 245 (−21.8), 236 (−30.0), 225 (−13.5), 219 (+74.9), 214 (+77.6).

Diol **21**: EPA, +22 °C, 295 (+0.8), 278 (−0.5), 251 (+1.0), 228 (−7.9), 215 (+11.9); −68 °C, 299 (+1.7), 280 (−1.5), 253 (+2.7), 245 (+3.6), 227 (−10.6), 217 (+12.2); −190 °C, 298 (+5.5), 282 (−4.7), 253 (+8.8), 245 (+10.2), 226 (−30.7), 217 (+40.3).

22-Bromolythranine *N*,*O*,*O*-Triacetate (**22**): methanol, 277 (−2.7), 250 (+4.4), 230 (−10.9), 207 (+87.5); ethanol, +20 °C, 2.78 (−3.3), 252 (+5.9), 230 (−13.9); +30 °C, 278 (−3.1), 253 (+4.9), 230 (−12.5); +40 °C, 277 (−2.9), 253 (+3.7), 230 (−12.5); +50 °C, 277 (−2.7), 253 (+2.5), 230 (−12.9); EPA, +25 °C, 280 (−4.8), 253 (0); −25 °C, 280 (−5.0), 251 (+9.5); −68 °C, 279 (−5.8), 251 (+20.9); −190 °C, 277 (−4.1), 252 (41.9).

References and Notes

1) Part XI: K. Fuji, K. Ichikawa and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1066.
2) For a review, see E. Fujita and K. Fuji, "International Review of Science, Organic Chemistry Series Two," Vol. 9, ed. by K. Wiesner, Butterworths, London, 1976, p. 119.
3) For the classification of Lythraceae alkaloids, see K. Fuji, T. Yamada, E. Fujita and H. Murata, *Chem. Pharm. Bull.*, **26**, 2515 (1978). For a different system of classification, see J. Quick. C. Mondello, M. Humora and T. Brennan, *J. Org. Chem.*, **43**, 2705 (1978).
4) F. Vogtle and P. Neuman, *Tetrahedron*, **26**, 5847 (1970).
5) E. Fujita and K. Fuji, *J. Chem. Soc. (C)*, **1971**, 1651.
6) J. P. Ferris, C. B. Boyce, R. C. Briner, U. Weiss, I. H. Qureshi and N. E. Sharpless, *J. Am. Chem. Soc.*, **93**, 2963 (1971).
7) J. A. Berson, *J. Am. Chem. Soc.*, **78**, 4170 (1956).
8) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, Chapter 6.
9) Buttressed biphenyls such as 2,2′,6,6′-tetramethoxy-3,3′-dicarboxybiphenyl have been resolved. See N. Kawano, M. Okigawa, N. Hosaka, I. Kouno, Y. Kawahara and Y. Fujita, *J. Org. Chem.*, **46**, 389 (1981).
10) G. Krow, "Topics in Stereochemistry," Vol. 5, ed. by E. L. Eliel and N. L. Allinger, John Wiley and Sons, New York, 1970, p. 31.
11) R. J. McClure and G. A. Sim, *J. Chem. Soc., Perkin Trans. 2*, **1972**, 2073.
12) There are four theoretically possible conformations, i, ii, iii, and iv, of the biphenyl group of these alkaloids. It has been shown that the CD curves corresponding to rotamers i and ii would be opposite each other,[13] though they have the same symbol according to a sequence rule developed by Cohn, Ingold, and Prelog. However, conformations ii and iv are excluded in this case, because Lythraceae alkaloids and their derivatives in question have a cyclic ring system. Consequently, the inversion of the pattern in CD curves corresponds to a change between rotamers i and iii, which are opposite in conformational chirality (helicity).



13) J. J. Dannenberg and A. L. Blackwood, *J. Am. Chem. Soc.*, **97**, 4753 (1975).

14) K. Fuji, T. Yamada, E. Fujita, M. Shiro and H. Nakai, *Chem. Pharm. Bull.*, **32**, 63 (1984).

15) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon and G. H. Wahl, Jr., *J. Am. Chem. Soc.*, **86**, 1710 (1964), and preceding papers in this series.

16) Strictly speaking, the assumption is not valid, because innumerable rotamers with different torsional angles exist in each conformer.

17) E. Fujita, K. Bessho, K. Fuji and A. Sumi, *Chem. Pharm. Bull.*, **18**, 2216 (1970).

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