Reactions of the Lythraceae alkaloids. Regio and stereoselective methoxylations and hydroxylations of lythrine

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This paper is dedicated to the memory of Dr. Léo Marion

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Mercuric acetate assisted methoxylations and hydroxylations of lythrine resulted in a regio and stereoselective introduction of the substituent at the benzylic position with *S*-stereochemistry. The compounds obtained are thus epimeric at C13 with the naturally hydroxylated alkaloid lythridine and its derivatives. The implications of the results in planning the total synthesis of lythrine is discussed.

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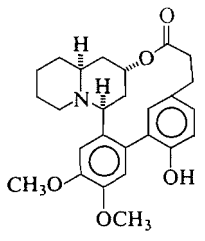
Les méthoxylations et hydroxylations de la lythrine assistées par l'acétate mercurique conduisent à une introduction régiosélective et stéréosélective d'un substituant en position benzylique avec une stéréochimie *S*. Les composés obtenus sont donc épimères au niveau du carbone en position 13 de l'alcaloïde naturel lythridine hydroxylé et de ses dérivés. On discute des implications de ces résultats dans la planification de la synthèse totale de la lythrine.

[Traduit par le journal]

Since their initial isolation (1) alkaloids of the Lythracea plant family have provided a wealth of research opportunities for workers primarily interested in their structural elucidation (2) or total synthesis (3). Structurally, they are classified into five distinct classes (4*a*) depending on the presence of a quinolizidine ring in either the *cis*- or *trans*-configuration or of a piperidinyl moiety and whether these are associated with a biphenyl or diphenyl ether aromatic fragment.

Previous work within our laboratories described the isolation (1*b*), structure elucidation (2*b*), and total synthesis of decinine (**1**) (3*a*), and decamine (**2**) (3*b*), compounds with *trans* and *cis*-quinolizidine configuration respectively, linked to biphenyl moieties. That report, as well as those of others (3*c*), which describe the total synthesis of the analogous diphenyl ether, utilizes methodology appropriate for the synthesis of alkaloids containing a fully saturated methylene chain in the macrocyclic lactone portion. Extension of this basic synthetic scheme to the biosynthetically related lythrine[2] (**3**) and lythridine (**5**), necessitated an investigation into some of the reactions and potential interconversions of these species, and these results are disclosed herein. We anticipated that the previously known conformation of the macrocyclic lactone ring in **3** and **5** (2*b*, *c*) would facilitate the interpretation of the stereochemical course of the reaction.

Mercuric acetate assisted methoxylation (5) of methyl lythrine (**6**) over a period of 48 h resulted in the formation of a single methoxy derivative **7** (Scheme 1). The proton nmr of this newly formed compound suggested that the methoxy substituent entered at the benzylic position. Spectral comparison of **7** with the dimethyl derivative of lythridine (**8**), prepared by MeI/NaH treatment of the natural product **5**, revealed that both compounds exhibited methine proton signals of the ABX spectral pattern, centered within the same range of the spectra at 4.50 ppm (however, while the Hx quartet in the spectrum of **7** derived from splitting by coupling constants of 2 and 6 cps, the corresponding signals



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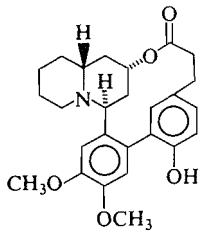

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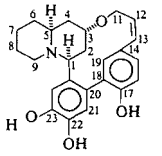
[2]Throughtout the text all alkaloids are referred to by their trivial names in common usage. Systematic names can be derived from the core name *lythran* assigned to the basic structure below with the numbering system according to ref. 6. We have included these Chem. Abstr. names in the Experimental.



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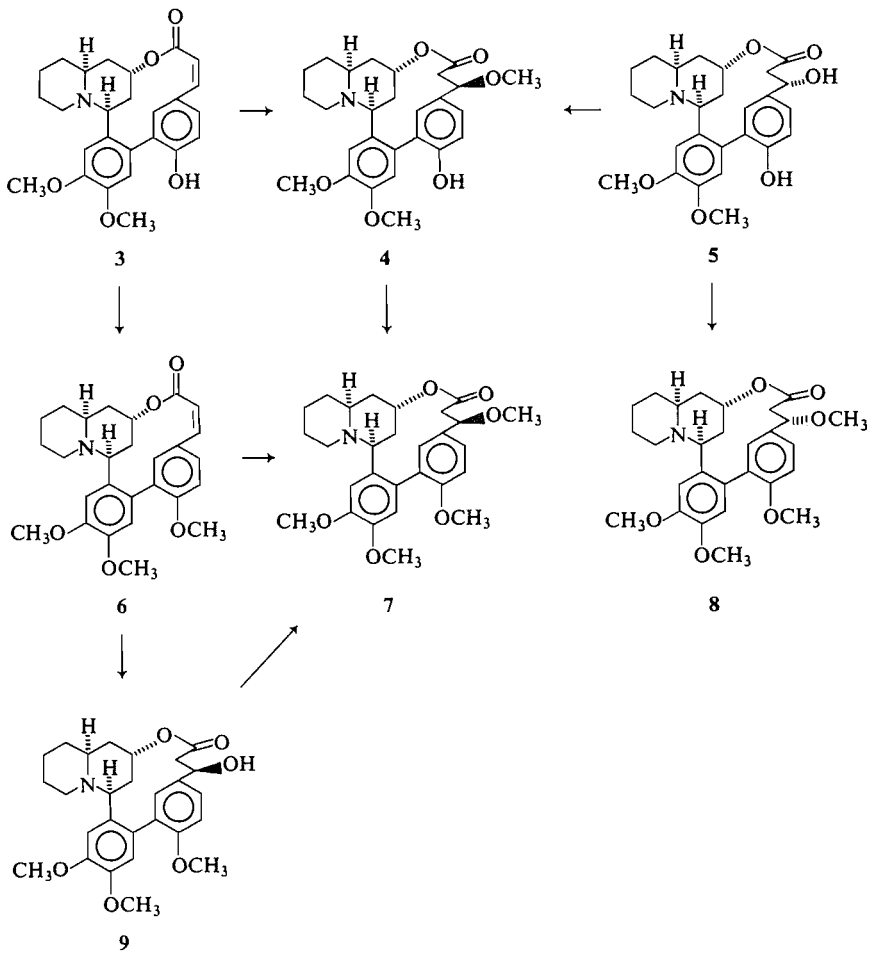

SCHEME 1

in the nmr of **8** had splittings of 3 and 10 cps and were thus a much broader pattern). Since no other change could be detected from a spectral comparison of **7** and **8**, the two compounds were assigned epimeric structures at C13. This assignment was unequivocally proven by the series of conversions shown in Scheme 1.

Conversion of lythridine to the *epi*- series took advantage of the solvolytic lability of the secondary benzylic hydroxyl group in its molecule. We had expected that treatment with methanol under strongly acidic conditions would lead to unimolecular displacement resulting in at least partial inversion of this asymmetric centre. We were quite surprised, however, to find that stirring **5** in MeOH·BF_3 at room temperature for 0.5 h resulted in the formation of a single methoxy derivative **4**, in better than 80% yield, which was identical to the methoxy compound obtained from lythrine (**3**) with $Hg(OAc)_2$/MeOH.

The methine proton signals in the spectrum of **4** displayed a pattern typical of **7** with splitting constants of 2 and 5 cps, and the structural relationship with **7** was fully established by methylation with MeI/K_2CO_3. The ease with which transformation 5 → 4 occurred excludes the probability of structural changes taking place other than epimerization at C13 and thus unambiguously supports our structural assignments for **4** and **7**. It is noteworthy that in the above methoxylation no methoxy compound with the natural C13-*R*-stereochemistry was formed.

Hydroxylation of **6** with mercuric acetate in aqueous THF followed the same stereochemical course. A single hydroxy compound (**9**) was isolated which proved to be epimeric with lythridine at C13 through its conversion to the *epi*-dimethyl compound **7**, by MeI/NaH or $CH(OCH_3)_3$·BF_3 (7).

The foregoing results indicate that mercury assisted additions to the α,β-unsaturated lactone of lythrine take place in a fully regio and stereoselective manner. The newly formed substitutent always

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enters at the benzylic β-position and obtains the *S*-stereochemistry, epimeric to the naturally hydroxylated alkaloids. Furthermore, it is also seen that the benzylic substituent readily undergoes ionization under the influence of Lewis acids, and trapping of the carbonium ion by the solvent always affords the thermodynamically more stable *epi*-substituted products. Our experimental finding that hydroxy compound **9** afforded dimethyl *epi*-lythridine (**7**) via both basic methylation and acid assisted methoxylation further supports this unimolecular methoxylation mechanism.

Oxymercuration studies in the literature (8, 9) suggest a mechanistic course highly dependent on the substitution pattern about the olefin and its geometry. Both *syn* and *anti* additions of the mercurial and nucleophile have been observed. An examination of the molecular geometry of lythrine, based on the X-ray model (2*b*), indicates a rather rigid framework with substantial steric crowding from the pro-*R* face of the double bond. As a stereochemical consequence *direction of mercurial approach* (8) governs the product configuration in analogy with strained ring oxymercuration reactions. The nature of the intermediate seems to be a highly stabilized mercury substituted carbonium ion as previously suggested by Brown and Kawakami (10).

Our results are relevant in the design of a synthetic scheme toward the total synthesis of lythrine and lythridine. We have previously attempted to prepare lythrine (**3**) from the open *cis*-α,β-unsaturated hydroxy acid precursor but this was unsuccessful. Our present work suggests a more accessible intermediate, *epi*-lythridine (**9**), whose preparation requires no stereochemical control at the dihydroxy acid stage because of its much preferred formation in the ring closed macrocycle. We are currently working on methods to transform the *epi*-hydroxy group to the *cis* olefinic linkage of the natural product. The total synthesis of lythridine (**5**), on the other hand, will require a dihydroxy acid precursor with defined stereochemistry together with mild conditions for the cyclization to avoid epimerization of the C13 asymmetric centre.

Experimental

Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Infracord spectrophotometer and ^{1}H nmr spectra were obtained on a Varian Associates model T-60 spectrometer. Signal positions are given in δ units with tetramethylsilane as internal standard.

Preparation of 17-Methyllythrine (17,22,23-Trimethoxylythran-11-one, 6)

To a stirred solution of lythrine (47.0 g, 0.108 mol) in 1.4 L of 10% sodium hydroxide and 800 mL of dioxane was added dropwise 140 mL dimethyl sulfate. The reaction was allowed to stir overnight at ambient temperature and the precipitated product was filtered and crystallized from chloroform – petroleum ether (1:1) mixture to afford 34.0 g (72%) of **6**, mp 236–237°C; ir (Nujol): 1694, 1257, 1123, 1030 cm^{-1}; ^{1}H nmr ($CDCl_3$): 7.13 (s, 1H, aromatic), 6.95 (m, 5H, aromatic), 6.84 and 5.82 (AB system, 2H, J = 13 Hz, CH=CH), 5.26 (m, 1H, C*H*—OCO), 3.90, 3.84, and 3.76 (s, 3 × 3H, 3 × CH_3O), 2.8 to 1.3 (m, 14H). *Anal.* calcd. for $C_{17}H_{31}NO_5$: C 72.14, H 6.95, N 3.12; found: C 72.34, H 7.24, N 3.02.

Preparation of 13,17-Dimethyl-13-epilythridine (12,13-Dihydro-13(S),17,22,23-tetramethoxylythran-11-one, 7)

Method A: To a solution of **6** (2.0 g, 4.5 mmol) in 50 mL of methanol was added 4.3 g of mercuric acetate and the solution was stirred at room temperature for 96 h. After cooling the reaction mixture in an icebath, sodium borohydride (0.8 g, 21 mmol) was slowly added and the resulting dark grey suspension was diluted with water to 120 mL. The solution was extracted with chloroform, the organic extract was dried over anhydrous magnesium sulfate, and after filtration was evaporated to an oil which was crystallized by trituration with ether. A yield of 1.2 g (54%) of **7** was obtained by this method, mp 222–223.5°C, ir (Nujol): 1709, 1250, 1197, 1123 cm^{-1}; ^{1}H nmr ($CDCl_3$): 7.1 (s, 1H, aromatic), 7.0 (m, 3H, aromatic), 6.9 (s, 1H, aromatic), 5.1 (br s, 1H, CHOCO), 4.52 (q, 1H, X part of ABX system, J_{AX} = 2 Hz, J_{BX} = 6 Hz, C*H*OCH_3), 3.92, 3.86, 3.76, and 3.35 (s, 4 × 3H, 4 × OCH_3), 3.2–1.1 (m). *Anal.* calcd. for $C_{28}H_{35}NO_6$: C 69.83, H 7.33, N 2.91; found: C 70.02, H 7.24, N 2.92.

Method B: 13-Methyl-*epi*-lythridine (**4**, 1.67 g, 3.5 mmol) was dissolved in a mixture of 50 mL dioxane and 50 mL 10% sodium hydroxide, and dimethyl sulfate (4.5 mL) was added over the period of 15 min. The mixture was allowed to stir overnight and was evaporated at reduced pressure to almost dryness, yielding a glassy residue which was diluted with 50 mL of water and was extracted with methylene chloride (150 mL). The organic extract was dried over anhydrous magnesium sulfate, was filtered, and the filtrate was evaporated to a glass which was triturated with ether and crystallized; 1.15 g of **7** was obtained (67%).

Method C: 17-Methyl-13-*epi*-lythridine (**9**, 2.0 g, 4.3 mmol) was dissolved in 30 mL of dimethylformamide, and sodium hydride (50% oil, 0.2 g, 4.5 mmol) was added. The anion was generated with stirring at room temperature for 0.5 h and methyl iodide (0.7 g, 5 mmol) was added to the suspension. Stirring was continued overnight and the reaction was diluted with water to 100 mL. The product was extracted with ether, the ethereal solution was dried over anhydrous magnesium sulfate, and after filtration the filtrate was evaporated at reduced pressure to a glass. The product (1.8 g, 88%) was obtained crystalline by trituration with ether.

Preparation of 13-Methyl-epi-lythridine (12,13-Dihydro-17-hydroxy-13(S),22,23-trimethoxylythran-11-one, 4)

Method A: To a solution of 2.0 g (4.75 mmol) of lythrine in 50 mL of methanol was added mercuric acetate (4.3 g) and the mixture was stirred at ambient temperaturs for 3 days. The solution was cooled in an ice bath and 1.0 g (26 mmol) of sodium borohydride was slowly added, resulting in a darkly colored mixture which was diluted with water to 120 mL and was extracted with chloroform. Evaporation of the chloroform extract at reduced pressure resulted in a glassy solid which was dissolved in 50 mL of methanol and was saturated with hydrogen sulfide gas. The alcoholic solution was filtered over a Celite bed and was evaporated to yield 2.07 g (98%) of **4**, which was recrystallized from methylene chloride – ether, mp 160–165°C; ir (Nujol): 3448, 1694, 1204, 1123, 1052 cm^{-1}; ^{1}H nmr ($CHCl_3$):

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7.3–7.0 (m, 3H, aromatic), 6.85 (s, 1H, aromatic), 5.05 (br s, 1H, C*H*OCO), 4.45 (q, X part of AB system, 1H, $J_{AX} = 2$ Hz, $J_{BX} = 5$ Hz, $CHOCH_3$), 3.90, 3.82, and 3.30 (s, 3 × 3H, 3 × OCH_3), 3.30–1.2 (m).

Method B: Boron trifluoride etherate (1.35 mL, 11 mmol) was added in one portion to a cooled solution of lythridine (1.3 g, 3 mmol) in 40 mL of methylene chloride followed by the dropwise addition of trimethylorthoformate (0.76 g, 7.2 mmol) over the period of 20 min. Stirring was maintained for an additional 0.5 h and the solution was diluted to 150 mL with methylene chloride. After washing the solution with 2 *N* hydrochloric acid (3 × 50 mL) and 5% sodium carbonate (2 × 50 mL), it was dried over anhydrous sodium sulfate, filtered, and evaporated to an oil at reduced pressure. Trituration of the oily residue with methylene chloride – ether mixture resulted in 0.9 g of the crystalline **4**.

Method C: Lythridine **5** (0.10 g, 0.2 mmol) was added to 2 mL of $BF_3 \cdot 2CH_3OH$ complex and the reaction was allowed to stand at room temperature for 0.5 h. Chloroform (30 mL) was added, and the resultant solution was washed with 5% sodium carbonate (2 × 30 mL) and saturated brine. After drying the solution over anhydrous magnesium sulfate it was filtered and the filtrate was evaporated to a glass at reduced pressure. Trituration with methylene chloride – ether obtained 0.07 g of solid product **4**.

*13,17-Dimethyllythridine (12,13-Dihydro-13(*R*),17,22,23-tetramethoxylythran-11-one, 8)*

To a solution of 0.9 g (2 mmol) of lythridine (**5**) in 20 mL dry tetrahydrofuran was added 0.29 g of sodium hydride (50% oil, 6 mmol) and the suspension was stirred at 0–5°C for 0.5 h. Methyl iodide (2.84 g, 20 mmol) was added to the resulting suspension and stirring continued at ice bath temperature for an additional 5 h. The reaction was diluted with water to 100 mL and was extracted with ether. The organic extract was washed with water, dried over anhydrous $MgSO_4$, and after filtration was evaporated to a glassy residue. Column chromatography of this material on Al_2O_3 with ether solvent yielded 0.3 g of the desired compound ($R_f = 0.62$), mp 138–140°C; ir (Nujol): 1724, 1123, 1052, 1030 cm^{-1}; ^1H nmr ($CDCl_3$): 7.45–6.7 (m, 5H, aromatic), 4.90 (s, 1H, C*H*OCO), 4.5 (q, X part of ABX system, 1H, $J_{AX} = 3$ Hz, $J_{BX} = 10$ Hz, C*H*OCH_3), 3.82, 3.75, 3.67, and 3.35 (s, 4 × 3H, 4 × OCH_3), 3.1–1.2 (m). *Anal.* calcd. for $C_{28}H_{35}NO_6 \cdot 1/2\ H_2O$: C 68.55, H 7.40, N 2.86; found: C 68.57, H 7.50, N 2.76.

*17-Methyl-13-*epi*-lythridine (12,13-Dihydro-17,22,23,-trimethoxy-13(*S*)-hydroxylythran-11-one, 9)*

A solution of **6** (2.0 g, 4.2 mmol) in 50 mL of aqueous (1:1) tetrahydrofuran was treated with 4.6 g (6.3 mmol) of mercuric acetate at room temperature for 96 h. The solution was cooled in an icebath while 1.0 g (30 mmol) of sodium borohydride was slowly added. The product was separated from the metallic mercury precipitate by extraction with chloroform (3 × 40 mL) and the organic extract was dried over anhydrous sodium sulfate. After filtration the chloroform solution was chromatographed on an alumina column using ethyl acetate solvent. After elution of 0.8 g of recovered starting material, 1.2 g (57%) of product **9** ($R_f = 0.2$) was isolated, crystallized from petroleum ether – chloroform, mp 187–188°C; ir (Nujol): 1680, 1250, 1123, 1030 cm^{-1}; ^1H nmr ($CDCl_3$): 7.0–6.7 (m, 5H, aromatic), 4.90 (br s, 1H, CHOCO), 4.2 (br m, 1H, C*H*OH), 3.90, 3.80, and 3.70 (s, 3 × 3H, 3 × OCH_3), 3.15–1.3 (m). *Anal.* calcd. for $C_{27}H_{33}NO_6 \cdot 1/4\ H_2O$: C 68.89, H 7.15, N 2.96; found: C 68.40, H 7.13, N 2.93.

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