Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports

The Structure of O-methyllythrine Hydrobromide

The recently discovered[1-3] group of *Lythraceae* alkaloids has already been shown to contain approximately a dozen members. The first reported chemical work in this area[4] demonstrated two benzenoid nuclei substituted with hydroxyl and methoxyl patterns. These moieties generate extensive families of compounds (cf. aporphines and protoberberines[5]).

Lythrine from *Heimia myrtifolia* and *salicifolia* yields a dihydroderivative identical with decinine from *Decodon verticillatus*[1] (Lythraceae). Its properties are remarkably similar to those of the Lythraceous alkaloid vertine[6], which is obtained both from the *Heimia* spp. and *Decodon verticillatus*. A similar close relationship exists between decinine and dihydrovertine=decamine[4]. The central place of lythrine in the group is also demonstrated by mass spectral studies. Thus, the mass spectra of O-methyldecinine and O-methyldecamine as well as those of O,O-dimethyldecodine and O,O-dimethyldihydroverticillatine are almost identical. These results indicate that all of these compounds have the same basic skeleton and differ only in stereochemical detail[7] and aromatic methoxylation patterns[8].

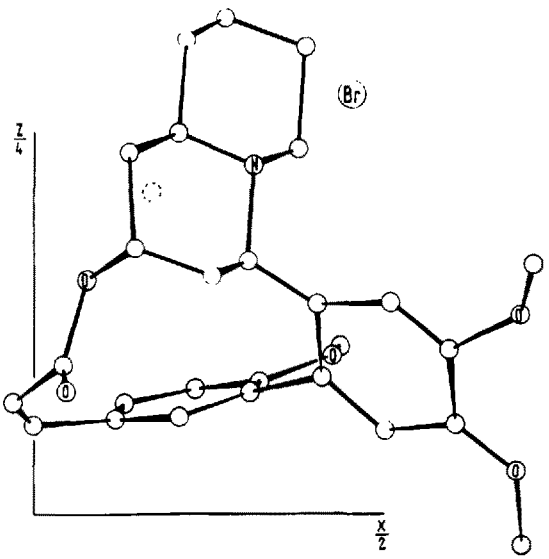
The hydrobromide of the methyl ether of lythrine was used in this study since no suitable single crystals of a heavy atom derivative of lythrine itself could be prepared. This salt, recrystallized from methanol-ethyl acetate, gave elemental analysis C 59.77, H 6.26, N 2.62 corresponding to one methanol of solvation; calculated for $C_{27}H_{32}BrNO_5 \cdot CH_3OH$, C 59.76, H 6.45, N 2.49. The crystal data obtained with CuKα radiation was orthorhombic with $a = 11.58$, $b = 9.64$, $c = 22.86$ Å, V = 2545 Å^3, space group $P2_12_12_1$, Z = 4, M = 562.2, $D_x = 1.47$ g/cm^3.

Three-dimensional X-ray diffraction intensity data were recorded at room temperature on equi-inclination Weissenberg photographs about the *a* and *b* axes. The intensities were estimated visually and gave 1266 independent observed structure amplitudes. The positions of the bromide atoms were deduced from a three-dimensional Patterson synthesis, and were used to calculate the heavy-atom phases of the observed structure amplitudes[9,11]. Successive three-dimensional Fourier syntheses and structure factor calculations progressively revealed the electron density distribution of the molecule. One atom of the solvent molecule was not resolved and is presumed to be the carbon atom disordered over several possible positions. The agreement index was R = 0.22, with isotropic atoms excluding the hydrogen atom and the disordered carbon atom. The configuration of the molecule derived from the final electron density map is shown in the Figure, projected down the *b* axis of the crystal. The broken circle represents the oxygen atom of the solvent molecule.

The nitrogen-containing part of the alkaloid is a quinolizidine ring system substituted at the 3-position by a hydroxyl group. The remainder of the molecule is a 4,4′,5′-trimethoxy-3-phenylcinnamoyl moiety which is attached at the 2′-position to the 1-position of the quinolizidine ring and forms an ester with the 3-hydroxyl group, as shown in I. This arrangement constrains the biphenyl system in the molecule to be non-polar as seen in the Figure.

The structure of the parent compound lythrine was determined to be II by oxidative procedures which yielded 4,5-dimethoxyphthalic acid, isolated as the anhydride and identified by an infrared spectral comparison.

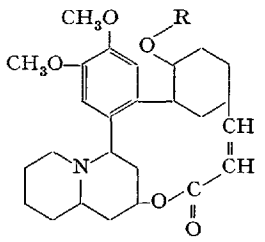
The lack of intense absorption in the UV-spectra of the *Decodon* alkaloids led to the original conclusion that a biphenyl chromophore was not present[1,4]. A further consideration of this matter led to an examination of an appropriate model compound, phenyldihydrothebaine, III. The absorption maximum and extinction coefficient



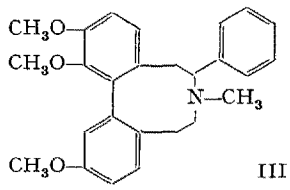
[1] J. P. Ferris, J. org. Chem. *27*, 2985 (1962).
[2] B. Douglas, J. L. Kirkpatrick, R. F. Raffauf, O. Ribeiro, and J. A. Weisbach, Lloydia *27*, 25 (1964).
[3] R. N. Blomster, A. E. Schwarting, and J. M. Bobbitt, Lloydia *27*, 15 (1964).
[4] J. P. Ferris, J. org. Chem. *28*, 817 (1963).
[5] H. G. Boit, *Ergebnisse der Alkaloid-Chemie bis 1960* (Akademie-Verlag, Berlin 1961).
[6] Vertine has been found to be completely identical with cryogenine[3] (kindly supplied by Dr. A. E. Schwarting) by comparison of melting point, mixed melting point, infrared spectra (KBr) and thin layer chromatography Rf values using silica gel and alumina systems.
[7] K. Biemann, *Mass Spectrometry, Organic Chemical Applications* (McGraw Hill, New York 1962).
[8] See [4] for the differences in aromatic ring methoxylation in these derivatives.
[9] The calculations were carried out on the IBM 7070 computer using the programs of Dr. R. Shiono[10,11].
[10] R. Shiono, *IBM 7070 Programs for Isotropic and Anisotropic Structure Factor Calculations*. Technical Report No. 29, University of Pittsburgh Computation and Data Processing Center (1962).
[11] R. Shiono, *Three-Dimensional Differential Fourier Synthesis Program for IBM 7070 Computer*, Technical Report No. 42, University of Pittsburgh Computation and Data Processing Center (1963).

(λ_{max} 281 mμ, ε 5600)[12] reported for this compound are almost identical with those reported for decodine[1]. Inspection of the Dreiding models clearly indicates appreciable hindrance to rotation about the biphenyl link, even with the lactone ring cleaved, so that the observed UV-spectra would be in accord with the structure of lythrine.

Elucidation of the detailed structures of the remaining Lythraceae alkaloids will be described in due course.



I R = CH_3; II R = H



III

Zusammenfassung. Die Struktur des O-Methyl-lythrin-hydrobromids wurde röntgen-kristallographisch ermittelt. Durch den oxydativen Abbau wurde das Hydrobromid mit dem unsubstituierten Lythrin verknüpft. Die Massenspektren zeigten, dass eine Reihe von weiteren Lythraceae-Alkaloiden das gleiche Grundgerüst besitzen.

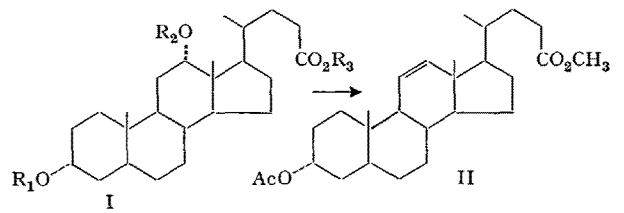
D. E. ZACHARIAS, G. A. JEFFREY*,
B. DOUGLAS, J. A. WEISBACH, J. L. KIRKPATRICK**,
J. P. FERRIS, C. B. BOYCE, and R. C. BRINER***

*Crystallography Laboratory, University of Pittsburgh** (*Pennsylvania*); *Smith Kline and French Laboratories, Philadelphia*** (*Pennsylvania*); *and Department of Chemistry, Florida State University, Tallahassee**** (*Florida, USA*), *November 9, 1964.*

[12] E. A. BRAUDE and W. F. FORBES, J. chem. Soc. *1955*, 3776.

Δ^{11}-Steroids

Despite their potential importance as precursors of physiologically active 11-oxygenated compounds, no really satisfactory method is available for the preparation of Δ^{11}-steroids from desoxycholic acid and its transformation products. It has now been found that the dehydrosulphonylation of 12α-sulphonate esters proceeds readily with potassium-*t*-butoxide (KO^{t}Bu) in dipolar aprotic solvents and in the case of dimethyl sulfoxide (DMSO) offers excellent yields of Δ^{11}-compounds.



I II

(a) $R_1 = CH_3CO$ $R_2 = H$ $R_3 = CH_3$
(b) $R_1 = CH_3CO$ $R_2 = p\text{-}CH_3 \cdot C_6H_4 \cdot SO_2$ $R_3 = CH_3$
(c) $R_1 = CH_3CO$ $R_2 = C_6H_5 \cdot SO_2$ $R_3 = CH_3$
(d) $R_1 = CH_3CO$ $R_2 = p\text{-}Cl \cdot C_6H_4 \cdot SO_2$ $R_3 = CH_3$
(e) $R_1 = CH_3CO$ $R_2 = CH_3SO_2$ $R_3 = CH_3$
(f) $R_1 = H$ $R_2 = C_6H_5 \cdot SO_2$ $R_3 = H$
(g) $R_1 = H$ $R_2 = p\text{-}CH_3 \cdot C_6H_4 \cdot SO_2$ $R_3 = H$

Treatment of methyl 3α-acetoxy-12α-hydroxy-cholanate[1] (Ia) with *p*-toluenesulphonyl chloride in pyridine at 55 ± 1°C for 96 h gave the crude tosylate (Ib) ($E^{1\%}_{1cm}$ 225 mμ = 205)[2] in ca. 93% yield. Dehydrotosylation with KO^{t}Bu in DMSO at 100–110° (bath temperature) for 1 h afforded, after methylation (diazomethane), acetylation, Florisil chromatography and crystallization from methanol, the known methyl 3α-acetoxy-Δ^{11}-cholenate[3] (II), m.p. 119–120° in ca. 74% yield. Similarly, the crude benzenesulphonate (Ic) ($E^{1\%}_{1cm}$ 217 mμ = 137) and the *p*-chlorobenzenesulfonate (Id) ($E^{1\%}_{1cm}$ 228 mμ = 214), obtained in 95 and 92% yields, furnished (II) in ca. 76 and 48% yields respectively. The lower yield with (Id) may be ascribed to the formation of benzyne-type intermediates with attendant complications. Dehydromesylation of the crude mesylate (Ie), derived from (Ia) in 97% yield, was complete within 40 min but gave (II) in diminished yield (55%). CHANG and WOOD[4] have recently reported a similar yield (58%) but on carrying out the reaction at room temperature for 48 h.

Variations of solvent and base in the elimination reaction did not prove rewarding. Thus, the replacement of DMSO by N-methylpyrrolidone, sulfolane and tetraethylene glycol dimethyl ether in dehydrotosylation of (Ib) gave (II) in 53, 39 and 54% yields respectively, whilst sodium methylsulfinyl carbanion[5], in place of KO^{t}Bu, in the dehydrobenzenesulfonylation of (Ic) provided 38% yield of (II) in 0.5 h. The disappointing result with dimsyl sodium, a strong base, is a consequence of the nature of the cation. The solvation of positively charged ions by dipolar aprotic solvents, such as DMSO, increases with the size of the ion[6]; consequently the base strength decreases in the order Cs > Rb > K ⋙ Na ⋙ Li. This is also strikingly demonstrated by the fact that anhydrous NaOAc gave hardly any Δ^{11}-compound (II), under conditions (2$^3/_4$ h at 100°) under which anhydrous KOAc in DMSO provided (II), m.p. 113–117° in ca. 47% yield from (Ic). Based on these considerations, dimsyl potassium

[1] T. F. GALLAGHER and W. P. LONG, J. biol. Chem. *162*, 521 (1946).
[2] UV-absorption spectra were measured in ethanol solution and optical rotations in alcohol-free chloroform. All melting points are uncorrected. New compounds gave satisfactory elemental analyses.
[3] O. WINTERSTEINER, M. MOORE, and K. REINHARDT, J. biol. Chem. *162*, 707 (1946). – J. PRESS and T. REICHSTEIN, Helv. chim. Acta *25*, 878 (1942).
[4] F. C. CHANG and N. F. WOOD, Steroids *4*, 55 (1964).
[5] E. J. COREY and M. CHAYKOVSKY, J. Am. chem. Soc. *84*, 866 (1962).
[6] D. J. CRAM, J. L. MATEOS, F. HAUCK, A. LANGEMANN, K. R. KOPECKY, W. D. NIELSEN, and J. ALLINGER, J. Am. chem. Soc. *81*, 5774 (1959). – T. J. WALLACE, J. E. HOFMANN, and A. SCHRIESHEIM, J. Am. chem. Soc. *85*, 2739 (1963).