

Isolation and Structure (X-Ray Analysis) of Manicoline A, a New α -Aminotropone from *Dulacia guianensis* (Olacaceae)

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Summary Two alkaloids, manicoline A and B, have been isolated from the root bark of *Dulacia guianensis* (Olacaceae); the structure of manicoline A, a novel α -aminotropone, has been established by X-ray analysis.

Dulacia guianensis (Engl.) O. Ktze (Olacaceae) is a fairly rare Guyanan tree† growing in the forests of Gallion, south of Cayenne. Previous studies of its root bark resulted in the isolation and structural determination of a eudesmane-type sesquiterpene with an aromatic A-ring, manicol (1).¹ Continuing our work on the constituents of *D. guianensis* we have now isolated two alkaloids which we have designated manicoline A and B. We herein report the structural elucidation of the major alkaloid, manicoline A.

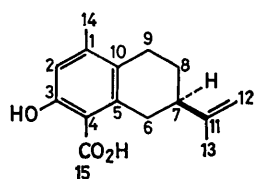
Chromatography of the alkaloidal extract (1.4 g) obtained from hexane-defatted, ground root bark (1 kg) of *D.*

guianensis over silica gel gave manicoline A and B (120 and 58 mg, respectively). Further purification by column chromatography over Sephadex LH 20 and crystallisation from ethyl acetate afforded pale yellow crystals of manicoline A (2), m.p. 197–199 °C, $[\alpha]_D^{22} + 69^\circ$ (c 0.9, CHCl₃ + 10% MeOH).

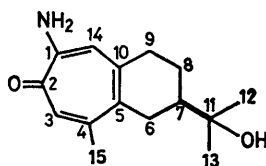
The molecular formula of (2) (C₁₅H₂₁NO₂) was established by microanalysis and by mass spectrometry [m/e 247.1573 (M^+), 229.1475 (60%; $M - H_2O$), 214.1238 (70%; $M - H_2O - CH_3$), and 186.1280 (91%; $M - H_2O - CH_3 - CO$)]. Fragmentation ions at m/e 188.1093 (16%; $M - C_3H_7O$) and 59.0506 (28%; C₃H₇O) were also observed.

The u.v. spectrum (EtOH) of (2) showed maxima at 252 (ϵ 32 110), 340 (13 170), and 420 nm (10 700), and shoulders at 266 (21 406) and 277 nm (10 700). The 400 MHz ¹H n.m.r. spectrum showed signals due to three methyl groups (δ 1.26, 1.28, and 2.36) assigned to 12-, 13-, and 15-H₃, respectively. It also revealed two one-proton singlets at δ 6.69 and 7.24 due to H-3 and H-14, respectively, and a two-proton signal at δ 5.44 exchangeable with D₂O (NH₂ group). Manicoline A gave a red-brown colour with alcoholic FeCl₃, was negative to ninhydrin reagent on t.l.c. (vinylogous amide), but could be extracted from a CH₂Cl₂ solution by dilute HCl.

The structure of manicoline A (2) was determined by X-ray analysis using crystals obtained from ethyl acetate.



(1)



(2)

† A sample (No. HJ 2165) of the material studied was deposited in the Herbarium du Muséum d'Histoire Naturelles, Paris.

Crystal data: monoclinic, space group $P2_1$, $a = 13.436$, $b = 11.305$, $c = 9.363$ Å, $\beta = 103.8^\circ$ for $Z = 4$. Two independent molecules with a different hydrogen bond network were observed in the asymmetric unit. Intensity data for 2197 independent reflections were measured using $\text{Cu-K}\alpha$ radiation. Lorentz and polarisation corrections were applied to 1817 reflections with $I \geq 2\sigma(I)$. The structure was solved by direct methods using the multiresolution technique² and was isotropically refined to $R = 15\%$. Hydrogen atoms were introduced at their theoretical positions (except those of the methyl groups) and the structure was refined with anisotropic thermal factors for the non-hydrogen atoms to a final conventional R factor of 10.1%. Although the determination of the nature and position of the heavy atoms did not present any particular difficulties, some discrepancies arose in establishing the bond distances of the two molecules in the unit cell; this was due to the bad mosaic structure of the crystal used in this study.

The molecular structure of (2) is shown in the Figure.† Manicoline A is the first naturally occurring α -aminotropone.

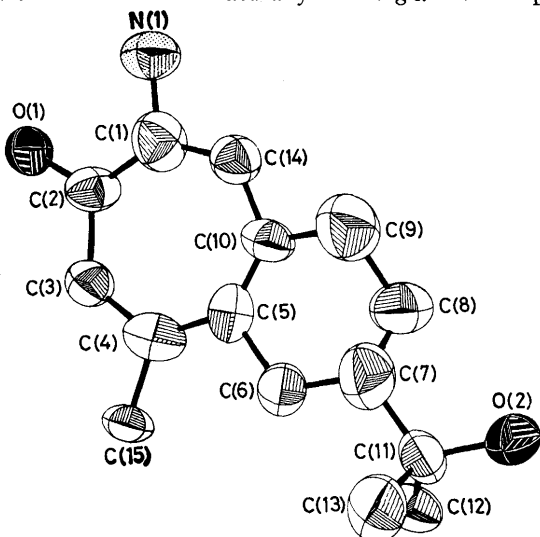
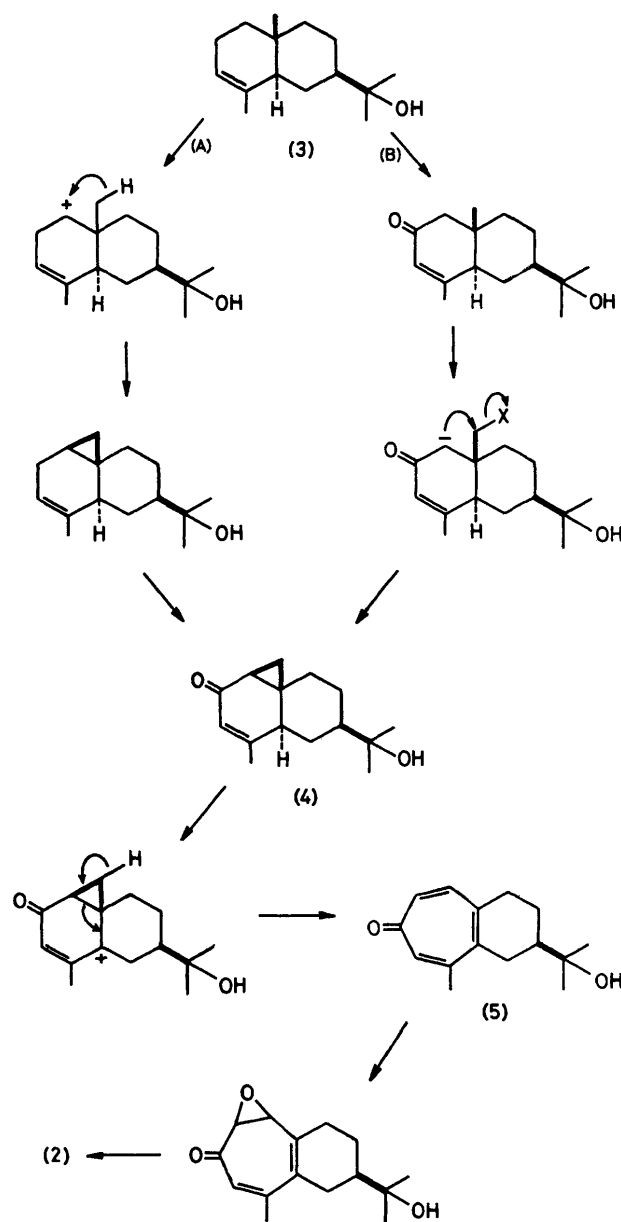


FIGURE. Molecular structure of manicoline A, (2), showing the crystallographic numbering scheme.

Manicol (1) obviously arises biogenetically from the sesquiterpene eudesmol (3) which undergoes a dienone-phenol rearrangement to give the aromatic ring. It seems reasonable to suppose that eudesmol (3) is also the precursor of manicoline A (2). Two routes, (A) or (B) (Scheme) can be envisaged. In the first a cyclopropane ring is formed as for cycloartenol, and the ketone function is then introduced. In the second the ketone function is used to facilitate cyclopropane formation. Both routes afford the hypothetical intermediate (4). By hydride abstraction at C-5 and rearrangement the second intermediate (5) would result. By epoxidation and amination manicoline A (2) would be formed.

Manicoline A (2) is not cytotoxic for chick embryo fibroblasts up to doses of 5 $\mu\text{g/ml}$ and does not inhibit cell



SCHEME. X = leaving group.

transformation induced by the Rous sarcoma virus.³ Studies of other kinds of biological activity are in progress.

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† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

¹ J. Polonsky, Z. Varon, H. Jacquemin, D. M. X. Donnelly, and M. J. Meegan, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2065.

² G. Germain, P. Main, and M. Woolfson, *Acta Crystallogr., Sect. A*, 1971, 27, 368.

³ M. Robert-Géro, F. Lawrence, G. Farrugia, A. Berneman, P. Blanchard, P. Vigier, and E. Lederer, *Biochem. Biophys. Res. Commun.*, 1975, 65, 1242.