

THE ABSOLUTE STRUCTURE OF ANOPTERINE

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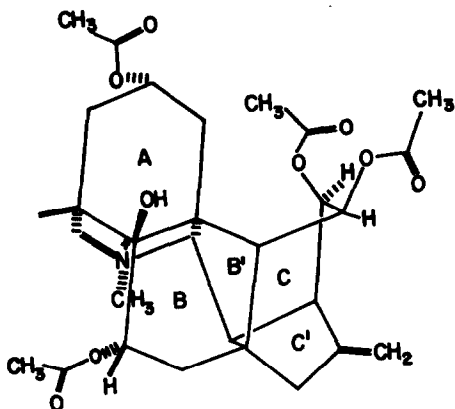
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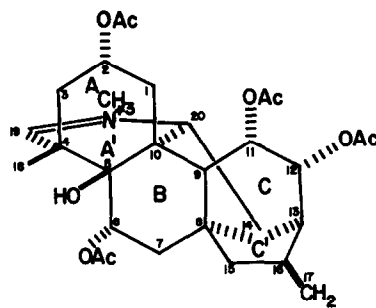
Anopterine, $C_{31}H_{43}NO_7$, m.p. 222-223°, $[\alpha]_D -12^\circ$ (c , 1.47 in $CHCl_3$), is the major alkaloid from both the bark and leaves of the Queensland species *Anopterus macleayanus* F. Muell. (Family Escalloniaceae), and it has also been isolated from the Tasmanian species *Anopterus glandulosus* Labill. Anopterine is an 0,0-ditigloyl ester and has two secondary and one tertiary hydroxy groups. The 100 MHz n.m.r. spectrum ($CDCl_3$) shows 3H singlets at δ 2.23 (N-methyl) and δ 1.15 (C-methyl), two 1H multiplets at δ 4.82 and δ 5.01 ($>C=CH_2$) and a broad 1H multiplet at δ 10.0 (strongly hydrogen-bonded hydroxyl). Hydrolysis of anopterine with ethanolic potassium hydroxide at reflux temperature afforded tiglic acid and an alcohol, anopteryl alcohol, $C_{21}H_{31}NO_5$, m.p. 258-261°, $[\alpha]_D +4^\circ$ (c , 0.76 in $CHCl_3/MeOH(1:1)$), M^+ 377, four secondary and one tertiary hydroxy groups.

Neither anopterine nor anopteryl alcohol, nor any of several acetyl derivatives in which the hydrogen-bonded hydroxy group is present, afforded a methiodide or crystalline hydrohalide salt; eventually it was found that 0,0,0,0-tetra-acetyl anopteryl alcohol, $C_{29}H_{39}NO_9$, m.p. 156-158°, $[\alpha]_D +88^\circ$ (c , 1.03 in $CHCl_3/MeOH(1:1)$), one tertiary and no secondary hydroxy group, reacted slowly with methyl iodide in acetone over a period of several weeks to give a crystalline iodine-containing compound, m.p. 276-268° (dec.), $[\alpha]_D +107^\circ$ (c , 0.57 in $MeOH/H_2O(1:1)$). This compound was at first presumed to be a methiodide of 0,0,0,0-tetra-acetylanopteryl alcohol, but x-ray crystal structure analysis established that, in addition to the iodine atom, there were only 39 non-hydrogen atoms and the molecular composition was eventually revised to $C_{29}H_{39}NO_9^+I^-$. X-ray measurements showed these crystals to belong to the monoclinic space group, $P2_1$, with lattice parameters, $a = 9.217$, $b = 15.118$, $c = 10.774$ Å and $\beta = 101.8^\circ$, $Z = 2$. 2434 independent intensities, of which 1245 were significant, were measured on a diffractometer with MoK_α radiation. The structure, analysis of which

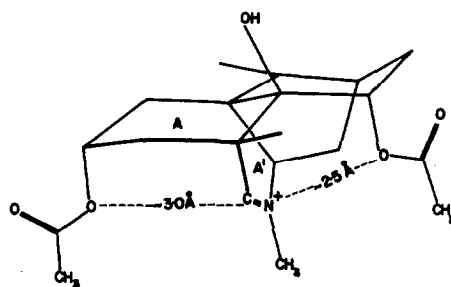
was initiated with the heavy atom, was unravelled in progressive stages until difference maps established that all peaks had been identified as atom sites. Refinement of the structure by least squares has proceeded to $R = 0.07$ and measurement of 60 Bijvoet pairs has established the absolute configuration as shown, I(a). A more conventional representation of the structure is shown in I(b). Dimensions within the molecule are typical within the limits of experimental error. The environment adjacent to the azomethine group is shown in I(c), the approximate distances indicated being measured from the respective oxygen atoms to the centre of the double bond. Full details of the analysis, configurational and conformational features will be presented separately.



I(a)

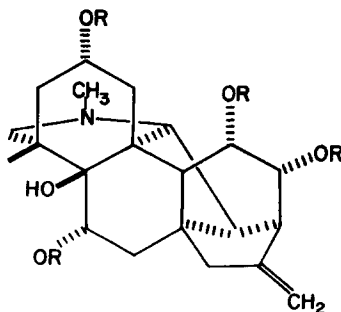


I(b)



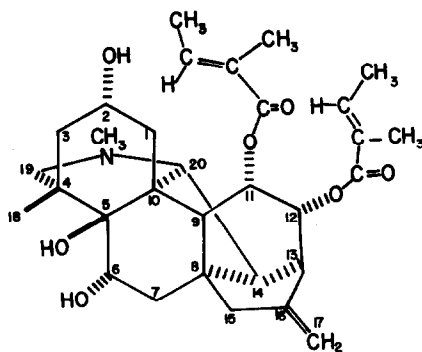
I(c)

From the crystal structure analysis, it was established that the crystalline iodide is the azomethine iodide (I) with the (-)-kaurene skeleton previously found in a number of diterpenoids including the alkaloids cuauchicine, garryfoline, napelline, songorine and lucidusculine (1). Anopterine is the first example of a kaurenoid group alkaloid with a C20-C14 linkage and is unusual in having a C5 tertiary hydroxy group. All four acetyl groups have a conformation relative to the adjacent ring hydrogen in accord with an earlier prediction of the preferred conformation of acetyl groups (2). The n.m.r. spectrum (CD_3OD) of the iodide shows a 1H singlet at $\delta 9.05$ assigned to C19-H, and is otherwise consistent with the structure determined by x-rays. It is clear, however, from chemical and spectroscopic evidence that, although anopteryl alcohol and 0,0,0,0-tetra-acetylanopteryl alcohol possess the main structural features of the iodide, I, they have a methylene group at C19, and it is considered that, during the slow reaction with methyl iodide, the C19-N double bond was introduced by oxidation with iodine and/or oxygen. The positions of the secondary hydroxyl groups at C2, C6, C11 and C12 in anopteryl alcohol have been confirmed by a study of a series of ketones obtained by oxidation under various conditions. 0,0,0,0-Tetra-acetyl anopteryl alcohol forms a normal hydriodide, $\text{C}_{29}\text{H}_{39}\text{NO}_9 \cdot \text{HI}$, [m.p. 295-298° (dec.), $[\alpha]_D^{25} +89^\circ$ (c, 0.68 in MeOH/H₂O (1:1))]. This hydriodide readily reverts to the tertiary base on treatment with ammonia, by contrast to the azomethine iodide, I, which gives a mixture of products with ammonia. On the assumption that no structural change other than introduction of the C19-N double bond occurred in the formation of the iodide, I, anopteryl alcohol and 0,0,0,0-tetra-acetyl anopteryl alcohol can be assigned structures II and III respectively.



II R = H
 III R = CH₃CO

From the structure assigned to anopteryl alcohol, the structure of anopterine can be shown from spectroscopic evidence to be IV. As indicated by reference to I(c), both the C2-axial hydroxyl and C6-axial hydroxyl in this skeletal disposition are appropriately situated for the formation of a hydrogen bond to the nitrogen, the dimensional situation favouring the C6 interaction, with ring A' in the boat form. Supporting evidence for the assignment of the hydrogen-bonded hydroxy group to the C6-position has been obtained from the n.m.r. spectra of anopterine and some of its derivatives. N.m.r. data indicate that the tigloyloxy groups of anopterine should be placed at the C11 and C12 positions. Each methine proton adjacent to an O-tigloyl group gives a signal (CDCl₃ solution) which indicates coupling to two other protons (δ 5.47, J6.0, 6.0Hz, C12-H; and δ 5.10, J6.0, 3.0Hz, C11-H) and, in a double resonance experiment, irradiation at the resonance frequency of C13-H sharpened the signals from the C17-methylene group protons by removing long-range couplings, and collapsed the δ 5.47 signal to a doublet (J6.0Hz). Full details of the chemical studies will be reported subsequently.



IV

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