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THE STRUCTURES OF ATHEROLINE AND MOSCHATOLINE

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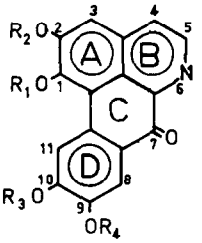
The phenolic alkaloid atheroline was extracted from the bark of Atherosperma moschatum (1) and was shown to yield the known but unnamed alkaloid I (2) on methylation of its phenolic group. The latter group was tentatively assigned to C_1 from its pronounced acidity, and from n.m.r. and i.r. evidence (1).

I. $R_1 = R_2 = R_3 = R_4 = Me$
II. $R_1 = H$, $R_2 = R_3 = R_4 = Me$
III. $R_1 = Et$, $R_2 = R_3 = R_4 = Me$
IV. $R_1 = R_2 = R_3 = Me$, $R_4 = Et$
V. $R_1 = R_2 = R_4 = Me$, $R_3 = Et$
VI. $R_1 = R_2 = R_3 = Me$, $R_4 = H$



An attempted synthesis of the substance with the structure II thus attributed to atheroline had only very limited success, through difficulties with the protection of the hydroxyl group in certain steps of the synthesis. The expected product, obtained in a yield so small that it could not be satisfactorily purified or analysed, seemed even more acidic than atheroline since it dissolved in aqueous sodium bicarbonate, and its solutions appeared to give an even more pronounced bathochromic shift than the latter base on addition of alkali. These properties cast doubt upon the correctness of structure II for atheroline; the structure was in fact shown to be untenable by

synthesis of the corresponding ethyl ether (III). Comparison with O-ethylatheroline revealed differences in i.r. spectra and melting points, and a depression of melting point on mixing.

A reexamination of the n.m.r. spectra of atheroline and its derivatives threw some light on the location of the hydroxyl group. It is well established that electron-withdrawing groups attached to an aromatic nucleus produce downfield shifts of the resonance positions of protons attached to the same ring, particularly those in ortho positions (3). Thus Highet and Highet (4) have shown that the absorptions of the aromatic protons of a phenol are practically unaffected on formation of the methyl ether, but are shifted downfield on acetylation. In the case of atheroline, the aromatic proton resonances for H_3, H_4 and H_5 (Table 1) were found at approximately the same positions for both the O-methyl and O-acetyl derivatives, but the H_8 and H_{11} resonances of O-acetylatheroline were depressed to lower fields as compared to those for O-methylatheroline, particularly the H_8 resonance. This would indicate that the acetoxy group was located in ring D, either at C_9 or, less probably, at C_{10}.

TABLE 1

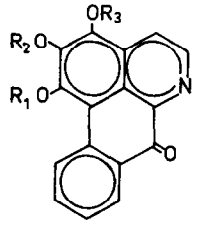
Aromatic Proton Resonances for Atheroline Derivatives (δ)

	H_3	H_4	H_5	H_8	H_{11}
O-Methylatheroline	7.08	7.63	8.76	7.93	8.65
O-Acetylatheroline	7.11	7.64	8.80	8.20	8.80

The corresponding compounds IV and V with ethoxy groups at C_9 and C_{10} respectively were synthesised and compared with O-ethylatheroline: The i.r. spectrum of the latter was

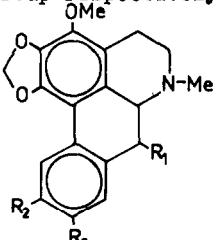
identical with the spectrum of IV, but differed significantly from that of V; the melting point of O-ethylatheroline was depressed on admixture of V but not of IV; thus atheroline has structure VI with a phenolic hydroxyl at C_9.

Another yellow base isolated in very small amount from the phenolic alkaloid fraction of Atherosperma moschatum by counter-current methods has been given the name moschatoline. The free base failed to crystallise, but yielded a yellow, crystalline O-acetyl derivative, m.p. 190-200°, and a pink hydrochloride. Moschatoline resembled atheroline in its reactions: it was soluble in carbonate, but not in bicarbonate, and it gave a positive ferric chloride test, and a negative test for a methylenedioxy group. Its u.v. and visible light absorption spectra (Table 2) indicated that, like atheroline, it possessed a 7-oxo-dibenzo-(de,g)-quinoline skeleton; this was supported by the i.r. spectrum of its O-acetyl derivative, which showed absorption peaks at 1775 cm^{-1} (acetyl carbonyl) and 1659 cm^{-1} (conjugated ring ketone). Owing to its low solubility, the free base was not amenable to n.m.r. spectroscopy, but its O-acetyl derivative showed 3-proton singlets at δ 3.91, 4.11 and 2.50 p.p.m. which could be ascribed to two methoxyls and an acetyl group respectively.



VII. $R_1 = R_2 = R_3 = Me$

XV. $R_1 = R_3 = Me$, $R_2 = H$



VIII. $R_1 = H$, $R_2 = OMe$

IX. $R_1 = OH$, $R_2 = H$

The absence of any one-proton singlet in the aromatic region around δ7.1 p.p.m. indicated that C_3 carried a substituent (5). Since C_1 and C_2 almost invariably bear oxy groups in alkaloids of the isoquinoline type, being derived biogenetically from a dopa unit (6), it would seem likely that ring A of moschatoline was fully substituted, while ring D had four adjacent protons; this was supported by the appearance in the i.r. spectrum of moschatoline of a medium-strength band at 740 cm^{-1} ascribable to the out-of-plane deformation of these aromatic proton bonds, and was confirmed by a comparison of O-methylmoschatoline with synthetic 1,2,3,-trimethoxy-7-oxo-dibenzo-(de,g)-quinoline (VII); the bases were identical in i.r. spectra, melting point and mixed melting point.

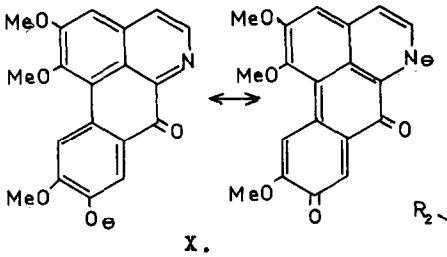
TABLE 2

U.V. and Visible Light Absorption Spectra of Moschatoline

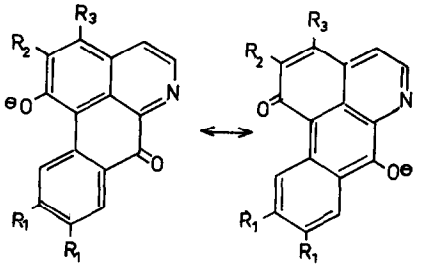
In EtOH		In 0.05N HCl(EtOH/H_2O)		In 0.05 NaOH(EtOH/H_2O)	
λmax,mμ	logεmax	λmax,mμ	log εmax	λmax,mμ	log εmax
237	4.47	246	4.37	247	4.42
272	4.41	281	4.40	283	4.31
315 (infl.)	4.10	-	-	310	4.25
374	3.55	390	3.63	407	3.99
440	3.67	496	3.36	517	3.33

O-methylmoschatoline shows methoxyl proton resonances at δ4.06, 4.10 and 4.18 p.p.m. in its n.m.r. spectrum. By comparison with the spectrum of the aporphine alkaloid ocoteine (7) (VIII), and of the modified aporphine guatterine (8) (IX), the low-field absorption may be assigned to the methoxyl on C_3, while the high-field one can be ascribed to that on C_1

from comparison with the spectrum of O-methylatheroline (1) (I) and of various aporphines (8,9). Both these resonances appear to be present in the spectrum of O-acetylmoschatoline, although they show an expected shift to higher field, particularly the C_1 methoxyl resonance, through proximity to the acetoxy group. This would indicate that the hydroxyl group of moschatoline is located at C_2, an assignment which is supported by the u.v. spectral data: On addition of alkali to an ethanolic solution of moschatoline, the u.v. and visible absorption bands undergo a bathochromic shift (Table 2) comparable in magnitude to that shown in the case of atheroline (1) (VI). As mentioned above, the isomer II of atheroline with the hydroxyl at C_1 gave a much greater bathochromic shift under these circumstances. This would be expected from comparison of the mesomeric anion (X) of atheroline with the anion (XI) derived from its isomer II, in which the main contributing forms would be of nearly equal energy. Thus of the three possible positions for the phenolic



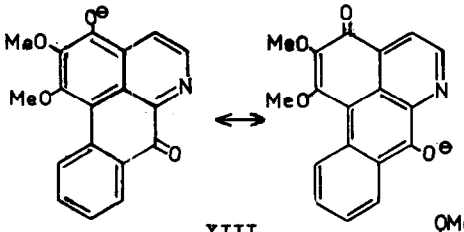
X.



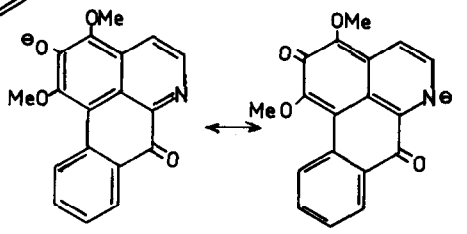
XI. $R_1 = R_2 = OMe$, $R_3 = H$

XII. $R_1 = H$, $R_2 = R_3 = OMe$

group in moschatoline, a C_1- located hydroxyl would give rise to the anion XII with a large bathochromic shift in alkali similar to that for XI; the same would apply to a C_3 hydroxyl where the anion XIII has similar mesomeric stabilisation and charge distribution. For the structure XV, however, with a hydroxyl at C_2, the bathochromic shift on formation of the anion XIV would be expected to be smaller, and comparable in magnitude with that of atheroline; the acidities of the two would presumably be similar also. The tentative structure XV



XIII.



XIV.

is thus put forward for moschatoline. Details of the isolation and synthetic work referred to will be published elsewhere.

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