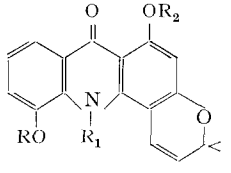
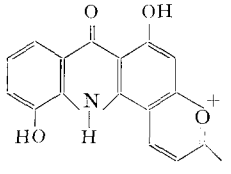
SPECIALIA

Extractives of Rutaceae: Atalaphyllidine, a New Acridone Base

Petroleum ether extract of the root bark of *Atalantia monophylla* Correâ afforded a mixture of acridone alkaloids together with a number of oxygen heterocycles[1-3]. The present communication is concerned with the elucidation of structure **1** for one of the minor bases, atalaphyllidine, $C_{18}H_{15}NO_4$ (M^+ 309), m.p. 275° (dec), λ_{max} (EtOH) 259, 270, 296, 324 and 405 nm (log ε; 4.72, 4.63, 4.43, 4.15, 3.82), absorption typical of that of 9-acridone alkaloids[4] and showed aluminium bathochromic shifts indicating the presence of hydroxy groups[5]. Its IR-spectrum showed a highly chelated CO at 1640 cm^{-1} and OH/NH at 3380 cm^{-1}. The existence of the OH function as phenolic hydroxyl was indicated by a green ferric reaction. 100 MHz NMR-spectrum of the base in C_5D_5N revealed the presence of a 2, 2-dimethylchromene system by the appearance of signals at 5.55 and 6.99 δ (d, J = 10 Hz each) and 1.48 δ (6 H, s). Amongst the aromatic protons, two of them appeared as multiplets around 7.32 δ, followed by the C-8 proton as a quartet at 8.14 δ. As expected, the C-2 proton appeared upfield at 6.52 δ.





(a)

1 R = R_1 = R_2 = H
2 R = Me, R_1 = R_2 = H
3 R = R_1 = R_2 = Me

The above spectroscopic data are consistent with structure **1** for atalaphyllidine which was compatible with the presence of mass fragmentation peaks at *m/e* 309 (M^+), 294 (100%, ion a), 155, 147, 133, 77, 69 and 43.

Methylation of the alkaloid with diazomethane gave a monomethyl ether **2** which also showed positive ferric reaction, thereby confirming the presence of chelated hydroxy group. The monomethyl ether **2**, $C_{19}H_{17}NO_4$ (M^+ 323), M.p. 200° showed UV- and IR-spectra essentially similar to that of the original base. NMR-spectrum (100 MHz; $CDCl_3$: DMSO 19:1) showed a 6 proton singlet at 1.42 δ (methyl protons), 3 proton singlet at 4.04 δ (methoxyl protons), 2 doublets at 5.6 and 6.52 δ (J = 10 Hz; chromene protons). The C-2 proton appeared as a singlet at 6.12 δ and the remaining aromatic protons appeared as multiplets between 7.08–7.16 δ (2H) and 7.8 δ (1H). The NH and the hydroxy proton at C-1 appeared as singlets at 8.62 and 10.32 δ which are exchangeable with D_2O.

Prolonged treatment of atalaphyllidine **1** in dry acetone with CH_3I in presence of anhydrous K_2CO_3 furnished a trimethyl derivative **3**, m.p. 175–176° which was identical with that of dimethyl derivative of alkaloid A[5] from m.m.p and superimposable IR-spectra, thus establishing structure **1** for the new base.

Summary. The structure of acridone alkaloid atalaphyllidine, has been established as 2′, 2′-dimethyl-[pyrano 5′, 6′: 3, 4]-1, 5-dihydroxy acridone, from spectroscopic data and chemical reactions.

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[6] Acknowledgments. The author is grateful to Dr. R. D. Bennett, California (USA) for the NMR-spectra, Dr. J. R. Lewis, Scotland for generous gift of an authentic sample of the dimethyl ether of alkaloid A and for informing its correct melting point, to Prof. P. K. Jena, Director, and Dr. S. N. Mahapatra of this Laboratory for encouragement.

Long Alkyl Chains-3-Substituted Pyrrole-2-Aldehyde (-2-Carboxylic Acid and Methyl Ester) from the Marine Sponge *Oscarella lobularis*

In the course of our continuing search for new metabolites from marine sponges, we undertook the determination of the chemical compounds of *Oscarella lobularis*, which was found to contain a novel group of substances characterized by saturated, mono- and di-unsaturated long alkyl chains linked at position 3 of pyrrol-2-aldehyde, -2-carboxylic acid and 2-carbomethoxy moieties.

Fresh tissues of the sponge, collected in the bay of Naples, were exhaustively exctracted with acetone. Ether-water partition of the residue and chromatography on silica gel of the ether extract (2.4 g from 22 g of the dry weighted animal) gave 3 fractions, viz a) in benzene, an ester fraction (60 mg; 0.3% based on dry weight of the animal); b) in 9:1 benzene-ether, an aldehyde fraction (150 mg; 0.8%) and c) in 7:3 benzene-ether, a carboxylic acid fraction (6 mg; 0.03%).

Aldehyde fraction. Chromatography of this fraction from 12% $AgNO_3$ – impregnated silica gel in 95:5 benzene-

ether gave 3 principal portions. The less polar one (8 mg), examined by combined GLC-m.s.[1], was clearly a mixture of 5 homologue components with molecular ions at M^+/e 361, 375, 389, 403 and 417 (relative proportions of 3.3, 12.5, 49, 25 and 10.2%, respectively, as determined from the GLC peaks). All components gave identical fragmentations in GLC-m.s. runs with major peaks at *m/e* 108.0453[2] (C_6H_6NO requires 108.0449) and 122.0599[2] (C_7H_8NO requires 122.0605), corresponding to fragments a and b. In the NMR-spectrum[3] of the total mixture, the aldehyde group was apparent (1 H singlet at 9.22 ppm); in the low field region there was two 1 H triplet at 6.76 and 5.94 ppm converted, on deuterium exchange of the NH proton (b signal at ca. 11.0 ppm), to two doublets with J 2.4 Hz, indicating a 2,3-disubstituted pyrrole ring[4]; in the remaining part of the spectrum there was a) a triplet (J 6 Hz) at 2.70 ppm ascribable to a methylene linked to the pyrrole ring, and b) a large signal at 1.26 ppm and a distorted triplet (J 6 Hz) at 0.9 ppm due to a normal unbranched aliphatic chain. The IR-spectrum[3] showed peaks corresponding to free (3445 cm^{-1}) and associated (3250 cm^{-1}) NH, bonded (1660 cm^{-1}) and free (1645 cm^{-1}) C = O groups indicating a 2-acylpyrrole moiety[5]. The UV-spectrum[3] likewise showed absorptions at 248 and 302 nm (ε 6000 and 17,500 assuming 389 as m.w.) consistent with a 3-alkyl-pyrrole-2-aldehyde[6]. From this we can conclude that the less polar portion of the aldehyde fraction comprises 5 components having structures **1** (*n* = 18 to 22).

By careful elution from the $AgNO_3$ – impregnated silica gel, the larger (60 mg), middle polar fraction, was recovered in 3 portions, of which the less polar contained **2** (10 mg) and the slightly more polar contained **3** (2 mg); the portions in between contained mixtures of **2** and **3**. The individual components gave single peaks in GLC and M^+/e in m.s. at 415 and 387, respectively, corresponding to monounsaturated C_{23} and C_{21} alkyl-substituted pyrrole-aldehydes. In both spectra 2 major fragments were seen at *m/e* 108 (100%, a) and 122 (84%, b). IR- and UV-spectra were identical to those of the mixture **1**, while the NMR-spectra, in addition to the signals corresponding to those assigned in the spectrum of **1** to an aldehyde proton, two pyrrole hydrogens and a normal unbranched aliphatic chain, showed a 2 H triplet (J 6 Hz) at δ 5.24 indicating a disubstituted double bond and a 4 H quartet (J 6 Hz) due to allylic methylene protons. The location of double bond in alkyl chains was ascertained by using the methoxy-mercuration-demercuration procedure followed by mass spectrometry, recently successfully applied by Minnikin et al.[7] to determination of double bond position in unsaturated fatty acid esters. For the preparation of the methoxy mercuriacetate derivatives we employed the modified procedure of WHITE[8], involving heating of the olefin with excess mercuric acetate in methanol under

a; *m/e* 108; R = CH=O
c; *m/e* 138; R = CO_2CH_3
d; *m/e* 124; R = CO_2H

b; *m/e* 122

1; *n* = 18 to 22

2

3

4

5

6

7

8 *n* = 18,19,20,22

9; *x* + *y* = 20
10; *x* + *y* = 18

11; *x* + *y* + *z* = 18

[1] Mass spectra (m.s.) were determined on the AEI MS-30 instrument at 70 eV, which for combination with gas-liquid chromatography (GLC) was attached to a Pyl-Unicam 104 instrument fitted with a glass column (3 mm × 1.5 m) packed with 1% – OV on silanized Chromosorb W (100–120 mesh) operating at 230–300° (6° min^{-1}) with He carrier at 40 ml min^{-1}.

[2] High resolution mass measurements were carried out on the total mixture, using the AEI MS-901 instrument at 70 eV.

[3] H'-NMR were measured at 100 MHz on a Varian XL-100 using CCl_4 solutions with $SiMe_4$ internal standard; infrared (IR) spectra in $CHCl_3$ solution using a Perkin-Elmer Infrared 257 spectrometer; ultra-violet (UV) spectra in CH_3OH solution using a Baush and Lomb Spectronic 505 apparatus.

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reflux for 1 h, which also gave rise to removal of the formyl group, probably via oxidation to carboxylic group followed by decarboxylation[9].

Treatment of the reaction mixture with sodium borohydride gave the isomeric methoxylated derivatives formulated as **4** (the NMR showed absence of the aldehyde proton, which was replaced by a pyrrol-α-H signal at δ 6.55, and the UV-absorption at 216 nm conformed with the literature data for an alkyl-substituted pyrrole), which were analyzed by GLC-m.s.[1].

The fragmentation patterns, characterized by peaks arising from cleavages adjacent to methoxyl groups (**4**) allowed the position of the original double bonds to be established as shown in **2** and **3**; peaks arizing by loss of methanol from the primary fragments also occurred and both the methoxylated derivatives gave the base peak at *m/e* 80. No evidence has been obtained to establish unambiguously the stereochemistry of the double bonds, but on the basis of the chemical shift of the allylic methylene protons (1.94 ppm), we tentatively assumed it to be *trans*[10].

The most polar component of the aldehyde fraction gave a single peak in GLC and a m.s. with substantially a single molecular ion at M^+/e 413, corresponding to a di-unsaturated C_{23} alkyl-3-substituted pyrrole-2-aldehyde (**5**). The UV- (λ_{max} 248, 302 nm; ε 6000 and 17,000), IR- (3445, 3250, 1660 and 1645 cm^{-1}) and NMR- [9.22 (1 H, s), 6.76 and 5.94 (each 1 H, d, J 2.4 Hz), 5.24 (4 H, t, J 6 Hz), 2.70 (2 H, t, J 6 Hz), 1.94 (8 H, q, J 6 Hz), 1.26 (bs) and 0.90 (3 H, distorted t) ppm spectra accord with this formulation. The methoxymercuration-demercuration procedure was also applied to this material. Direct GLC-m.s.[1] of the reaction mixture (organic layer) showed the presence of a monomethoxy derivative (M^+/e 417) and a dimethoxy derivative (M^+/e 449). The fragmentation patterns of the methoxylated materials were interpreted as shown in **6** and **7** and allowed the position of the original double bonds to be established as shown in **5**.

Ester fraction. Chromatography on 12% $AgNO_3$-impregnated silica gel in benzene of this fraction also gave 3 principal portions. The less polar portion (7 mg), examined by GLC-m.s.[1], contained 4 homologue components giving M^+/e at 447, 419, 405 and 391 (relative proportions 7, 40, 24 and 29%, respectively, determined from GLC peak areas). The mass spectra from all GLC peaks were marked by intense fragments at M^+-59 (loss of carbomethoxyl group) and *m/e* 138, which we supposed to be due to the ion c. From this we suggest that these correspond to alkyl-3-substituted pyrrole-2-carboxylic acid methyl esters **8**; the most relevant criteria confirming these assignements are the NMR- and UV-spectra. In the NMR this material showed 1 H doublets (J 2.4 Hz) at 6.64 and 5.84, a 3H s at 3.78, a 2H t (J 6 Hz) at 2.7 and also signals at 1.26 (bs) and 0.90 (distorted t) ppm. The UV-absorptions at 240 and 273 nm (ε, 5000 and 12,500 assuming a m.w. of 405) confirmed the relative position of the substituents (i.e. 2-carbomethoxy and 3-alkyl chain)[11]. The IR showed peaks corresponding to NH (3460 cm^{-1}) and C = O ester (1685 cm^{-1}).

The middle polar portion (15 mg) was a mixture of 2 compounds in the relative proportion of 7:3 giving in the GLC-m.s.[1] M^+/e at 445 and 417, respectively, and very similar fragmentations with major peaks at M^+-59 and *m/e* 138 (c). This together with UV, IR and NMR. [5.24 (2H, t, J 6 Hz), 1.96 (4H, q, J 6 Hz); disubstituted double bond] data of the mixture almost identical to those of **8** allowed us to suggest that these correspond to a C_{23} and C_{21} mono-unsaturated alkyl-3-substituted pyrrole-2-carboxylic acid methyl esters **9** and **10**, respectively. No attempts were made to locate double bonds.

The most polar fraction (10 mg) contained a single component giving in GLC-m.s.[1] M^+/e 443 corresponding to **11**; the UV, IR and NMR data, which inter alia excluded the presence of a conjugated diene, were consistent with this formulation.

Acid fraction. The minor, most polar fraction (6 mg), examined by m.s. contained 2 components giving M^+/e at 431 and 403 and a major peak at *m/e* 124 (ion d). Treatment with diazomethane gave a material identical in SiO_2-$AgNO_3$ TLC with the mixture of **9** and **10**.

Summary. A novel group of compounds characterized by saturated, mono- and di-unsaturated long alkyl chain (C_{18} to C_{23}) linked at position 3 of a pyrrol-2-aldehyde residue has been isolated from the marine sponge *Oscarella lobularis*, which also yielded a series of corresponding pyrrol-2-carboxylic acids and methyl esters.

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Chirality of (+)-Octoclothepin, a Stereospecific Neuroleptic Agent[1]

Two chiral neuroleptic agents exhibiting stereospecificity of biological action have been reported in the literature. These are methotrimeprazine, of which the (−)-enantiomer is the more potent[2] and butaclamol, of which the (+)-enantiomer is about as potent[3,4] as fluphenazine. The absolute configuration of (−)-methotrimeprazine is unknown, but that of (+)-butaclamol has been determined by X-ray crystal structure analysis[3].

We now find that the neuroleptic activity of octoclothepin[5,12] is confined to its (+)-enantiomer (see Table). This finding, though at variance with the earlier results

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