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NATURALLY OCCURRING 5-METHOXY-3(2H)-FURANONES. RE-ASSIGNMENT OF STRUCTURES TO THE ASPERTETRONIN GROUP OF NATURAL PRODUCTS

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Summary: Synthetic and spectroscopic investigations establish that the aspertetronin (also known as gregatin and graminin) group of natural products isolated from Aspergillus and Cephalosporium sp., has the 5-methoxy-3(2H)-furanone structure (4) rather than the previously assigned O-methyl tetronic acid structure (3).

The aspertetronins are a family of O-heterocycles found in Aspergillus and Cephalosporium sp.[†] The first two members of the family were isolated in 1969 from Aspergillus rugulosus,[1] and structural investigations suggested that the metabolites had the novel O-methyl tetronic acid structures (1a) and (2a). Optical antipodes of (1a) and (2a) accompanied by the acyl analogues (3a) and (3b) (R'=Me) were later isolated from Cephalosporium gregatum and A.panamensis[3], and the homologue (1b) of (1a) has been found in C. gramineum.[4] The aspertetronins all show significant antibacterial and antifungal activity. In the previous Letter[5] we described total syntheses of the structures (1a) and (3a, R'=Me) proposed for two natural aspertetronins, called aspertetronin A and gregatin B respectively. Comparative spectral data showed however that the natural products did not have the O-methyl tetronic acid structures proposed for them. We have now re-examined the spectral data reported for natural aspertetronins, and compared them with spectral data of synthetic model O-methyl tetronic acids and 5-methoxy-3(2H)-furanones. This study shows that the natural aspertetronins have the alternative 5-methoxy-3(2H)-furanone structure (4).

Both the synthetic O-methyl tetronic acids (1a) and (3a,R'=Me) were obtained as viscous oils, and each showed a single maximum in the electronic absorption spectrum centred at about 225 nm. By contrast, naturally derived aspertetronin A and gregatin B are crystalline solids (m.p. 72° and m.p. 83° respectively), and each shows strong absorption above 230 nm in its ultraviolet

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[†] The names 'gregatin' and 'graminin' have also been used to describe some members of this family of natural product.

spectrum. Moreover, whereas the O-methyl tetronic acids (1a) and (3a,R'=Me) show two very strong carbonyl absorption maxima, at 1760 and 1750 cm^{-1}, in their infrared spectra, the corresponding natural products instead show a single carbonyl absorption at 1705 cm^{-1} with a small shoulder at 1740 cm^{-1}. Although significant differences were also noted between the mass spectra of (1a) and natural aspertetronin A, apart from a difference in chemical shift between the OMe resonances (τ 6.28 natural: τ 5.95 synthetic), their p.m.r. spectra were closely similar.

The above data, and particularly the infrared data led us to suggest that our synthetic O-methyl tetronic acids and the natural aspertetronins were enol ether isomers of one another, with the natural products having the 5-methoxy-3(2H)-furanone structure (4).[6] To gain further insight into the physical characteristics of 5-methoxy-3(2H)-furanones we synthesised the enol ether (6) from the readily available dimethyltetronic acid (5).[7] Treatment of (5) with ethereal diazomethane, led to a 2:3 mixture of the crystalline furanones (6) (m.p. 48-50°) and (7) (m.p. 72-74°) which was separated by chromatography; the O-methyl tetronic acid (7) was identical with an authentic sample produced by an unambiguous route.[8] The ultraviolet and infrared spectral data obtained for (6) and (7), summarised on the formulae, mirrored those reported for the isomeric furanones (8) and (9) previously reported (see formulae).[9]

Comparison of the above sets of spectral data with those recorded for synthetic (1a) and (3a),[5] and for natural aspertetronin A and gregatin B establish that the latter have 5-methoxy-3(2H)-furanone structures. Since the structures of the related metabolites from Aspergillus and Cephalosporium sp. have all been deduced by comparison of spectral data with those of aspertetronin A, it follows that all known aspertetronins (gregatins, and graminins) have the 5-methoxy-3(2H)-furanone ring system rather than the O-methyl tetronic acid structure previously proposed for them.

To our knowledge 5-methoxy-3(2H)-furanones have not previously been reported in nature, whereas natural tetronic acid derivatives are widely distributed. It is interesting, that in the corresponding pyrone series of natural products, both α- and γ-pyrones e.g. luteoreticulin (10)[10] and aureothin (11)[11] have been found in Streptomyces sp.

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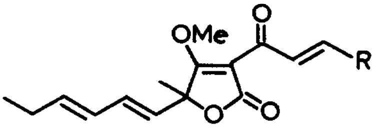
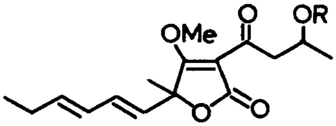


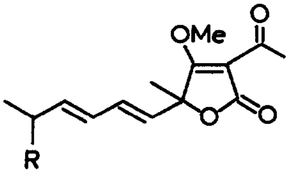
(1)

a R=Me; b R=n-Pr



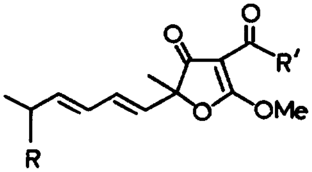
(2)

a R=H; b R=Me

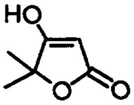


(3)

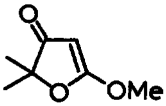
a R=H; b R=OH



(4)

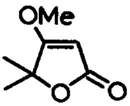


(5)



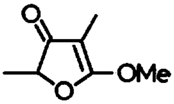
(6)

λ_{max} 249 nm; ν_{max} 1700 cm^{-1}



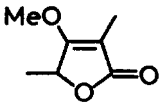
(7)

λ_{max} 218 nm; ν_{max} 1745 cm^{-1}



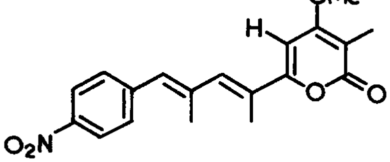
(8)

λ_{max} 256 nm; ν_{max} 1695 cm^{-1}

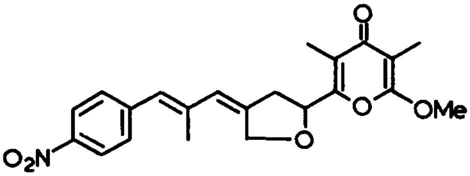


(9)

λ_{max} 229 nm; ν_{max} 1748 cm^{-1}



(10)



(11)

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