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UVARIAMICIN-I, II AND III: THREE NOVEL ACETOGENINS FROM *UVARIA NARUM*

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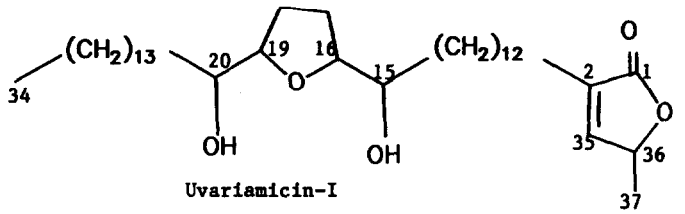
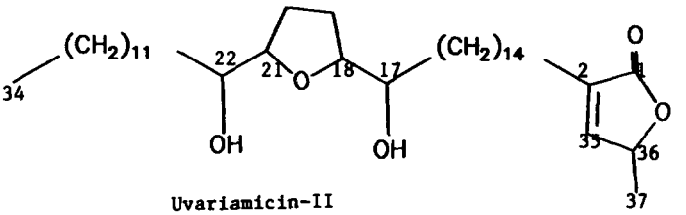
ABSTRACT: Uvariamicin-I, II and III, three novel acetogenins were characterized from the hexane extract of the root bark of Uvaria narum and their structures were elucidated on the basis of spectral evidence.

Isolation of 25 biologically active acetogenins has so far been reported from the genera *Uvaria, Rollinia, Asimina and Annona*, all belonging to the Annonaceae family (1). From these compounds, 18 belong to the C_{37} series containing two adjacent tetrahydrofuran (THF) rings, with the exception of two compounds bullatalicin and squamostatin-A, which contain two non-adjacent THF rings (1, 2). Six compounds, goniothalamicin, annonacin, annonacin-10-one, isoannonacin, isoannonacin-10-one and squamone are the reported members of the C_{35} series which contain only one THF ring in contrast to the more common C_{37} members with two THF rings (3, 4, 5) and neoannonin, which is the only member in C_{35} series with two THF rings (6). Almost all the compounds of both the C_{35} and C_{37} series have been found to possess potential cytotoxic, antitumour or pesticidal activities and, therefore, these compounds have attracted much interest. An investigation of the root bark of *Uvaria narum* (Annonaceae) from Kerala, India, has resulted in the isolation and characterization of several new acetogenins. In this communication we report the characterization of three novel acetogenins, which we named uvariamicin-I, II and III, and which are the first examples in the C_{37} series with only one THF ring.

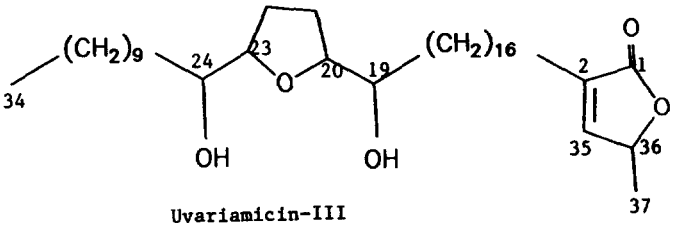
A mixture of uvarimicin-I, II and III, a whitish wax, was isolated from the hexane extract of rootbark after silica gel column chromatography (chloroform eluate) and preparative TLC. Uvariamicin-I, II and III could not be separated



Uvariamicin-I



Uvariamicin-II



Uvariamicin-III

from one another by column chromatography or preparative TLC because of their very close Rf values. They were found to be homogenous in many solvent systems and barely separated when applied in minimal concentration on silica gel plates (0.2 mm, Merck) using CH_2Cl_2:EtOAc (3:2) as the developing system. The ^1H and ^{13}C NMR spectra showed the characteristics of an α-β unsaturated γ-lactone, one THF ring, two hydroxyl groups and a long aliphatic chain. NMR studies could not distinguish the three positional isomers present in the mixture because of their identical chemical shifts. Mass spectral studies established that it was a mixture containing three positional isomers with structures I, II and III.

The molecular weight of the substance was found to be 592 from CIMS using CH_4 and NH_3 as reagent gases and positive FABMS which all resulted in a $(M + H)^+$ ion at m/z 593. The substance formed a diacetate, which upon FABMS showed a $(M + H)^+$ ion at m/z 677, and a diTMS derivative, which upon EIMS resulted in a $(M - CH_3^{\cdot})^+$ ion at m/z 721, indicating two hydroxyl groups. ^1H NMR pointed to two carbinol methine protons at δ 3.42 which were shifted to δ 4.87 in the diacetate derivative. In addition, ^{13}C NMR showed the presence of two carbinol

methine carbons at δ 74.34 and 74.05. The ^{1}H NMR signals at δ 6.99 (d, H-35), 4.98 (q, H-36), 1.40 (d, H-37) and ^{13}C NMR signals at 173.8 (C-1), 148.8 (C-35), 134.3 (C-2), 77.3 (C-36) and 19.2 (C-37) confirmed the presence of the α-ß unsaturated γ-lactone moiety. A two proton triplet at δ 3.81 in the ^{1}H NMR spectrum and a single peak for two carbons at δ 82.63 in the ^{13}C NMR spectrum were agreeable with a single THF ring. A triplet at δ 0.88 and a very large resonance at δ 1.25 in ^{1}H NMR suggested the long aliphatic chain. This was supported by the ^{13}C NMR shifts due to several methylene groups at δ 33.4, 34.1, 31.9, 22.7, 24.7, 25.2, 25.6, 27.2, 27.4, 28.1, 28.7, 29.1, 29.3, 29.6 and the resonance of a terminal methyl group at δ 14.1

The EIMS data of the product revealed the presence of three isomers which differ in the position of the THF ring and its surrounding hydroxyl groups from the following information. The major fragment ions in this type of compounds are formed by an α-cleavage of C-O bonds occurring between the oxygenated carbons and retain the charge on the α-ß unsaturated γ-lactone containing part of the molecule. The EI mass spectral data obtained for the underivatized products and their diTMS and diacetate derivatives are summarized in Figure 1. The two prevalent α-cleavages are indicated with A and B. The underivatized mixture showed major fragment ions at m/z 295 (100%), 323 (95%), 351 (96%), 347 (365-H_2O; 48%), 375 (393-H_2O; 40%) and 403

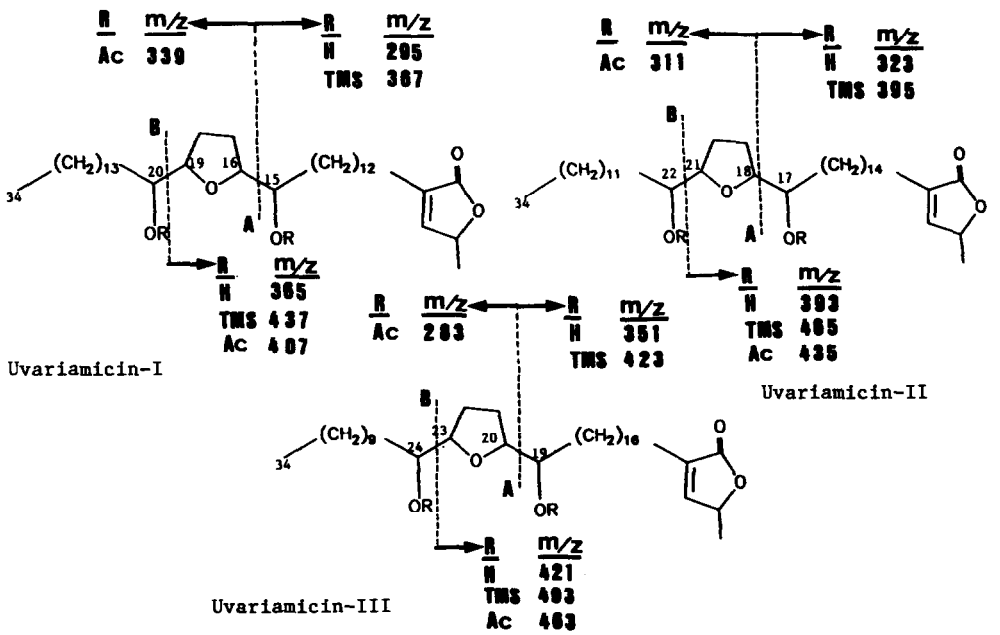


Figure 1 EIMS data for uvarimicin-I, II and III and for diTMS and diacetate derivatives thereof.

(421-H_2O; 38%). EIMS also indicated that the 3 isomers resulted in different evaporation profiles upon direct probe analysis. Mass chromatography of the ion pairs at m/z 295, 347 (I), m/z 323, 375 (II) and m/z 351, 403 (III) established the order of volatility as I>II>III. The HREIMS on the ions at m/z 295,323 and 351 confirmed their elemental compositions as $C_{18}H_{31}O_3$, $C_{20}H_{35}O_3$ and $C_{22}H_{39}O_3$ respectively, indicating the differences in chain length between these fragments. The EIMS data obtained for the diTMS derivative are in good agreement with those of the underivatized mixture, showing mass increments of 72 units for the characteristic ions formed by the A and B cleavages. With respect to the EIMS results obtained for the diacetate derivative, the fragment ions found showed mass increments of 42 units and could again be explained by the A and B cleavages with the exception, however, that the fragment ion formed by the A cleavage retains its charge on the THF containing moiety. In addition, the fragment ion formed by the B cleavage showed a corresponding ion due to loss of acetic acid.

The stereochemistry of C-36 in the three isomers is unknown. A proton chemical shift correlation methodology of the diagnostic protons in the diacetate with those in the Hoye and Suhaldonik model compounds (7) allowed to conclude that the isomers I, II and III have an identical relative configuration, i.e., a threo/trans /threo, in the chiral centres of the THF ring and the surrounding hydroxyl bearing carbons. The high field ^1H NMR (300 MHz, $CDCl_3$) spectrum of the acetate showed only one acetate methyl singlet at δ 2.077 indicating that both relationships between the carbon atoms in the THF ring and their adjacent acetate bearing carbons (i.e., C-15/C-16 and C-19/C-20 in isomer I, C-17/C-18 and C-21/C-22 in isomer II, and C-19/C-20 and C-23/C-24 in isomer III) are threo. Similarly, the ^1H NMR shifts of the oxymethine protons in the THF ring at δ 3.98 suggested a trans relationship for C-16/C-19 in isomer I, C-18/C-21 in isomer II and C-20/C-21 in isomer III. The bioactivitiy of the mixture is under investigation.

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