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SYNCARPUREA, A NOVEL METABOLITE FROM *UVARIA AFZELII*

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Summary: The isolation and structure determination of syncarpurea (**1**), a novel urea from *Uvaria afzelii* is reported.

Several novel compounds have recently been isolated from the African shrub *Uvaria afzelii* Scot Eliot (Annonaceae).[1,2,3] Careful examination of the polar column fractions has yielded an additional interesting constituent, syncarpurea (**1**), which is the subject of this report. Syncarpurea (**1**) was isolated as an optically inactive crystalline material. Silica gel column[2] chromatography with 64% ether in benzene followed by ether yielded an approximately 500 mg fraction from which 162 mg of **1** was obtained by crystallization from large volumes of $CHCl_3$, m.p. 239-240°. The molecular formula, $C_{15}H_{20}O_3N_2$, was established by elemental analysis and low resolution mass spectrometry. The UV spectrum showed λ_{max} (MeOH) 306 nm (ε 5.52×10^3) and 236 (ε 4.31×10^3). Upon addition of sodium hydroxide, the solution turned yellow and gave an additional band at λ_{max} 362 nm. The IR (KBr) showed a broad band at 3230 cm^{-1} and strong bands at 1720, 1690 and 1650 cm^{-1}. The 90 MHz ^1H NMR spectrum ($CDCl_3$) displayed one proton signals at δ 9.25 (slowly exchanges with D_2O), 4.39 (dd, J=10.1, 5.4Hz), 3.85 (m), 3.35 (m), 2.80 (m) and 1.60 (m). Other salient features included a two proton multiplet at δ 1.90 and two singlets at 1.54 and 1.35 which integrated for six protons each. The EI mass spectrum displayed m/z 276 (M^+,25%), 262 (M^+-14,54%), 261 (M^+-15, 100%), and 248 (M^+-28,27%). Syncarpurea (**1**) crystallized ($CHCl_3$/benzene) in the monoclinic crystal class with **a**=13.488(2), **b**=5.973(1), **c**=23.892(2)Å, and β=96.83(2)°. The crystal density, systematic extinctions, and lack of optical activity were uniquely accomodated by space group $P2_1/n$ with $C_{15}H_{20}N_2O_3 \cdot C_6H_6$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected using variable speed, $1°$ ω-scans and graphite monochromated CuKα radiation (1.54178Å). After correction for Lorentz, polarization and background effects, 2275 reflections were judged observed ($|F_o| \geq 3\sigma(F_o)$).[4] A phasing model was achieved uneventfully and block diagonal least squares refinements with anisotropic heavy atoms including a benzene of crystallization and isotropic hydrogens have converged to a current residual of 0.046 for the observed reflections.[5] A computer generated perspective drawing of the final x-ray model is given in Figure 1.

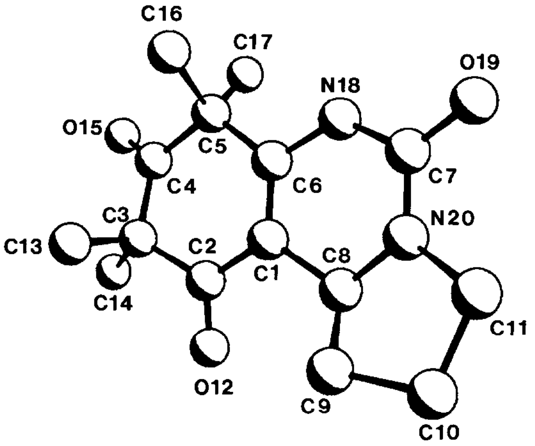
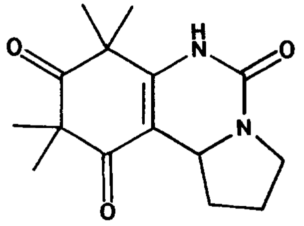
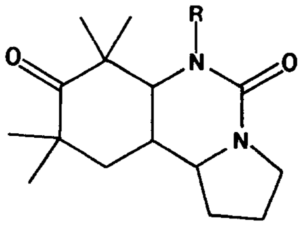


Figure 1. A computer generated perspective drawing of the final x-ray model of syncarpurea (1). Hydrogens are omitted for clarity.



1



2 R= H
3 R= Ac

Structure 1 for syncarpurea is completely consistent with the spectroscopic data. Specifically the signal at δ 9.25 is assigned to the NH proton; 4.39, H8; 3.85 and 3.35, H11; 2.80, H9β6; 1.90(2H), H10; 1.60(1H), H9α; 1.54(6H) and 1.35(6H) CH_3's. Irradiation at δ 4.38 (H8) simplified the signals at 2.80 (H9β) and 1.60(H9α) but did not affect the signals at 3.85 and 3.35 (H11). Irradiation at δ 2.80 collapsed the signal at 4.39 to a doublet (J=5Hz) and simplified the resonances at δ 1.90 and 1.60. Again the signals at δ 3.85 and 3.35 were not affected. Irradiation at δ 1.90 collapsed the signals at 3.35 and 3.85 to a pair of AB doublets (J=12Hz) in addition to perturbing the signals at δ 2.80 and 1.60. Structure **1** is also consistent with the ^{13}C NMR ($CDCl_3$, 15.03 MHz) which displayed signals for three carbonyls at δ 211.9 (s, C4), 195.6 (s, C2), 154.4 (s, C7); two olefinic carbons at 151.4 (s, C6), 105.7 (s, C1); aliphatic carbons at 55.5 (s, C5), 45.6 (s, C3); two aliphatic carbons attached to nitrogen at 57.2 (d, C8), 44.4 (t, C11); two aliphatic carbons at 33.1 (t, C9), 29.7 (t, C10); and four methyls at 25.9(q), 24.8(q), 22.7(q), and 21.5(q).

The degradative chemistry of syncarpurea (**1**) was not straightforward. Catalytic hydrogenation of **1** (ethanol, 10% Pd-C, 30 psi) gave a product which has been assigned structure **2**.[7] The molecular formula, $C_{15}H_{24}O_2N_2$, was established from low resolution mass spectral data and elemental analysis. The overall transformation could be rationalized if the carbonyl at C2 were first reduced to the allylic alcohol, which then underwent hydrogenolysis, and finally hydrogenation of the double bond. The UV spectrum of **2** showed a weak λ_{max} at 300 and 225 nm but did not become colored upon addition of base. The IR showed bands at 3280, 3250, 1690 and 1640 cm^{-1}, and the ^{1}H NMR[7] was consistent with formulation **2**. Poor solubility prevented us from obtaining a ^{13}C NMR spectrum of **2**, however acetylation (Ac_2O/pyridine, reflux) converted **2** to a $CHCl_3$ soluble monoacetate, **3**. The ^{1}H NMR spectrum[8] of **3** showed H6 as a doublet at δ 5.18, the protons at H8 and H11 as a multiplets between δ 3.9 and 3.3, H1 as a multiplet at δ 2.85, and the expected methyl resonances. Spin-spin decoupling experiments confirmed these assignments. Irradiation at δ 5.18 simplified the signal at 2.85 but did not affect the signals between 3.3 and 3.9. Irradiation at δ 2.85 collapsed the 5.18 signal to a singlet. The ^{13}C NMR data[8] for **3** were also consistent with the proposed structure.

Syncarpurea (**1**) is one of the few nitrogen containing metabolites to be isolated from Uvaria and the overall structure is unprecedented. It is related to syncarpic acid and can formally be viewed as the condensation product of syncarpic acid with an N-carboxy-Δ^1-pyrrolinium ion.

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3. M. Leboeuf, A. Cave, P. K. Bhaumik, B. Mukherjee, and R. Mukherjee, Phytochemistry, **21**, 2783-2813 (1982).

4. The principal crystallographic programs employed were: REDUCE and UNIQUE, by M. E. Leonowicz, Cornell University, 1978; MULTAN 78 (locally modified to perform all Fourier calculations including Patterson syntheses), by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, University of York, England, 1978; NQEST, by C. M. Weeks at the Medical Foundation of Buffalo, Inc., 1976; BLS78A, by K. Hirotsu, and E. Arnold, Cornell University, 1980; CRYSTALS, by D. J. Watkin and J. R. Carruthers, Chemical Crystallography Laboratory, University of Oxford, 1981; ORTEP, by C. K. Johnson, Oak Ridge National Laboratory (ORNL-3794), 1970; PLUTO78, by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, by K. Hirotsu, Cornell University, 1978.

5. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.

6. Assignment of this signal to the H9β follows from the spin-spin decoupling data given in the text and inspection of molecular models which show that H9β falls in the deshielding cone of the unsaturated carbonyl system.

7. Chemical and spectral data for **2**: m.p. 267-270° ($CHCl_3$-ethanol); UV (MeOH) λ_{max} 300 nm (ε 52) and 225 nm (ε 295); IR (KBr) 3280, 3250, 1690 and 1640 cm^{-1}; MS m/z 264 (M^+, 1%), 249 (M^+-15, 1%); ^1H NMR ($CDCl_3$) δ 4.50 (NH, s, ex D_2O), 3.70 (1H, m), 3.5 (2H, m), 2.6(1H, m), 2.0-1.5 (7H, complex pattern), 1.22 (3H, s), 1.20 (3H, s), 1.09 (3H, s) and 1.05 (3H, s); anal. calcd. $C_{15}H_{24}O_2N_2$: C, 68.13; H, 9.15; N, 10.60; found: C, 68.20; H, 9.19; N, 10.05.

8. Chemical and spectral data for **3**: m.p. 152-154° (hexane); UV (MeOH) λ_{sh} 300 (ε 70), λ_{max} 237 (ε 497); IR (KBr) 1702 and 1660 cm^{-1}; MS m/z 306 (M^+, 0.5%), 291 (M^+-15, 0.5%) and 151 (100%); ^1H NMR ($CDCl_3$) δ 5.18 (1H, d, J=10.5Hz, H6), 3.9-3.3 (3H, m, H8 and H11), 2.85 (1H, m, H1), 2.28 (3H, s, $COCH_3$), 2.2-1.5 (6H, complex pattern), 1.19 (3H, s, CH_3), and 1.08 (9H, s, CH_3's); ^{13}C NMR ($CDCl_3$) 217.1 (s, C4), 170.1 (s, $CH_3\underline{C}O$), 155.6 (s, C7), 57.4 and 54.4 (both d, C8 and C6), 51.2 (s, C5), 45.3 (t, C11), 42.0 (s, C3), 35.9 (d, C1), 34.6 (t, C9), 27.0 and 24.8 (both t, C2 and C10), 28.5, 25.4, 24.8, 23.7 and 22.5 (all q, CH_3's).

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