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The reactions between the aldehyde-anhydride fujenal and ammonia, hydrazine and hydroxylamine

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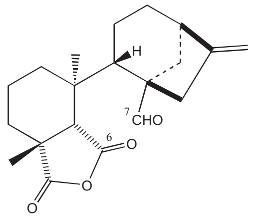
The structures of the products obtained from the reactions of the aldehyde-anhydride fujenal with ammonia, hydrazine and hydroxylamine have been established by X-ray crystallography.

Keywords: fujenal, diterpenoids, aldehydes, anhydrides, nitrogen nucleophiles

When the diterpenoid fungal metabolite fujenal (**1**) was first isolated from *Gibberella fujikuroi*,[1] a number of nitrogen containing derivatives, including some anils and an oxime, were prepared in order to characterise the aldehyde. However, because the interactions[2,3] between the aldehyde and the anhydride functional groups were not understood at the time, the structures of the products, particularly the oxime, were not established. We now report the preparation and X-ray crystal structures of three nitrogen-containing compounds prepared from the reaction of fujenal with ammonia, hydrazine and hydroxylamine. The formation of these compounds illustrates several aspects of the chemistry of fujenal.



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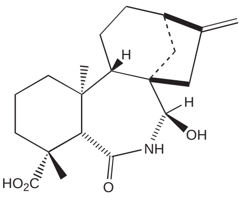

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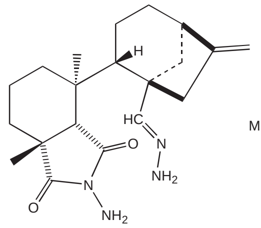

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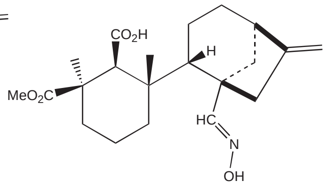

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Fujenal (**1**) did not react easily with ammonia at room temperature, but on heating with methanolic ammonia it gave a lactam (**2**) (ν_{max} 3293 (N-H), 1703 (C=O) cm^{-1}) lacking the IR absorptions characteristic of the five-membered ring anhydride. The compound was difficult to crystallise but an X-ray crystal structure of an acetone solvate (see Fig. 1) was eventually obtained. This showed that the compound was a seven-membered lactam. The formation of the aminol from the C-7 aldehyde had been followed by aminolysis of the anhydride. An interesting feature is the geometry at C-7, in which the hydroxyl group has taken up an axial conformation comparable to that of the C-7 pseudo-esters.[4] This stereochemistry is presumably determined by the anomeric interaction between the lone pairs on the amide nitrogen and the C-7 oxygen.

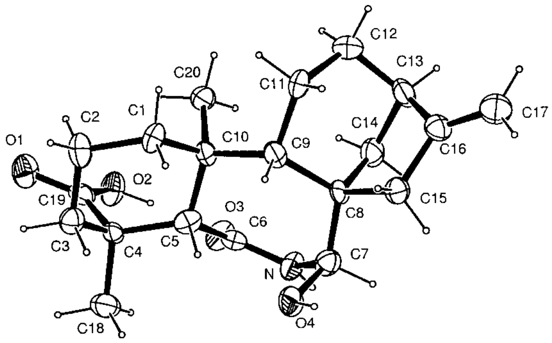

Fig. 1 X-Ray crystal structure of compound **2**.

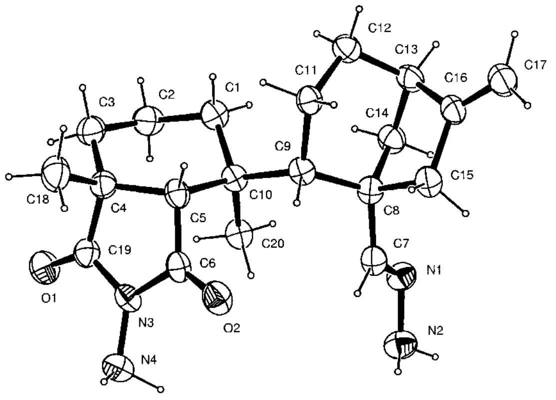

Fig. 2 X-Ray crystal structure of compound **3**.

When fujenal was treated with hydrazine hydrate, it formed a derivative **3** in which both the anhydride and the aldehyde had separately reacted with hydrazine to give a hydrazide and a hydrazone. The structure of this derivative was again established by X-ray crystallography (see Fig. 2). In this case the anhydride has formed a five-membered hydrazide (*N*-aminoimide).

Treatment of fujenal with methanolic hydroxylamine hydrochloride and pyridine gave an oxime **4** in which the anhydride ring had undergone methanolysis. The X-ray crystal structure (see Fig. 3) showed that not only had methanolysis occured but that the structure had undergone rotation about the 9:10 bond. This conformation is stabilised in the crystal by hydrogen bonding between the oxime of one molecule and the carboxylic acid of another. In the original work,[1] the oxime was prepared in aqueous ethanol and the analytical data of the product were in accord with a dicarboxylic acid rather than a mono-ester.

Whereas the product from the treatment of fujenal with aniline was an anil, the compound formed from *p*-toluidine was formulated as a *p*-tolylimide since it had retained the aldehydic IR absorption but had lost that of the anhydride. In our hands reaction with 3,4-dimethylaniline gave an anil which possessed anhydride absorption in the IR (ν_{max} 1848,

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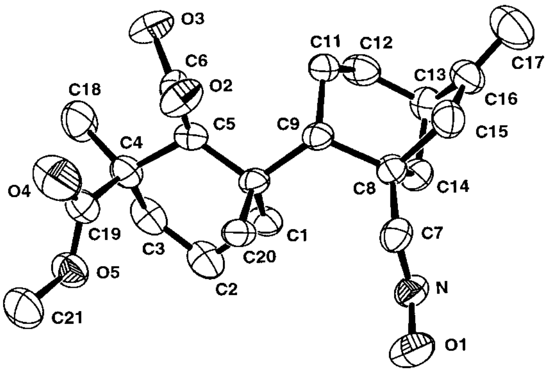

Fig. 3 X-Ray crystal structure of compound **4** (hydrogen atoms omitted).

1772 cm^{-1}). The aldehyde C–H resonance in the ^{1}H NMR spectrum had been replaced by a CH=N signal (δ_H 7.64).

The formation of these different products can be rationalised in terms of the easy dehydration of the tetrahedral intermediate to form the hydrazone and oxime. On the other hand, the aminol has sufficient lifetime to allow the amine to open the anhydride ring to form the lactam, providing a further example of reactions that involve both the aldehyde and the anhydride of fujenal.

Experimental

IR spectra were determined as nujol mulls. ^{1}H NMR spectra were determined at 300 MHz on a Bruker AMX spectrometer for solutions in deuteriochloroform.

The reaction of fujenal with ammonia: Fujenal (1 g) was dissolved in methanol (50 cm^3) and treated with 0.880 ammonia (5 cm^3). The mixture was heated under reflux for 2 h. The methanol was evaporated, the solution was cooled and diluted with water. The product was recovered in ethyl acetate. The lactam **2** (300 mg) crystallised from acetone, m.p. 210–213 °C. IR: ν_{max}/cm^{-1} 3293, 1703, 1627; NMR: δ_H 0.91 (3H, s, 20-H), 1.01 (3H, s, 18-H), 0.8–2.2 (17H, overlapping multiplets), 3.80 (1H, s, NH), 4.14 (1H, s, 7-H), 4.55 and 4.62 (each 1H, s, 17-H). (Found: C, 69.1; H, 8.5; N, 4.0. $C_{20}H_{29}NO_4$ requires C, 69.4; H, 8.4; N, 4.0 %)

The reaction of fujenal with hydrazine: Fujenal (1 g) was dissolved in methanol (20 cm^3) and treated with hydrazine hydrate (5 cm^3). The mixture was heated under reflux for 2 h. The methanol was evaporated, the solution was cooled and diluted with water. The product was extracted into ethyl acetate. The hydrazone derivative **3** (350 mg) crystallised from methanol, m.p. 246 °C. IR: ν_{max}/cm^{-1} 3395, 1703, 1696. NMR: δ_H 0.78 (3H, s, 20-H), 1.34 (3H, s, 18-H), 0.9–2.2 (17H, overlapping multiplets), 4.75 and 4.82 (each 1H, s, 17-H), 7.73 (1H, s, 7-H). (Found: C, 66.5; H, 8.4; N, 15.3. $C_{20}H_{30}N_4O_2$ requires C, 67.0; H, 8.4; N, 15.6 %)

The reaction of fujenal with hydroxylamine: Fujenal (1 g) in methanol (20 cm^3) was treated with hydroxylamine hydrochloride (250 mg) and pyridine (1 cm^3). The mixture was heated under reflux for 2 h. The methanol was evaporated, the solution was cooled and diluted with water. The product was taken into ethyl acetate. The oxime derivative **4** (400 mg) crystallised from methanol, m.p. 216–218 °C. IR: ν_{max}/cm^{-1} 3351, 3260, 1736,1700, 1663; NMR: δ_H 0.81 (3H, s, 20-H), 0.94 (3H, s, 18-H), 0.8–2.2 (17H, overlapping multiplets), 3.04 (3H, s, OMe), 4.71 and 4.82 (each 1H, s, 17-H), 7.37 (1H, s, 7-H). (Found: C, 66.7; H, 8.2; N, 3.8. $C_{21}H_{31}NO_5$ requires C, 66.8; H, 8.3; N, 3.7 %)

The reaction of fujenal with 3,4-dimethylaniline: Fujenal (1 g) was dissolved in methanol (50 cm^3) and treated with 3,4-dimethylaniline (350 mg). The mixture was heated under reflux for 2 h. The methanol was evaporated, the solution was cooled and diluted with water. The product was recovered in ethyl acetate. The 3,4-dimethylanil (300 mg) crystallised from methanol, m.p. 190 °C. IR: ν_{max}/cm^{-1} 3412, 1848, 1772, 1640, 1598; NMR: δ_H (pyridine-d_5) 1.12 (3H, s, 20-H), 1.37 (3H, s, 18-H), 0.8–2.2 (17H, overlapping multiplets), 2.22 (6H, s, Ar-Me), 4.92 and 5.00 (each 1H, s, 17-H), 7. 04 and 7.21 (each 1H, d, J = 7.9 Hz, Ar-H), 7.10 (1H, s, Ar-H), 7.64 (1H, s, 7-H). (Found: C, 76.0; H, 8.0; N, 3.0. $C_{28}H_{35}NO_3$ 0.5H_2O requires C, 76.0; H, 8.2; N, 3.2 %)

X-ray crystallographic data and structure determinations: *Compound* **2**, $C_{20}H_{29}NO_4.2C_3H_6O$, M_r 463.60, orthorhombic, space group $P2_12_12_1$ (No.19), a = 8.9058(6), b = 9.0191(5), c = 31.3392(17) Å, $\alpha = \beta = \gamma = 90°$, V = 2517.2(3)Å^3, Z = 4, D_{calc} = 1.11g cm^{-3}, μ = 0.09 mm^{-1}, F(OOO) = 1008. Data were collected from a crystal of size 0.20 × 0.15 × 0.02 mm^3 on a KappaCCD diffractometer. A total of 9002 reflections were collected for $1.30 < \theta < 21.97$ ° and $-9 \le h \le 8$, $-8 \le k \le 9$, $-32 \le l \le 30$. There were 3076 independent reflections and 2159 reflections with $I > 2\alpha(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full-matrix least squares on F^2. The final R indices were [$I > 2\alpha(I)$] R_1 = 0.079, wR_2 = 0.181 and all data R_1 = 0.127, wR_2 = 0.208. The goodness-of-fit on F^2 was 1.122 and the largest difference peak and hole was 0.41 and –0.45 e.Å^{-3}. The diffraction from the thin plate crystal was very weak.

Compound **3**: $C_{20}H_{30}N_4O_2$, M_r 358.48, orthorhombic, space group $P2_12_12_1$ (No.19), a = 6.3691(7), b = 13.4478(17), c = 21.623(3)Å, $\alpha = \beta = \gamma = 90°$, V = 1852.0(4) Å^3, Z = 4, D_{calc} = 1.29 g cm^{-3}, μ = 0.09 mm^{-1}, F(OOO) = 776. Data were collected from a crystal of size 0.20 × 0.15 ×0.10 mm^3 on a KappaCCD diffractometer. A total of 5238 reflections were collected for $3.77 < \theta < 21.95$ ° and $-6 \le h \le 6$, $-14 \le k \le 12$, $-20 \le l \le 22$. There were 2185 independent reflections and 2012 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full-matrix least squares on F^2. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.037, wR_2 = 0.084 and all data R_1 = 0.043, wR_2 = 0.087. The goodness-of-fit on F^2 was 1.056 and the largest difference peak and hole was 0.11 and –0.13 e.Å^{-3}.

Compound **4**: $C_{21}H_{31}NO_5$, M_r 377.47, orthorhombic, space group $P2_12_12_1$ (No.19)), a = 6.5629(3), b = 8.7937(3), c = 34.4800(19) Å, $\alpha = \beta = \gamma = 90$, V = 1989.9(2)Å^3, Z = 4, D_{calc} = 1.26 g cm^{-3}, μ = 0.09 mm^{-1}, F(OOO) = 816. Data were collected from a crystal of size 0.1 × 0.1 × 0.1 mm^3 on a KappaCCD diffractometer. A total of 8442 reflections were collected for $4.24 < \theta < 22.98$ ° and $-7 \le h \le 5$, $-9 \le k \le 7$, $-24 \le l \le 37$. There were 2730 independent reflections and 1987 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full-matrix least squares on F^2. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.052, wR_2 = 0.103 and all data R_1 = 0.086, wR_2 = 0.116. The goodness-of-fit on F^2 was 1.044 and the largest difference peak and hole was 0.23 and –0.24 eÅ^{-3}. The crystals of this compound were all small and diffracted weakly.

The crystallographic data of compounds **2**, **3** and **4** have been deposited at the Cambridge Crystallographic Data Centre, as CCDC nos 235 184-6 respectively.

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