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Structure of 6-[Cinnamoyl(2-morpholinoethyl)amino]-1,3-dimethyluracil, $C_{21}H_{26}N_4O_4$

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Abstract. $M_r = 398{\cdot}46$, triclinic, $P\bar{1}$, $Z = 2$, $a = 10{\cdot}833\,(7)$, $b = 10{\cdot}465\,(7)$, $c = 11{\cdot}725\,(6)$ Å, $\alpha = 98{\cdot}02\,(5)$, $\beta = 123{\cdot}54\,(4)$, $\gamma = 93{\cdot}62\,(4)°$, $V = 1081{\cdot}8$ Å^3, $D_x = 1{\cdot}21$, $D_m = 1{\cdot}17$ Mg m^{-3}, μ(Mo $K\alpha$) $= 5{\cdot}2$ mm^{-1}, λ(Mo $K\alpha$) $= 0{\cdot}7109$ Å, $F(000) = 424$, $T = 293$ K, final $R = 0{\cdot}05$, 2155 measured reflections. The X-ray analysis reveals that the exocyclic N atom of the title compound is sp^2 hybridized and that the uracil and cinnamoyl planes are perpendicular. This may explain the lack of biological activity of the above derivative in comparison with its *C*-substituted isomer. A water molecule seems to be attracted by the morpholinoethyl moiety.

Introduction. To increase the water solubility of intercalating antitumor 6-amino-5-cinnamoyl-1,3-dimethyluracils, we introduced a dialkylaminoalkylamino chain at the 6-position of the uracil ring. The structure of a compound in this series has been studied in solution and by X-ray crystallography (Warin, Baert, Bernier & Henichart, 1984).

The synthesis of such a compound involved the acylation of a 6-(dialkylaminoalkylamino)uracil intermediate which has been found to occur at the C(5) position in acidic medium leading to the expected product but also at the N(6) position, in neutral conditions. The structure in the solid state of this isomeric form (NSC 329685) (Fig. 1) is here reported.

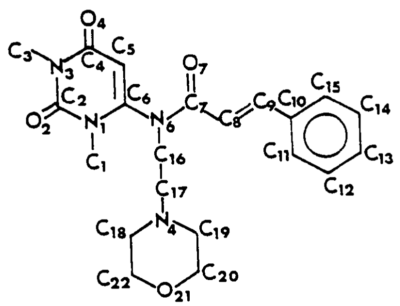

Fig. 1. The atomic numbering scheme.

Experimental. Single crystals obtained from an ethanol solution by slow evaporation. Colorless crystal $0{\cdot}5 \times 0{\cdot}4 \times 0{\cdot}6$ mm. D_m measured by flotation. 25 reflections for determination of lattice parameters. 5592 reflections measured, Philips PW 1100 diffractometer, graphite-monochromated Mo $K\alpha$ radiation, ω–2θ scan, $2\theta_{\max} = 30°$, h -13 to 13, k -14 to 14, l 0 to 14, invariant scan width $1{\cdot}8°$. Lorentz and polarization corrections. No absorption or extinction corrections. 2155 reflections with $I > 3\sigma(I)$ used in the analysis. Three standard reflections, intensity variation 2%. Structure solved by direct methods with *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). All H atoms located in difference synthesis and their temperature parameters maintained throughout the refinement equal to those of the atoms to which they are bonded. Structure refined (on *F*) by full-matrix least squares with *SHELX*76 (Sheldrick, 1976) with anisotropic thermal parameters for the non-hydrogen atoms. Refinement converged to $R = 0{\cdot}05$, $R_w = 0{\cdot}46$ for 2155 reflections; $w = 1/[\sigma(F_o)]^2$. Scattering factors for heavy atoms from Hanson, Herman, Lea & Skillman (1964), for H from Stewart, Davidson & Simpson (1965). Peaks and troughs in final difference synthesis $\leq |0{\cdot}25|$ e Å^{-3}. $(\Delta/\sigma)_{\max} = 0{\cdot}14$.

Discussion. The final atomic parameters are listed in Table 1.* The bond distances and angles (Table 2) are in agreement with accepted values. The C—H and O—H bond lengths are in the range $0{\cdot}88$ to $1{\cdot}14$ Å.

The distances of O(H_2O) to C(15), C(22), N(4) and C(18) are respectively 3·27, 2·99, 2·77, 3·08 Å. The H_2O molecule seems to be attracted by the morpholinoethyl molecule. All the other intermolecular distances are greater than the sum of the van der Waals radii of the atoms involved.

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39411 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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The hyperconjugation of the cinnamoyl explains the small values of the thermal parameters of the cinnamoyl group in comparison with those of other atoms of the molecule.

Table 1. *Atomic coordinates* ($\times 10^4$) *and* U_{eq} *values* ($\times 10^3$)

$$U_{\text{eq}} = \tfrac{1}{3}[U_{11} + U_{22} + U_{33} + 2(U_{23}\cos\alpha + U_{13}\cos\beta + U_{12}\cos\gamma)].$$

	x	y	z	U_{eq}(Å^2)
N(1)	0248 (3)	9084 (3)	1632 (3)	33 (5)
C(1)	0951 (5)	10373 (4)	2565 (5)	54 (5)
C(2)	−1167 (4)	8996 (4)	0412 (4)	40 (4)
O(2)	−1731 (3)	9970 (3)	0116 (3)	57 (5)
N(3)	−1866 (3)	7770 (3)	−0414 (3)	35 (5)
C(3)	−3381 (4)	7674 (5)	−1698 (4)	55 (6)
C(4)	−1283 (4)	6636 (4)	−0107 (4)	37 (5)
O(4)	−2029 (3)	5575 (3)	−0879 (3)	57 (6)
C(5)	0221 (4)	6816 (4)	1116 (4)	33 (5)
C(6)	0922 (4)	7988 (4)	1925 (3)	29 (4)
N(6)	2449 (3)	8227 (3)	3093 (3)	32 (4)
C(7)	2918 (4)	8115 (4)	4417 (4)	36 (4)
O(7)	4252 (3)	8372 (3)	5350 (3)	47 (5)
C(8)	1763 (4)	7676 (3)	4639 (4)	37 (5)
C(9)	2169 (4)	7554 (4)	5902 (4)	47 (5)
C(10)	1239 (5)	7071 (4)	6345 (5)	53 (6)
C(11)	−0278 (6)	6595 (5)	5408 (5)	67 (6)
C(12)	−1107 (6)	6106 (5)	5871 (6)	86 (7)
C(13)	−0447 (9)	6117 (6)	7254 (8)	96 (7)
C(14)	1015 (9)	6568 (7)	8161 (7)	83 (7)
C(15)	1891 (6)	7066 (6)	7748 (5)	81 (7)
C(16)	3573 (4)	8604 (4)	2802 (4)	37 (4)
C(17)	4269 (4)	7432 (4)	2658 (4)	48 (5)
N(4)	5187 (3)	7710 (3)	2143 (3)	51 (5)
C(18)	6544 (5)	8654 (4)	3174 (5)	80 (7)
C(19)	5634 (5)	6516 (5)	1795 (5)	75 (6)
C(20)	6576 (6)	6798 (5)	1256 (5)	95 (8)
O(21)	7877 (3)	7724 (4)	2238 (4)	89 (7)
C(22)	7461 (6)	8902 (6)	2581 (7)	112 (9)
O(H_2O)	4457 (6)	9415 (7)	0331 (7)	66 (6)

Table 2. *Interatomic distances* (Å) *and angles* (°)

C(6)–C(5)	1·321 (5)	C(17)–N(4)	1·454 (7)
N(1)–C(6)	1·380 (5)	C(18)–N(4)	1·457 (5)
C(6)–N(6)	1·423 (3)	C(18)–C(22)	1·522 (5)
C(5)–C(4)	1·433 (4)	C(22)–O(21)	1·420 (8)
C(4)–N(3)	1·378 (5)	O(21)–C(20)	1·406 (5)
C(4)–O(4)	1·227 (4)	C(20)–C(19)	1·502 (10)
C(2)–N(3)	1·371 (5)	C(19)–N(4)	1·454 (7)
C(2)–N(1)	1·389 (4)	C(8)–C(9)	1·321 (7)
C(2)–O(2)	1·215 (6)	C(9)–C(10)	1·458 (9)
C(3)–N(3)	1·477 (4)	C(10)–C(11)	1·381 (6)
C(1)–N(1)	1·462 (5)	C(11)–C(12)	1·387 (11)
C(16)–N(6)	1·480 (6)	C(12)–C(13)	1·362 (11)
C(16)–C(17)	1·517 (6)	C(13)–C(14)	1·330 (10)
C(7)–N(6)	1·368 (6)	C(14)–C(15)	1·387 (13)
C(7)–O(7)	1·217 (4)	C(15)–C(10)	1·387 (8)
C(7)–C(8)	1·472 (7)		

N(1)–C(6)–C(5)	121·8 (3)	C(16)–N(6)–C(6)	115·7 (3)
N(6)–C(6)–C(5)	122·7 (3)	C(7)–N(6)–C(6)	124·7 (4)
N(6)–C(6)–N(1)	115·3 (3)	C(7)–N(6)–C(16)	119·6 (3)
C(4)–C(5)–C(6)	120·8 (4)	N(4)–C(17)–C(16)	111·4 (4)
N(3)–C(4)–C(5)	115·2 (3)	N(4)–C(18)–C(22)	109·6 (5)
O(4)–C(4)–C(5)	124·7 (4)	O(21)–C(22)–C(18)	110·7 (5)
O(4)–C(4)–N(3)	120·1 (3)	O(21)–C(20)–C(19)	112·0 (5)
N(1)–C(2)–N(3)	116·6 (4)	N(4)–C(19)–C(20)	110·3 (4)
O(2)–C(2)–N(3)	123·0 (3)	C(9)–C(8)–C(7)	119·4 (3)
O(2)–C(2)–N(1)	120·5 (3)	C(10)–C(9)–C(8)	128·8 (3)
C(17)–C(16)–N(6)	110·2 (3)	C(11)–C(10)–C(9)	122·1 (5)
O(7)–C(7)–N(1)	119·4 (5)	C(15)–C(10)–C(9)	119·4 (4)
C(8)–C(7)–N(6)	117·5 (3)	C(15)–C(10)–C(11)	118·4 (6)
C(8)–C(7)–O(7)	123·1 (4)	C(12)–C(11)–C(10)	120·1 (5)
C(2)–N(3)–C(4)	125·0 (3)	C(13)–C(12)–C(11)	120·6 (6)
C(3)–N(3)–C(4)	118·6 (3)	C(14)–C(13)–C(12)	119·6 (10)
C(3)–N(3)–C(2)	116·4 (3)	C(15)–C(14)–C(13)	121·9 (7)
C(2)–N(1)–C(6)	120·3 (3)	C(14)–C(15)–C(10)	119·4 (5)
C(1)–N(1)–C(6)	122·9 (3)	C(18)–N(4)–C(17)	114·0 (4)
C(1)–N(1)–C(2)	116·7 (3)	C(19)–N(4)–C(17)	110·2 (4)
		C(19)–N(4)–C(18)	108·1 (3)
		C(20)–O(21)–C(22)	109·4 (4)

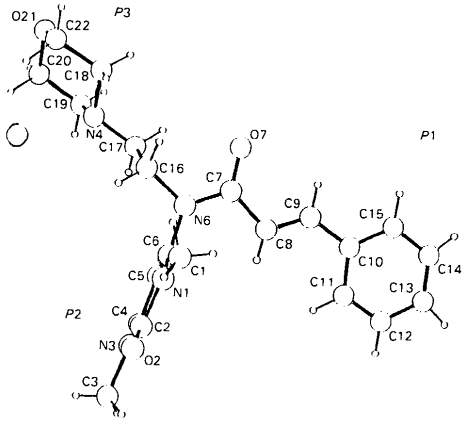

Fig. 2. Perspective view of the molecule (*PLUTO*, Motherwell & Clegg, 1978).

The calculated least-squares planes show that the phenyl ring (*P*1) and the uracil ring (*P*2) are perpendicular (Fig. 2) ($P1 \wedge P2 = 82°$).

The X-ray analysis reveals that the exocyclic nitrogen N(6) is sp^2 hybridized despite forming three valence bonds, and that the uracil plane is perpendicular to the cinnamoyl one. The N(6) lone pair of electrons is delocalized with the cinnamoyl π cloud.

These results reveal interesting information concerning the mechanism of this *N*-acylation involving a proton transfer (J. L. Bernier, J. P. Henichart and V. Warin, to be published). Furthermore, unlike its C(5)-substituted isomer (Warin, Baert, Bernier & Henichart, 1984), NSC 329685 exhibits no significant antitumor activity, which agrees well with the proposed mechanism of action of the planar 6-amino-5-cinnamoyl-1,3-dimethyluracil derivative (Warin, Foulon, Baert, Bernier & Henichart, 1980).

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References

Hanson, H. P., Herman, F., Lea, J. D. & Skillman, S. (1964). *Acta Cryst.* **17**, 1040–1044.

Main, P., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1978). *MULTAN78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

Motherwell, S. & Clegg, W. (1978). *PLUTO.* A program for drawing crystal and molecular structures. Univ. of Cambridge, England.

Sheldrick, G. M. (1976). *SHELX76.* Program for structure determination. Univ. of Cambridge, England.

Stewart, R. F., Davidson, E. R. & Simpson, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

Warin, V., Baert, F., Bernier, J. L. & Henichart, J. P. (1984). *Acta Cryst.* C**40**, 127–129.

Warin, V., Foulon, M., Baert, F., Bernier, J. L. & Henichart, J. P. (1980). *Acta Cryst.* B**36**, 1721–1723.