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Structure of 5-Cinnamoyl-1,3-dimethyl-6-[(2-morpholinoethyl)amino]uracil Hydrochloride, $C_{21}H_{27}N_4O_4^+.Cl^-$

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Abstract. $M_r = 434{\cdot}92$, orthorhombic, *Pbca*, $a = 24{\cdot}635$ (9), $b = 14{\cdot}463$ (3), $c = 12{\cdot}147$ (6) Å, $Z = 8$, $V = 4327{\cdot}9$ Å^3, $D_x = 1{\cdot}33$, $D_m = 1{\cdot}22$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 1{\cdot}851$ mm^{-1}, $F(000) = 1832$, $T = 294$ K, final $R = 0{\cdot}049$ for 1423 observed reflexions. The introduction of a morpholinoethyl group at the N(6) position of 6-amino-5-cinnamoyl-1,3-dimethyluracil in order to increase the solubility has deformed the planarity of the molecule and its length. The disruption of the planarity leads to a higher toxicity of the molecule and overall lower biological activity.

Introduction. In the field of research aimed at providing new antitumour drugs, we have worked on 5-acyl-6-amino-1,3-dimethyluracils (Bernier, Lefebvre, Henichart, Houssin & Lespagnol, 1976). Among these compounds, 6-amino-5-cinnamoyl-1,3-dimethyluracil (NSC 290115) has revealed interesting antileukaemia activity (National Cancer Institute Report, Bethesda, 1980, unpublished results). Unfortunately, owing to a lack of solubility, the pharmacological activity was limited although significant. To increase the solubility and the therapeutic index, we decided to introduce a dialkylaminoalkyl chain at the N(6) position. The structure of this family (NSC 350087) has been determined to establish the structure–activity relationships.

Experimental. Crystals obtained from an ethanol solution, D_m determined by flotation, colourless crystal 0·4 × 0·5 × 0·6 mm, 25 reflexions used for measuring lattice parameters, $2\theta_{max} = 46°$, h 0 to 22, k 0 to 13, l 0 to 9, 1972 reflexions measured, Philips PW 1100 diffractometer, graphite-monochromated Cu $K\alpha$ radiation, θ–2θ scan, invariant scan width of 1·2°, data corrected for Lorentz and polarization effects but not for absorption or extinction, 1423 reflexions with $I > 3\sigma(I)$ used in the analysis; three standard reflexions, intensity variation 2%. Structure solved by direct methods, 300 reflexions with $|E| \geq 1{\cdot}4$ used in *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); a Fourier synthesis based on the solution with the highest $\sum_2$ consistency revealed the complete structure; refinement (on F) carried out by *SHELX*76 (Sheldrick, 1976) with anisotropic thermal parameters for the non-hydrogen atoms; H atoms located from a difference synthesis and included in the refinement with the isotropic temperature factor of the carrier atom; scattering factors for the heavy atoms from Hanson, Herman, Lea & Skillman (1964), for H from Stewart, Davidson & Simpson (1965); refinement converged to $R = 0{\cdot}049$ (unit weights); peaks and troughs in final difference synthesis did not exceed ± 0·25 e Å^{-3}.

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Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters*

$$B_{eq} = \tfrac{1}{3}\sum_i\sum_j B_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq} (Å^2)
Cl	11141 (1)	−197 (1)	2171 (1)	5·9 (5)
N(1)	9428 (2)	−16 (3)	1128 (4)	3·5 (3)
C(1)	9802 (3)	−779 (4)	1411 (5)	4·5 (3)
C(2)	8909 (3)	−251 (5)	837 (5)	4·3 (3)
O(2)	8784 (2)	−1079 (3)	713 (4)	5·5 (4)
N(3)	8537 (2)	427 (4)	714 (4)	3·5 (3)
C(3)	7983 (3)	185 (5)	451 (6)	5·5 (4)
C(4)	8680 (3)	1388 (5)	721 (5)	3·5 (3)
O(4)	8314 (2)	1936 (3)	505 (3)	4·7 (4)
C(5)	9229 (2)	1590 (4)	954 (5)	2·8 (3)
C(6)	9593 (2)	90 (4)	1252 (5)	3·5 (3)
N(6)	10089 (2)	1027 (3)	1675 (4)	3·4 (3)
C(7)	9412 (2)	2545 (4)	691 (5)	3·3 (3)
O(7)	9847 (2)	2676 (3)	230 (4)	4·7 (4)
C(8)	9065 (2)	3333 (4)	1024 (5)	3·6 (3)
C(9)	9202 (2)	4197 (4)	751 (5)	3·8 (3)
C(10)	8905 (3)	5046 (4)	1029 (5)	3·6 (3)
C(11)	9174 (2)	5882 (4)	861 (5)	4·3 (3)
C(12)	8910 (3)	6699 (4)	1120 (6)	4·7 (4)
C(13)	8395 (3)	6708 (5)	1506 (6)	5·2 (4)
C(14)	8119 (3)	5876 (6)	1655 (6)	5·9 (5)
C(15)	8382 (3)	5047 (4)	1422 (6)	4·8 (4)
C(16)	10254 (2)	1863 (4)	2277 (5)	3·5 (3)
C(17)	10737 (2)	2342 (4)	1794 (5)	3·5 (3)
N(4)	11270 (2)	1922 (3)	2077 (4)	3·0 (3)
C(18)	11717 (3)	2289 (4)	1372 (5)	4·4 (3)
C(19)	11429 (3)	2078 (4)	3248 (6)	4·9 (4)
C(20)	11964 (3)	1660 (6)	3474 (6)	5·7 (5)
O(21)	12380 (2)	2020 (3)	2793 (5)	5·9 (5)
C(22)	12249 (3)	1887 (5)	1666 (7)	5·6 (4)

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

N(1)–C(1)	1·479 (8)	C(10)–C(11)	1·394 (8)
N(1)–C(2)	1·369 (9)	C(10)–C(15)	1·374 (9)
N(1)–C(6)	1·395 (7)	C(11)–C(12)	1·386 (9)
C(2)–O(2)	1·246 (9)	C(12)–C(13)	1·351 (11)
C(2)–N(3)	1·350 (9)	C(13)–C(14)	1·395 (11)
N(3)–C(3)	1·444 (8)	C(14)–C(15)	1·392 (10)
N(3)–C(4)	1·435 (8)	N(6)–C(16)	1·471 (7)
C(4)–O(4)	1·228 (8)	C(16)–C(17)	1·495 (8)
C(4)–C(5)	1·413 (9)	C(17)–N(4)	1·488 (7)
C(5)–C(6)	1·387 (8)	N(4)–C(19)	1·492 (9)
C(5)–C(7)	1·486 (8)	N(4)–C(18)	1·493 (8)
C(6)–N(6)	1·340 (7)	C(18)–C(22)	1·479 (10)
C(7)–O(7)	1·225 (7)	C(19)–C(20)	1·477 (10)
C(7)–C(8)	1·481 (8)	C(20)–C(21)	1·415 (9)
C(8)–C(9)	1·336 (9)	O(21)–C(22)	1·420 (11)
C(9)–C(10)	1·469 (8)		
C(2)–N(1)–C(6)	122·4 (5)	C(9)–C(10)–C(11)	117·0 (5)
C(2)–N(1)–C(1)	117·1 (5)	C(9)–C(10)–C(15)	123·1 (5)
C(6)–N(1)–C(1)	120·2 (5)	C(11)–C(10)–C(15)	119·8 (5)
N(1)–C(2)–N(3)	118·8 (6)	C(10)–C(11)–C(12)	118·9 (6)
N(1)–C(2)–O(2)	120·1 (6)	C(11)–C(12)–C(13)	121·9 (6)
O(2)–C(2)–N(3)	121·1 (6)	C(12)–C(13)–C(14)	119·6 (7)
C(2)–N(3)–C(4)	122·4 (5)	C(13)–C(14)–C(15)	119·3 (6)
C(2)–N(3)–C(3)	119·3 (5)	C(14)–C(15)–C(10)	120·5 (6)
C(3)–N(3)–C(4)	117·9 (5)	C(6)–N(6)–C(16)	123·7 (4)
N(3)–C(4)–O(4)	116·3 (6)	N(6)–C(16)–C(17)	113·9 (5)
N(3)–C(4)–C(5)	115·9 (5)	C(16)–C(17)–N(4)	115·0 (5)
O(4)–C(4)–C(5)	127·7 (6)	C(17)–N(4)–C(18)	111·9 (5)
C(4)–C(5)–C(6)	121·4 (5)	C(17)–N(4)–C(19)	113·0 (5)
C(4)–C(5)–C(7)	116·0 (5)	C(18)–N(4)–C(22)	112·1 (6)
C(6)–C(5)–C(7)	121·9 (5)	N(4)–C(18)–C(22)	112·1 (6)
C(5)–C(6)–N(6)	126·3 (5)	N(4)–C(19)–C(20)	110·5 (5)
C(5)–C(7)–O(7)	120·4 (5)	C(18)–C(22)–O(21)	112·4 (6)
C(5)–C(7)–C(8)	118·8 (5)	C(22)–O(21)–C(20)	110·4 (5)
O(7)–C(7)–C(8)	120·7 (5)	O(21)–C(20)–C(19)	112·8 (6)
C(7)–C(8)–C(9)	120·4 (5)	N(1)–C(6)–N(6)	115·8 (5)
C(8)–C(9)–C(10)	126·8 (5)	N(1)–C(6)–C(5)	117·8 (5)

Discussion. The final atomic parameters are listed in Table 1,* and bond distances and angles are given in Table 2. Fig. 1 shows the atom numbering.

The compound studied here (NSC 350087) has revealed antitumour activity against leukaemia L 1210 cells (National Cancer Institute Report, Bethesda, 1982, unpublished results).

The molecule is twisted (see Fig. 1) with an angle of 35° between the uracil plane and the cinnamoyl group. Indeed, the Cl atom is involved in hydrogen bonding with two protons: the morpholine N(4) proton and that of N(6). It is noteworthy that the C(1) and C(20) protons also seem to be attracted by the electronegative Cl^- as has been recently reported (Taylor & Kennard, 1982), delineating a sort of anion cage (see Fig. 2). Distances (Å) and angles (°) concerning these interactions are:

$$Cl \overset{2\cdot07}{\cdots\cdots} H(N4) \overset{1\cdot03}{—} N(4) = 3\cdot08;\ \text{angle } 167$$
$$Cl \overset{2\cdot18}{\cdots\cdots} H(N6) \overset{1\cdot04}{—} N(6) = 3\cdot20;\ \text{angle } 167$$
$$Cl \overset{2\cdot72}{\cdots\cdots} H(C1) \overset{1\cdot04}{—} C(1) = 3\cdot53;\ \text{angle } 135$$
$$Cl \overset{2\cdot89}{\cdots\cdots} H(C20)B \overset{1\cdot16}{—} C(20) = 3\cdot71;\ \text{angle } 127.$$

Owing to the steric hindrance of the anion and to its involvement in H interactions with many protons, in particular with the N(6) proton, the molecule is no longer stabilized in a planar conformation by H bonding between the N(6) proton and the C(7) carbonyl as in NSC 290115 (Warin, Foulon, Baert, Bernier & Henichart, 1980).

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, distances involving H atoms, and angles between mean planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38843 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

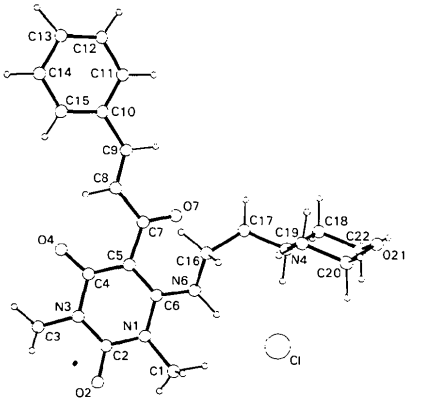

Fig. 1. A perspective view of the molecule.

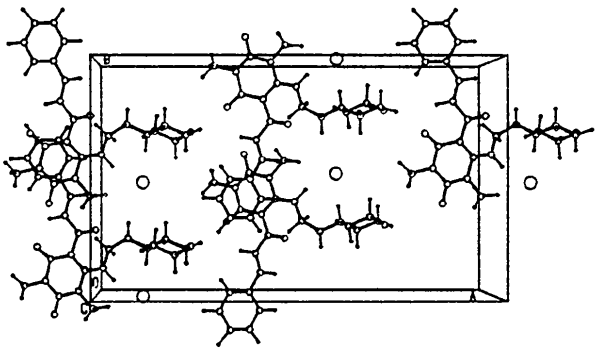

Fig. 2. The molecular packing (*PLUTO*, Motherwell & Clegg, 1978).

The disruption of the planarity leads to a higher toxicity of the molecule and overall a lower biological activity which confirms the fact that the antitumour properties of the molecule can be induced by its intercalation between two adjacent base pairs of DNA. The activity seems to be related to the planarity of the molecule which is in accordance with a postulated intercalative process.

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Structure of 2,2,6,6-Tetramethylpiperidinium Bromide, $C_9H_{20}N^+.Br^-$

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Abstract. $M_r = 222$, $P2_12_12_1$, $a = 8{\cdot}885$ (2), $b = 9{\cdot}300$ (2), $c = 13{\cdot}089$ (2) Å, $U = 1081{\cdot}6$ Å^3, $Z = 4$, $D_x = 1{\cdot}36$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 37{\cdot}1$ cm^{-1}, $F(000) = 464$, $T = 293$ K, $R = 0{\cdot}040$ for 883 observed unique reflections. The piperidinium ring has a distorted chair conformation. Comparişon of the structure with that of similar compounds is made.

Introduction. The 2,2,6,6-tetramethylpiperidyl (tmp) ligand has been used for the stabilization of main-group compounds with low coordination numbers (Lappert, Power, Slade, Hedberg, Hedberg & Schomaker, 1979; Nöth, Staudigl & Wagner, 1982). We were interested, therefore, in the possibility of synthesizing the diphosphene, (tmp)P=P(tmp). We have found, however, that the reaction of $(tmp)PBr_2$ (Markovskii, Romanenko & Ruban, 1979) with Mg in tetrahydrofuran results in the dimer, $[(tmp)P]_4$, and traces of 2,2,6,6-tetramethylpiperidinium bromide. Presumably the latter product arose *via* hydrolysis of either $(tmp)PBr_2$ or $[(tmp)P]_4$.

The X-ray crystal structure of the bromide salt does, however, provide interesting structural information, particularly when compared with the more widely studied 4-substituted tetramethylpiperidyl compounds (Cygler, Markowicz, Skolimowski & Skowroński, 1980).

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