9-[3-(Dimethyloxyamino)propylimino]-1-nitro-9,10-dihydroacridine Monohydrate

By A. Hempel* and S. E. Hull

Department of Physics, University of York, Heslington, York YO1 5DD, England
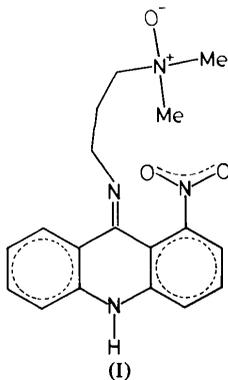
and M. Bogucka-Ledochowska and Z. Dauter

Department of Pharmaceutical Technology and Biochemistry, Technical University, 80-952 Gdańsk, Poland

Abstract. $C_{18}H_{20}N_4O_3 \cdot H_2O$, orthorhombic, *Pbca*, $a = 22 \cdot 67$ (2), $b = 20 \cdot 07$ (2), $c = 7 \cdot 75$ (1) Å, $V = 3526$ Å^3, $Z = 8$, $D_m = 1 \cdot 33$, $D_c = 1 \cdot 35$ Mg m^{-3}, $F(000) = 1520$, $\mu = 0 \cdot 059$ mm^{-1}. Direct methods were used to solve the structure, and refinement was by full-matrix least-squares methods. The final weighted R value for 1481 reflexions was $0 \cdot 100$. The acridine nucleus is not planar and the nitro group is twisted out of the plane of the acridine-moiety side ring.

Introduction. The title compound (I), designated C-684 and hereafter referred to as such, was obtained in the Department of Pharmaceutical Technology and Biochemistry of the Technical University of Gdańsk, Poland, in the course of a research programme on the synthesis of new antineoplastic agents. One of its predecessors, C-283 [9-(3-dimethylaminopropylimino)-1-nitro-9,10-dihydroacridine (Dauter, Bogucka-Ledochowska, Hempel, Ledochowski & Kosturkiewicz, 1976)], was found to possess antineoplastic properties and after extensive investigations has been registered in Poland as an antitumour drug. C-684, which contains an additional O atom at the dimethylamino N atom, is a modification of C-283. It is also biologically active and its activity is similar to that of C-283. The hydrochloride form of this compound was

(I)

* Present address: Department of Pharmaceutical Technology and Biochemistry, Technical University, 80-952 Gdańsk, Poland.

recently prepared for clinical investigation. The X-ray analysis of this therapeutically promising compound was undertaken to determine the conformation of the molecule and to establish the relationship between the molecular structure and biological activity.

The crystals were obtained from a solution in a mixture of acetone and 95% ethanol as very thin yellow plates which diffracted poorly; attempts to grow better crystals failed. However, because of the importance of the compound we decided to proceed with the analysis.

Precession photographs indicated the space group *Pbca*. The intensities were measured on a Hilger & Watts four-circle automatic diffractometer. Unit-cell constants were refined by the least-squares fit of 21 high-angle reflexions. With a θ–2θ scan technique and Nb-filtered Mo $K\alpha$ radiation, 1765 reflexions were

Table 1. *Fractional coordinates of the non-hydrogen atoms* ($\times 10^4$)

	x	y	z
C(1)	2789 (3)	581 (4)	−466 (9)
C(2)	2544 (4)	−5 (4)	−1027 (11)
C(3)	1941 (4)	−77 (4)	−834 (11)
C(4)	1580 (4)	421 (4)	−165 (11)
C(5)	1314 (4)	2674 (4)	1367 (11)
C(6)	1505 (5)	3301 (5)	1494 (12)
C(7)	2100 (5)	3450 (4)	1320 (14)
C(8)	2519 (4)	2945 (4)	1190 (11)
C(9)	2743 (3)	1716 (3)	1041 (9)
N(10)	1492 (3)	1520 (3)	937 (8)
C(11)	2462 (3)	1099 (4)	272 (9)
C(12)	1860 (3)	1016 (3)	370 (10)
C(13)	1730 (3)	2153 (3)	1136 (10)
C(14)	2326 (3)	2276 (3)	1145 (9)
N(15)	3419 (3)	667 (4)	−868 (10)
O(16)	3561 (2)	1111 (3)	−1842 (8)
O(17)	3757 (3)	263 (3)	−238 (8)
N(18)	3268 (2)	1637 (3)	1582 (8)
C(19)	3588 (4)	2157 (4)	2502 (12)
C(20)	4112 (4)	1851 (5)	3420 (11)
C(21)	4554 (5)	1641 (6)	2009 (14)
N(22)	5004 (3)	1159 (3)	2681 (10)
C(23)	4675 (6)	504 (7)	3175 (23)
C(24)	5422 (5)	953 (8)	1319 (17)
O(25)	5291 (2)	1386 (3)	4127 (7)
O(26)	4883 (4)	1348 (8)	7393 (14)

recorded up to $\theta_{max} = 21°$. Of these, 1481 had significant intensities [$I > 2\sigma(I)$]. The structure was solved by direct methods using the *MULTAN* 78 program package (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). The first E map showed the whole molecule. The atoms of the water molecule and also the H atom at N(10) were found from a difference electron density map. The remaining H atoms were geometrically fitted to the molecule. The structure was refined by full-matrix least squares using *SHELX* 76 (Sheldrick, 1976). Anisotropic temperature factors for atoms other than H and isotropic temperature factors for H atoms were allowed. The usual Lorentz and polarization corrections were applied, but no absorption corrections were made. The final weighted R index for 1481 structure factors* was 0·100 {$w = 1/[\sigma^2(F_o) + 0·0011|F_o|^2]$ and $R_w = \sum w^{1/2}||F_o| - k|F_c||/ \sum w^{1/2}|F_o|$} and the final unweighted R index was 0·119. The final residual electron density peaks did not exceed 0·55 e Å^{-3}. The University of York DEC-10 system was used throughout the calculations. The coordinates of the atoms are given in Tables 1 and 2.

Discussion. Bond distances and angles are presented in Tables 3 and 4. The molecule is illustrated in Fig. 1.

---

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34012 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Hydrogen-atom coordinates* ($\times 10^4$)

	x	y	z
H(20)	2823 (28)	−269 (32)	−1594 (88)*
H(30)	1741 (28)	−452 (34)	−1263 (82)*
H(40)	1135 (28)	262 (31)	−117 (78)*
H(50)	881 (27)	2555 (32)	1391 (84)*
H(60)	1269 (29)	3632 (33)	1384 (85)*
H(70)	2232 (36)	3735 (35)	1129 (113)*
H(80)	2959 (28)	3041 (30)	1184 (81)*
H(100)	1000 (30)	1465 (32)	1244 (82)*
H(191)	3755 (29)	2426 (35)	1753 (93)†
H(192)	3379 (26)	2394 (32)	3548 (92)†
H(201)	4307 (27)	2195 (31)	4194 (94)†
H(202)	3925 (28)	1486 (35)	4186 (89)†
H(211)	5035 (28)	1991 (32)	1403 (80)†
H(212)	4345 (28)	1338 (33)	1094 (91)†
H(231)	4346 (50)	1086 (66)	3358 (158)‡
H(232)	5183 (51)	279 (57)	3092 (156)‡
H(233)	4372 (47)	415 (63)	2164 (162)‡
H(241)	5160 (49)	912 (63)	164 (155)‡
H(242)	5726 (50)	628 (58)	1796 (155)‡
H(243)	5543 (51)	1525 (66)	1436 (154)‡
H(261)	5063 (51)	1307 (60)	6261 (164)‡
H(262)	4591 (59)	1264 (65)	7866 (185)‡

* $U = 0·024$ (8) Å^2.
† $U = 0·032$ (8) Å^2.
‡ $U = 0·143$ (17) Å^2.

The results obtained show that the unusual conformational features of C-283 (Dauter *et al.*, 1976) are fully retained in the structure of C-684 (Figs. 2 and 3). The acridine nucleus is bent across the C(9)---N(10) line (dihedral angle 19°). The nitro group is twisted out of the acridine side-ring plane around the C(1)—N(15) bond by 64°. The sum of the valence angles at C(9) is 360° which is the theoretical

Table 3. *Bond lengths* (Å)

C(1)—C(2)	1·37 (1)	N(10)—C(12)	1·38 (1)
C(1)—C(11)	1·40 (1)	N(10)—C(13)	1·39 (1)
C(1)—N(15)	1·47 (1)	C(11)—C(12)	1·38 (1)
C(2)—C(3)	1·38 (1)	C(13)—C(14)	1·37 (1)
C(3)—C(4)	1·39 (1)	N(15)—O(16)	1·21 (1)
C(4)—C(12)	1·41 (1)	N(15)—O(17)	1·22 (1)
C(5)—C(6)	1·34 (1)	N(18)—C(19)	1·46 (1)
C(5)—C(13)	1·42 (1)	C(19)—C(20)	1·51 (1)
C(6)—C(7)	1·39 (2)	C(20)—C(21)	1·54 (1)
C(7)—C(8)	1·39 (1)	C(21)—N(22)	1·50 (1)
C(8)—C(14)	1·41 (1)	N(22)—C(23)	1·56 (2)
C(9)—C(11)	1·52 (1)	N(22)—C(24)	1·48 (2)
C(9)—C(14)	1·47 (1)	N(22)—O(25)	1·37 (1)
C(9)—N(18)	1·27 (1)		

Table 4. *Bond angles* (°)

|			
C(2)—C(1)—C(11)	123 (1)	C(5)—C(13)—N(10)	116 (1)
C(2)—C(1)—N(15)	115 (1)	C(5)—C(13)—C(14)	121 (1)
C(11)—C(1)—N(15)	121 (1)	N(10)—C(13)—C(14)	123 (1)
C(1)—C(2)—C(3)	117 (1)	C(8)—C(14)—C(9)	122 (1)
C(2)—C(3)—C(4)	123 (1)	C(8)—C(14)—C(13)	118 (1)
C(3)—C(4)—C(12)	117 (1)	C(9)—C(14)—C(13)	120 (1)
C(6)—C(5)—C(13)	119 (1)	C(1)—N(15)—O(16)	118 (1)
C(5)—C(6)—C(7)	121 (1)	C(1)—N(15)—O(17)	117 (1)
C(6)—C(7)—C(8)	121 (1)	O(16)—N(15)—O(17)	125 (1)
C(7)—C(8)—C(14)	119 (1)	C(9)—N(18)—C(19)	123 (1)
C(11)—C(9)—C(14)	112 (1)	N(18)—C(19)—C(20)	109 (1)
C(11)—C(9)—N(18)	115 (1)	C(19)—C(20)—C(21)	107 (1)
C(14)—C(9)—N(18)	133 (1)	C(20)—C(21)—N(22)	112 (1)
C(12)—N(10)—C(13)	118 (1)	C(21)—N(22)—C(23)	108 (1)
C(1)—C(11)—C(9)	123 (1)	C(21)—N(22)—C(24)	112 (1)
C(1)—C(11)—C(12)	117 (1)	C(23)—N(22)—C(24)	104 (1)
C(9)—C(11)—C(12)	120 (1)	C(21)—N(22)—O(25)	113 (1)
C(4)—C(12)—N(10)	116 (1)	C(23)—N(22)—O(25)	108 (1)
C(4)—C(12)—C(11)	122 (1)	C(24)—N(22)—O(25)	112 (1)
N(10)—C(12)—C(11)	122 (1)		
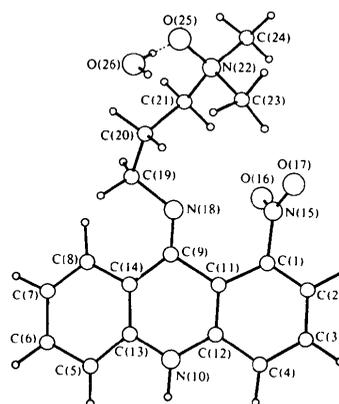
Fig. 1. The molecule and atom numbering.

value for sp^2 hybridization. The short distance C(9)—N(18) = 1·27 Å proves the existence of a double bond between the two atoms. This observation is entirely explained by the fact that the H atom supposed to be on N(18) was found at N(10) in the acridine ring. Consequently the molecule is forced to adopt the imino tautomeric form with reduced aromatic character and increased bond lengths in the central ring of the acridine. The non-bonded C(8)···C(19) = 3·07 Å contact makes the angles C(14)—C(9)—N(18) = 133 and C(9)—N(18)—C(19) = 123° which are greater than the expected theoretical value of 120°. These observations indicate that the conformational peculiarity of C-684 is a result of steric interactions between the nitro group and the side chain.

The results suggest that the biological activity displayed by C-283 and C-684 is mainly attributable to a different conformation from the biologically inactive C-264 [9-(3-dimethylaminopropylamino)-2-nitroacridine (Hempel, Hull, Dauter, Bogucka-Ledochowska & Konitz, 1979)] in which the nitro group and the acridine moiety lie in a single plane.

The unusual N(22)$^+$—O(25)$^-$ bond is 1·37 Å, similar to that found in trimethylamine oxide by Caron, Palenik, Goldish & Donohue (1964).

The crystal packing is illustrated in Fig. 4. The molecules are stacked in a head-to-head manner in exactly the same way as in C-283 (Dauter *et al.*, 1976).
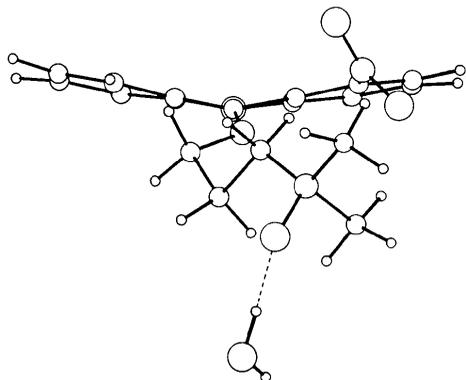
Table 5. *Characteristic hydrogen-bond distances* (Å)

N(10)^I···O(25)^{II}	2·74	O(26)^I···O(25)^I	2·70
H(100)^I···O(25)^{II}	1·64	H(261)^I···O(25)^I	1·74
N(10)—H(100)	1·15	O(26)—H(261)	0·97

Symmetry code

(I) x, y, z (II) $x - 0·5, y, 0·5 - z$

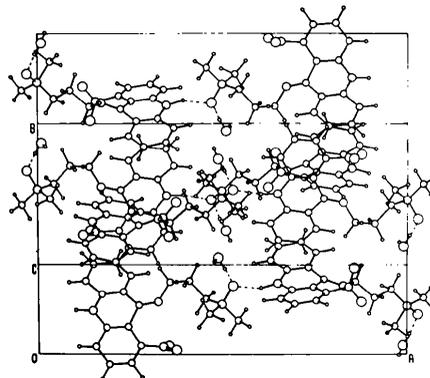Fig. 4. The packing diagram.

The closest approach between molecules is about 3·9 Å. The water molecule is hydrogen-bonded to O(25) which also has a hydrogen-bonded contact through H(100) with N(10) of the acridine ring. Table 5 summarizes the short intermolecular distances. The molecules in the crystal form infinite chains parallel to the *b* axis with only van der Waals interactions between them.

Fig. 2. The view down C(9)···N(10) of C-684.
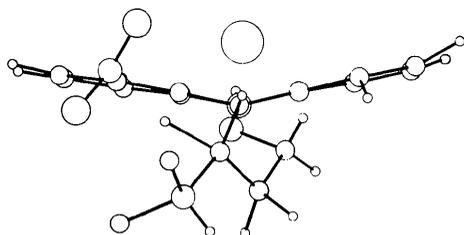
Fig. 3. The view down C(9)···N(10) of C-283.

References

CARON, A., PALENIK, G., GOLDISH, E. & DONOHUE, J. (1964). *Acta Cryst.* **17**, 102–108.

DAUTER, Z., BOGUCKA-LEDOCHOWSKA, M., HEMPEL, A., LEDOCHOWSKI, A. & KOSTURKIEWICZ, Z. (1976). *Rocz. Chem.* **50**, 1573–1586.

HEMPEL, A., HULL, S. E., DAUTER, Z., BOGUCKA-LEDOCHOWSKA, M. & KONITZ, A. (1979). *Acta Cryst.* B**35**, 477–479.

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J. P. & WOOLFSON, M. M. (1978). *MULTAN 78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univ. of York, England.

SHELDRICK, G. M. (1976). *SHELX 76. Program for crystal structure determination.* Univ. of Cambridge, England.