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Molecular Distortions in 1-Nitro-9-methylacridine and 1-Nitro-9-aminoacridine

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The high antitumor activity of certain 1-nitroacridines has been reported, and Ledakrin (1-nitro-9-(3-dimethylaminopropylimino)-acridine) is used clinically in Poland as an antineoplastic agent. To investigate the role of the 1-nitro group in enhancing antitumor activity, the crystal structures of 1-nitro-9-aminoacridine and 1-nitro-9-methylacridine have been determined. 1-Nitro-9-methylacridine crystallizes in the orthorhombic space group *Pbca*, with $Z = 8$ and $a = 13.822(4)$, $b = 9.927(3)$, $c = 17.248(6)$ Å, $V = 2217(1)$ Å^3. The final R value, after least-squares refinement, is 0.056, for 2155 observed intensities. The structure of 1-nitro-9-aminoacridine is approximately isomorphous with that of the 9-methyl derivative, with unit cell dimensions $a = 13.217(2)$, $b = 10.011(1)$, $c = 16.373(1)$ Å, $V = 2166.4(5)$ Å^3. The final R value, after least-squares refinement, is 0.058, for 1534 observed intensities. The structures were solved independently by direct methods. The steric interference between the 1-nitro and the 9-methyl- or 9-amino-substituents on the acridine ring system causes considerable deviations from planarity in both structures. There are two possible intramolecular hydrogen bonds between the amino group and the disordered nitro group in 1-nitro-9-aminoacridine. Unlike N^9-alkyl derivatives of 1-nitroacridines that have been previously described, in the 9-amino derivative the exocyclic nitrogen adopts the amino rather than the imino form.

INTRODUCTION

The antitumor properties of 1-nitro-9-(3-dimethylaminopropylimino)-acridine (Ledakrin), illustrated as the monoiodide (I), $C_{18}H_{21}N_4O_2I$, and of other deriva-

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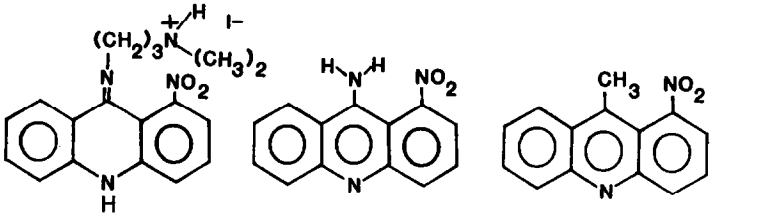
tives of 1-nitro-9-aminoacridine (*1*) have stimulated considerable interest in finding those structural features of the molecules that are responsible for their biological activity. The three-dimensional structures of acridine derivatives such as proflavine, 9-aminoacridine, and acridine orange have been studied. These are planar molecules and are found to intercalate between the bases of DNA (*2*). At neutral pH the ring nitrogen is protonated and the ring system is positively charged (*3–5*).



I Ledakrin

II 1-nitro-9-amino acridine

III 1-nitro-9-methyl acridine

Because of the electron-withdrawing properties of the nitro group and the steric hindrance between substituents at positions 1 and 9, the reported structures of some 1-nitro-9-aminoacridine derivatives exhibit some unusual features (*6–8*). In these structures, substitution of a nitro group in position 1 results in the formation of the neutral imino tautomer rather than the cationic amine. The ring system is folded at an angle along the C(9) · · · N(10) line, and the central ring is not aromatic. The nitro group is twisted out of the plane of the three-ring acridine system by 56 to 64° and is no longer conjugated with the aromatic ring. The nonplanarity of these 1-nitro derivatives would seem to preclude intercalation as a mode of action *in vivo*. It has been suggested on the basis of DNA melting experiments that Ledakrin and similar drugs act by crosslinking DNA (*9*).

The structure determination of 1-nitro-9-aminoacridine (**II**) was undertaken since it is the parent compound of the alkyl-substituted derivatives already described. This compound adopts the amino rather than the imino form, with a fully aromatic acridine ring system. The structure of 1-nitro-9-methylacridine (**III**) is very similar, and provides information on those features of the crystal structure that are not dependent on the presence of a 9-amino group.

EXPERIMENTAL

Crystals of 1-nitro-9-methylacridine and 1-nitro-9-aminoacridine were grown from a preparation of the material as previously described (*10, 11*). Preliminary measurements of lattice constants for both crystals were obtained from precession photographs; systematically absent reflections indicated that the space group is

TABLE 1

CRYSTAL DATA

	1-Nitro-9-methylacridine	1-Nitro-9-aminoacridine
Empirical formula	$C_{14}H_{10}N_2O_2$	$C_{13}H_9N_3O_2$
Formula weight	238.25	239.23
$F(000)$	992	992
Space group	*Pbca* (orthorhombic)	*Pbca* (orthorhombic)
Z	8	8
a	13.822(4) Å	13.217(2) Å
b	9.927(3) Å	10.011(1) Å
c	17.248(6) Å	16.373(1) Å
V	2217(1) Å^3	2166.4(5) Å^3
D_x	1.428 g cm^{-3}	1.488 g cm^{-3}
Solvent from which crystallized	Benzene/hexane/heptane	Ethanol/hexane
Crystal size	0.2 × 0.2 × 0.2 mm	0.4 × 0.3 × 0.1 mm
Crystal shape	Rhomboid columns	Plate
Crystal color	Yellow	Red
Melting point	170–172°	246° (decomp.)
Temperature of data collection	−70°C	25°C
λ	0.71069 Å (MoK_α)	1.5418 Å (CuK_α)
μ	MoK_α (1.04 cm^{-1})	CuK_α (8.70 cm^{-1})
2θ limit (sin θ/λ)	65° (0.756 Å^{-1})	138° (0.61 Å^{-1})
Number of reflections measured (excluding those systematically absent)	4037	2016
Criterion for threshold intensity	2.5σ	2.0σ
Instrumental uncertainty (δ)	0.03	0.02
Number of reflections above threshold	2155	1534
Number of parameters in refinement	203	209
Highest peak in final difference map	0.33 electrons Å^{-3}	0.21 electrons Å^{-3}
Final R value = $\Sigma[(\|\|F_o\| - \|F_c\|\|)/\Delta \geq F_o\|]$	0.056	0.058

Pbca. Final cell parameters (Table 1) were obtained by a least-squares analysis of 15 centered reflections obtained from diffractometer measurements.

Data for the methyl derivative were collected at −70°C on a Syntex $P2_1$ four-circle diffractometer with MoK_α radiation and a highly oriented graphite monochromator. Data for the 9-amino derivative were collected at room temperature with monochromatized CuK_α radiation. The θ-2θ scan technique (bisecting mode)

was used at a variable scan speed of 2 to 29.3° min^{-1} depending upon intensity. Three check reflections measured every 97 reflections showed no decay in intensity. The ratio of scan to background time was 2.0. Values of $\sigma(I)$ were determined from counting statistics; values of $\sigma(F)$ were calculated as $\sigma(F) = (F/2)[\sigma^2(I)/(I)^2 + \delta^2]^{1/2}$, where δ is an instrumental uncertainty determined from the variation in the intensity of the check reflections. The data were corrected for Lorentz and polarization factors and put on an absolute scale with a Wilson plot. No absorption correction was made, since the absorption coefficient was small in both cases. Details of the data collection are presented in Table 1.

Structure Determination and Refinement

Both structures were solved by direct methods, using the MULTAN computer programs (*12*). Values of E were calculated using molecular scattering factors obtained from a similar acridine structure (*8*).

The data set for 1-nitro-9-methylacridine consisted of 2155 intensities (all measured reflections, including those systematically absent, to $\sin\theta/\lambda = 0.756$ $Å^{-1}$); 128 phase sets were generated and the E map produced from the best solution (absolute figure of merit (1.91) and residual (39.) revealed all 18 nonhydrogen atoms). Hydrogen atoms were located in the electron density map after several cycles of anisotropic least-squares refinement, and their positions were refined isotropically. Correction for secondary extinction was made ($\alpha = 6.74 \times 10^{-8}$).

In the 9-amino derivative, the correct solution had the highest combined figure of merit (2.66). All 20 nonhydrogen atoms were found among the 70 highest peaks, including the four oxygen atoms from the disordered nitro group. A structure factor calculation with all nonhydrogen atoms except the nitro oxygens gave an electron density map with four oxygen peaks around the nitrogen atom. Two of these peaks were selected and included in isotropic refinement. Temperature factors for these oxygens were high (above 9.0 $Å^2$) and the two highest peaks in the difference electron density map were due to alternate oxygen atom positions. Refinement of position and occupancy factor of these four (with B held fixed at 4.50 $Å^2$) gave the following occupancy factors: 0.54, 0.45, 0.46, and 0.41. Thus, the nitro group was demonstrated to be disordered and oxygen atoms were assigned occupancy of 0.5.

For the 9-amino derivative, acridine ring hydrogen atom positions were found from a difference map at an intermediate stage of refinement ($R = 0.12$). The amino hydrogens, H(18A) and H(18B) were not as well resolved. Positions for them were detected from a difference map at $R = 0.06$, in which their peak heights were 0.45 and 0.39 $Å^{-3}$, respectively.

A full-matrix least-squares procedure was used to refine both structures. The quantity minimized was $\Sigma w[||F_o| - |F_c||]^2$ where the weights w were $1/\sigma^2(F)$. Atomic scattering factors for nonhydrogen atoms were those listed by Cromer and Mann (*13*), and for hydrogen atoms those given by Stewart *et al.* (*14*). The computer programs used are part of the Crystallographic Program Library written at the Institute for Cancer Research (*15, 16*). The fractional coordinates of the atoms are given in Tables 2 and 3.

TABLE 2

1-NITRO-9-METHYLACRIDINE[a]

Atom	x	y	z	$\langle B \rangle$
C(1)	0.2495(2)	-0.0896(2)	0.0642(1)	1.79(6)
C(2)	0.1723(2)	-0.1566(2)	0.0311(1)	2.29(8)
C(3)	0.0778(2)	-0.1244(2)	0.0573(1)	2.47(8)
C(4)	0.0651(1)	-0.0258(2)	0.1142(1)	2.20(7)
C(5)	0.1739(2)	0.2919(2)	0.3093(1)	2.14(8)
C(6)	0.2444(2)	0.3592(2)	0.3505(1)	2.35(8)
C(7)	0.3428(2)	0.3322(2)	0.3336(1)	2.33(8)
C(8)	0.3690(1)	0.2378(2)	0.2768(1)	2.02(7)
C(9)	0.3202(1)	0.0652(2)	0.1721(1)	1.57(6)
N(10)	0.1235(1)	0.1327(2)	0.2098(1)	1.82(6)
C(11)	0.2428(1)	0.0076(2)	0.1287(1)	1.51(6)
C(12)	0.1452(1)	0.0416(2)	0.1520(1)	1.61(6)
C(13)	0.2974(1)	0.1646(2)	0.2312(1)	1.56(6)
C(14)	0.1975(1)	0.1947(2)	0.2479(1)	1.68(6)
N(15)	0.3412(1)	-0.1128(2)	0.0221(1)	2.17(6)
O(16)	0.3821(1)	-0.0072(2)	-0.0047(1)	2.86(6)
O(17)	0.3685(1)	-0.2373(2)	0.0128(1)	3.48(7)
C(18)	0.4232(1)	0.0173(2)	0.1610(1)	2.07(7)
H(2)	0.183(2)	-0.219(2)	-0.012(1)	2.5(5)
H(3)	0.026(2)	-0.169(3)	0.035(1)	3.2(5)
H(4)	0.002(2)	0.002(2)	0.134(1)	2.1(4)
H(5)	0.106(2)	0.302(2)	0.320(1)	2.0(5)
H(6)	0.225(2)	0.429(3)	0.390(1)	2.8(5)
H(7)	0.393(2)	0.383(3)	0.362(2)	3.3(5)
H(8)	0.439(2)	0.222(2)	0.266(1)	1.4(4)
H(18)	0.425(2)	-0.086(2)	0.149(1)	2.8(5)
H(19)	0.455(2)	0.075(2)	0.123(1)	2.2(5)
H(20)	0.461(2)	0.035(3)	0.210(1)	3.2(6)

[a] Positional parameters are given as fractions of cell edges. Isotropic temperature factors are expressed as $\exp(-B \sin^2\theta/\lambda^2)$ with B values given in Å^2. The standard deviations for each parameter, determined from the inverted full matrix, are given in parentheses and apply to the last specified digits.

Tables of anisotropic temperature factors and observed and calculated structure factors are available as supplementary material.[3]

RESULTS

The bond lengths and interbond angles in the two molecules are illustrated in Fig. 1. These values are similar in the two molecules. The N(18)–C(9) distance in the 9-amino compound is 1.341(3) Å, indicating that the imino tautomer is proba-

[3] See NAPS document No. 04023 for 29 pages of supplementary material. Order from ASIS/NAPS, Microfiche Publications, P. O. Box 3513, Grand Central Station, New York, N.Y. 10163. Remit in advance $4.00 for microfiche copy or for photocopy, $7.75 up to 20 pages plus $.30 for each additional page. All orders must be prepaid. Institutions and Organizations may order by purchase order. However, there is a billing and handling charge for this service of $15. Foreign orders add $4.50 for postage and handling, for the first 20 pages, and $1.00 for additional 10 pages of material. $1.50 for postage of any microfiche orders.

TABLE 3

1-NITRO-9-AMINOACRIDINE[a]

Atom	x	y	z	B
C(1)	0.2628(2)	-0.0822(3)	0.0805(1)	4.4(1)
C(2)	0.1840(2)	-0.1457(3)	0.0444(2)	6.1(1)
C(3)	0.0851(2)	-0.1164(3)	0.0677(2)	6.3(1)
C(4)	0.0690(2)	-0.0271(3)	0.1268(2)	5.5(1)
C(5)	0.1676(2)	0.2835(3)	0.3273(2)	4.9(1)
C(6)	0.2397(2)	0.3574(3)	0.3671(2)	5.2(1)
C(7)	0.3407(2)	0.3386(3)	0.3512(2)	5.0(1)
C(8)	0.3720(2)	0.2484(3)	0.2950(1)	4.6(1)
C(9)	0.3306(2)	0.0761(2)	0.1884(1)	3.8(1)
N(10)	0.1224(1)	0.1226(2)	0.2270(1)	4.5(1)
C(11)	0.2532(2)	0.0114(2)	0.1444(1)	3.7(1)
C(12)	0.1493(2)	0.0377(3)	0.1675(1)	4.1(1)
C(13)	0.3013(2)	0.1706(2)	0.2496(1)	3.7(1)
C(14)	0.1969(2)	0.1893(2)	0.2666(1)	3.9(1)
N(15)	0.3617(2)	-0.1179(2)	0.0439(1)	5.2(1)
N(18)	0.4294(1)	0.0539(3)	0.1755(1)	5.8(1)
O(16A)	0.4074(3)	-0.0216(4)	0.0140(2)	6.7(2)
O(16B)	0.4220(3)	-0.1850(5)	0.0867(3)	8.9(3)
O(17A)	0.3870(3)	-0.2336(5)	0.0417(3)	6.9(3)
O(17B)	0.3844(4)	-0.0834(7)	-0.0228(3)	9.5(4)
H(2)	0.195(2)	-0.210(3)	-0.002(2)	6.8(7)
H(3)	0.016(2)	-0.157(3)	0.051(1)	9.7(8)
H(4)	0.011(2)	-0.004(2)	0.143(1)	5.9(6)
H(5)	0.089(1)	0.293(2)	0.342(1)	4.2(5)
H(6)	0.217(2)	0.428(3)	0.400(1)	5.8(6)
H(7)	0.380(2)	0.396(2)	0.379(1)	4.9(6)
H(8)	0.447(2)	0.224(2)	0.291(1)	6.5(7)
H(18A)*	0.479	0.094	0.205	7.0
H(18B)*	0.450	0.003	0.130	7.0

[a] Positional parameters are given as fractions of cell edges. Isotropic temperature factors are expressed as $\exp(-B \sin^2\theta/\lambda^2)$ with B values given in Å^2. Standard deviations for each parameter are given in parentheses and apply to the last specified digits.

* Positions of these hydrogen atoms were derived from a difference Fourier electron density map, but not refined.

bly not formed. This distance is shorter in N^9-alkyl derivatives which have been found to exist in the imino form (1.31(2), 1.27(1), and 1.28(1) Å) (*6–8*). In 1-nitro-9-aminoacridine and 1-nitro-9-methylacridine, respectively, the N(10)–C(12) and N(10)–C(14) distances (1.341(3), 1.356(3), 1.341(2), 1.346(6) Å) and the C(12)–N(10)–C(14) angle (117.8(2)°, 117.7(2)°) indicate that N(10) is not protonated.

The steric hindrance between the substituents at positions 1 and 9 is illustrated in Fig. 2. For the amino- and methyl derivatives, respectively, the relevant torsion angles are (N(18) or C(18))–C(9)–C(11)–C(1) = −1.4(5)°, −7.1°; C(9)–C(11)–C(1)–N(15) = −6.1(5)°, −16.2; C(11)–C(1)–N(15)–O(16) = −59.0(5) (O16A), 70.4(5)° (O16B), −55.6°. These torsion angles describe the fact that the nitro group is rotated approximately 60° out of the plane of the acridine, and that substituents at C(9) are also bent out of the plane. The disorder in the nitro group in the 9-amino compound represents two possible modes of rotation (clockwise

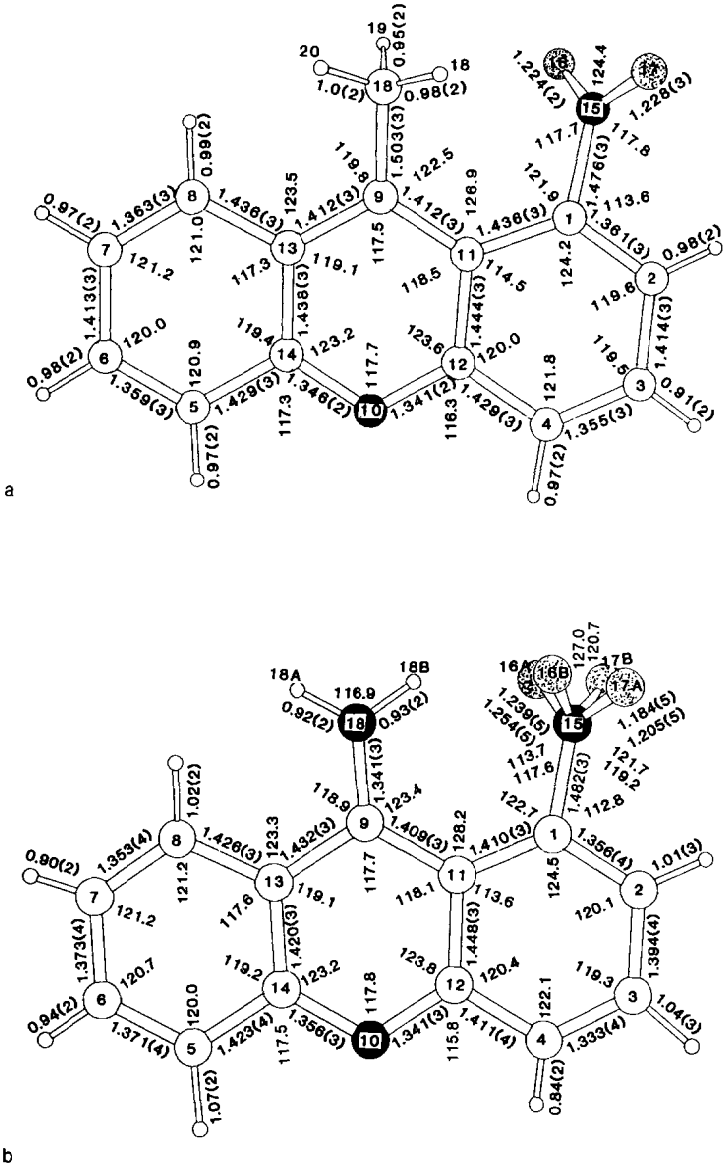


FIG. 1. Bond lengths (Å) and bond angles (°) for (a) 1-nitro-9-methylacridine (mean standard deviations for angles are 0.2°) and (b) 1-nitro-9-aminoacridine (mean standard deviations for angles are 0.3°). Hydrogen atoms are numbered identically to the atoms to which they are bonded.

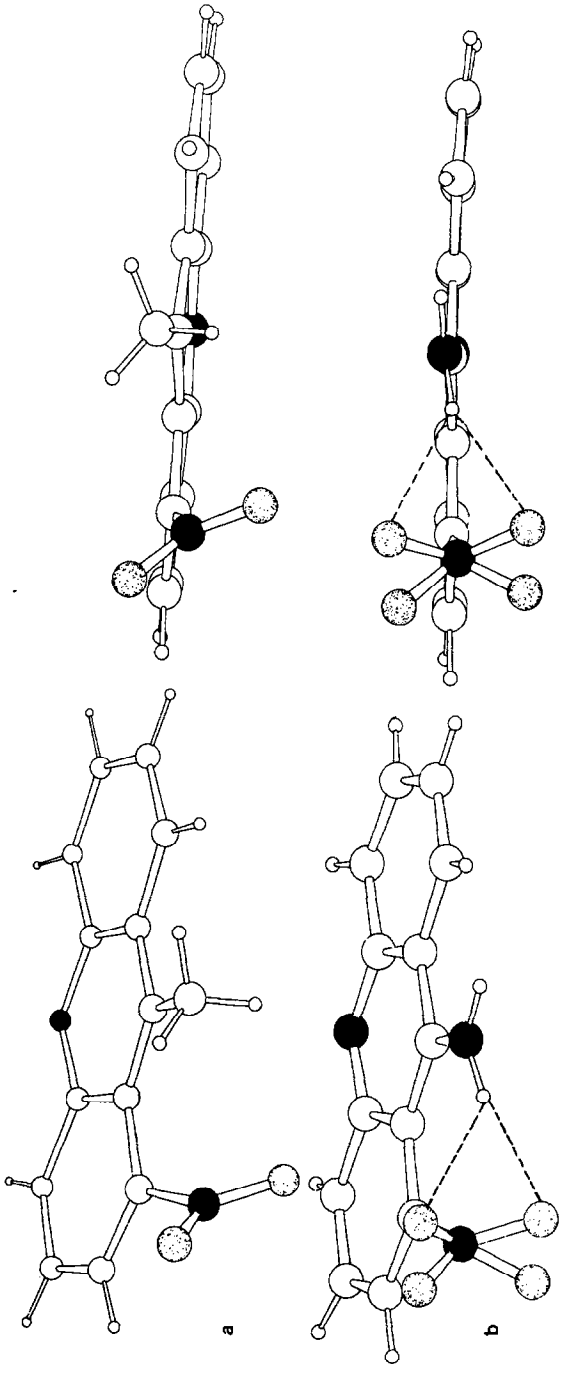


FIG. 2. Steric hindrance between substituents on positions 1 and 9 of the acridine ring causes nonplanarity of the nitro group and of the ring system. (a) In 1-nitro-9-methylacridine the oxygen atoms of the nitro group are tilted away from the hydrogen atoms of the methyl group. (b) In 1-nitro-9-aminoacridine the oxygen atoms of the nitro group are disordered; 2 intramolecular hydrogen bonds are possible.

TABLE 4

COMPARISONS OF SOME GEOMETRICAL FEATURES OF NITROACRIDINES[a]

Code name				C-283 (Ledakrin)	C-684	C-264
Reference	This work	This work	(*8*)	(*6*)	(*7*)	(*17*)
Position of Nitro group substitution	1	1	1	1	1	2
Substituent at position 9	CH_3	NH_2	$NCH(CH_3)-CH_2-N(CH_3)_2$	$N(CH_2)_3N^+(CH_3)_2 \cdot I^-$	$N(CH_2)_3N^+(CH_3)_2O^-$	$NH(CH_2)_3N(CH_3)_2$
C(11)–C(1)–N(15)-O (°)	57	61	56	64	64	0
C(1)–N(15) (Å)	1.476(3)	1.482(3)	1.47	1.44(2)	1.47(1)	1.45(1)
C(9)–N(18) or C(18) (Å)	1.503(3)	1.341(3)	1.285	1.31(2)	1.27	1.33(1)
Angle at N(10) (°)	117.7(2)	117.8(2)	123	122(1)	118	116
N(10)–C (Å)	1.341(3), 1.345(3)	1.341(3), 1.356(3)	1.36, 1.38	1.38(2), 1.40(2)	1.38, 1.39	1.34, 1.36
Angle between the planes of rings *A* and *C* (°)	2.99	1.96	10.22	19.81	19.17	2.08

[a] Distances in angstroms (Å) and angles in degrees.

and anticlockwise). In addition there are distortions at C(9), C(11), and C(1) in this area so that extraannular angles, normally expected to be approximately 120°, are 123°, 127–128°, and 122–123°. The fold angles between the *A* (C(5), C(6), C(7), C(8), C(13), C(14)) and *C* (C(1), C(2), C(3), C(4), C(11), C(12)) planes in the acridine ring system are 2.99(5)° and 1.96(7)° for the 9-methyl and the 9-amino compounds, respectively. 1-Nitro compounds with a long side chain in position 9 have a larger fold angle of 10 to 20° (Table 4).

Table 5 lists the intramolecular contacts shown by the 9-methyl derivative and the dimensions of intra- and intermolecular hydrogen bonding in 1-nitro-9-amino-

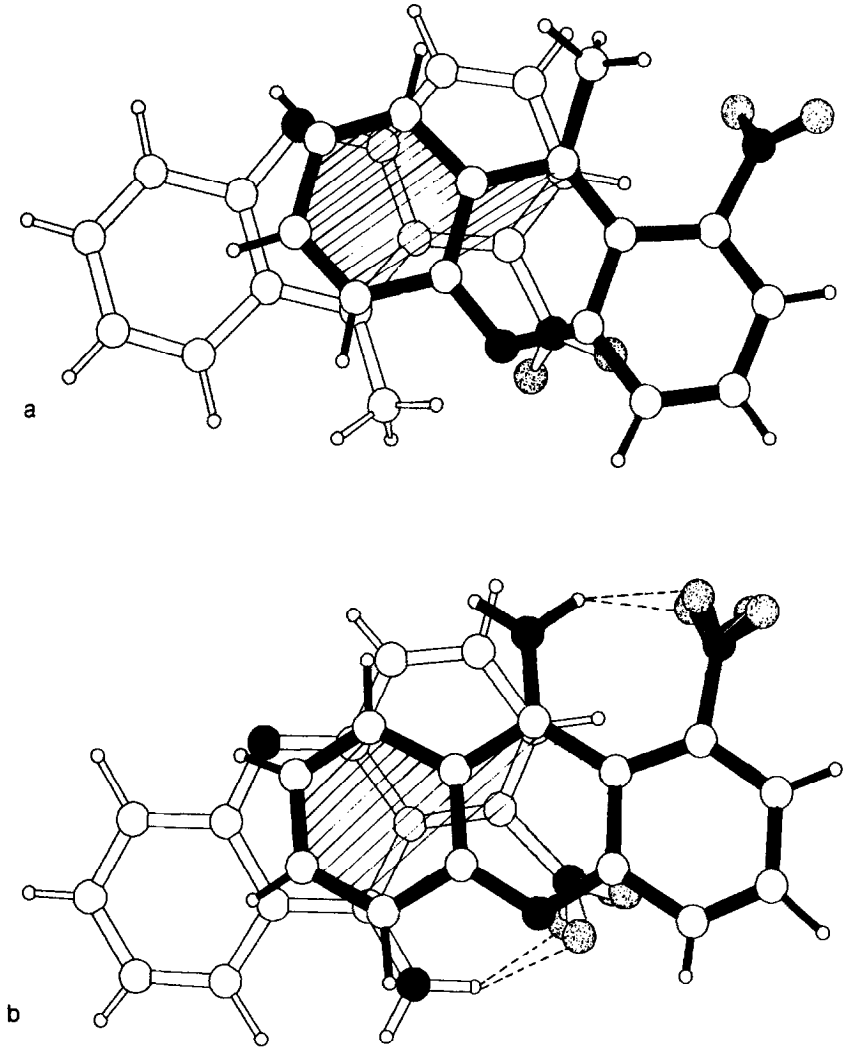


FIG. 3. Packing diagrams for 1-nitro-9-methylacridine and 1-nitro-9-aminoacridine, viewed down the shortest axis, **y**. The shading indicates the overlap.

TABLE 5

CLOSE CONTACT AND HYDROGEN BOND DISTANCES (Å) AND ANGLES (°) IN (a) 1-NITRO-9 AMINOACRIDINE AND (b) 1-NITRO-9-METHYLACRIDINE[a]

D–H · · · A	Symmetry transformation for A	D–H	D · · · A	H · · · A	⟨D-H · · · A°
(a) 9-Amino derivative					
C(8)–H(8) · · · N(10)	$-\frac{1}{2}+x, y, -\frac{1}{2}-z$	1.02(2)	3.557(3)	2.553(2)	170(2)
N(18)–H(18)B · · · O(16)A	x, y, z	0.932(2)	2.766(4)	2.007(4)	137.3(2)
N(18)–H(18)B · · · O(16)B	x, y, z	0.932(2)	2.801(6)	2.055(5)	135.9(2)
N(18)–H(18)A · · · N(10)	$-\frac{1}{2}+x, y, -\frac{1}{2}-z$	0.915(2)	3.086(3)	2.210(2)	160.2(1)
(b) 9-Methyl derivative					
C(8)–H(8) · · · N(10)	$-\frac{1}{2}+x, y, -\frac{1}{2}-z$	0.993(2)	3.659(3)	2.716(2)	158.5(2)
C(18)–H(19) · · · O(16)	x, y, z	0.952(2)	2.922(3)	2.530(2)	104.8(2)
C(18)–H(18) · · · O(17)	x, y, z	0.986(2)	3.565(3)	2.842(2)	130.7(2)
C(18)–H(18) · · · N(10)	$-\frac{1}{2}-x, -\frac{3}{2}+y, z$	0.986(2)	3.730(3)	2.899(2)	142.5(2)
C(18)–H(20) · · · N(10)	$-\frac{1}{2}+x, y, -\frac{1}{2}-z$	0.997(3)	3.713(3)	2.800(2)	152.5(2)

[a] Standard deviations are in parentheses.

acridine. H(18B) on N(18) is hydrogen bonded to the disordered oxygen atoms O(16A) and O(16B) on the nitro group, as illustrated in Fig. 2. The other hydrogen atom, H(18A), on N(18) is hydrogen bonded to the endocyclic (nonprotonated) N(10) of another molecule. These hydrogen bonding interactions can be formed by the 9-amino but not by the 9-methyl compound. The effect of hydrogen bonding is seen in the slightly smaller cell dimensions of the 9-amino derivative compared to the 9-methyl derivative. In spite of this difference, the two crystal structures are very similar. This similarity is illustrated in Fig. 3, in which the packing of the two molecules is viewed down the shortest axis, y. From this we infer that it is the interactions between the acridine ring systems, rather than N · · · N hydrogen bonding, which determine the nature of the crystal packing. As shown in Fig. 4, the nitro group of both 9-amino and the 9-methyl derivative lies under N(10) of a symmetry related molecule. The stacking distance is 3.57 Å, 3.55 Å for the 9-amino and 9-methyl derivatives. This type of overlap is similar to that found for acridine orange (*4*); further, the stacking is head-to-tail, which is unlike the stacking for other nonaromatic, 1-nitro derivatives (*6, 7, 9*) but similar to that for the planar, aromatic 2-nitroacridine (*17*).

DISCUSSION

This work has disclosed the importance of acridine–acridine stacking versus hydrogen bonding as a determinant of crystal structure. Other studies have shown that alkylation at N(18) makes it possible for the 1-nitro compounds to exist in an imino form. This intramolecular change affects the intermolecular stacking interactions. It appears that the aromaticity of the central *B* ring of the acridine mole-

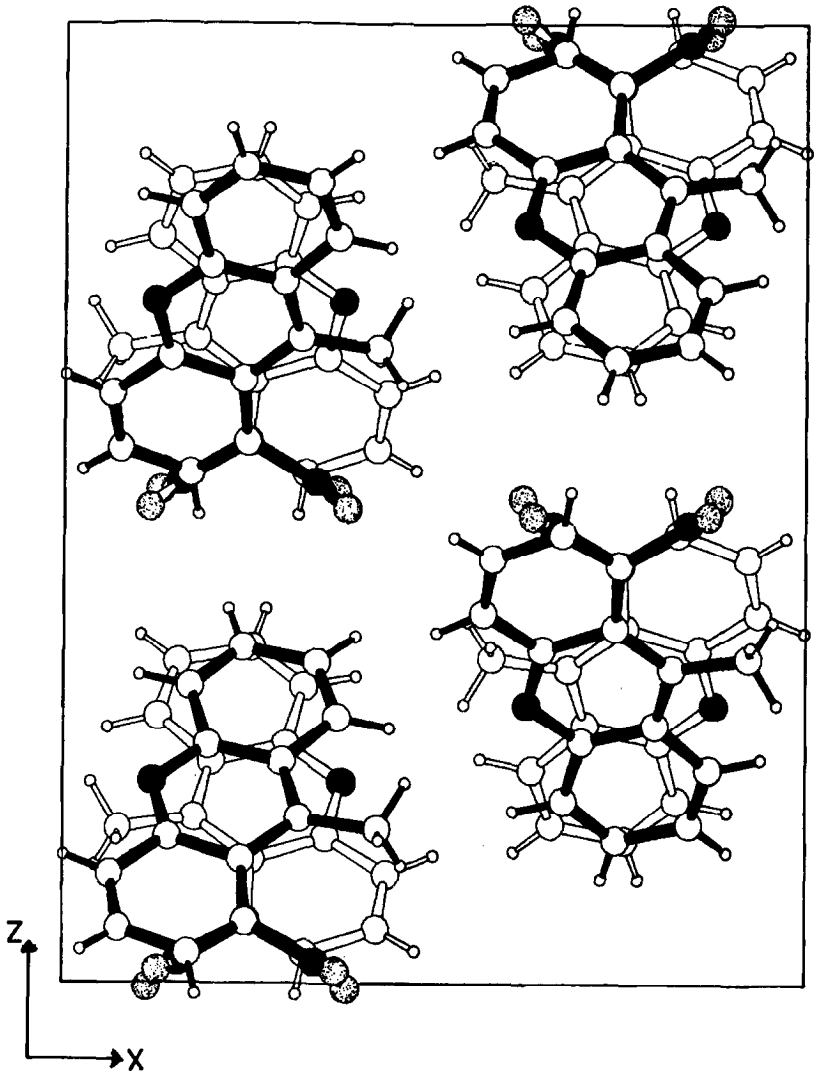


FIG. 4. Overlap of ring systems, in (a) 1-nitro-9-aminoacridine and (b) 1-nitro-9-methylacridine. Two molecules related by $\frac{1}{2} - x, \frac{1}{2} + y, z$ are stacked at 3.57 Å (9-amino derivative) and 3.55 Å (9-methyl) apart.

cule as detected by the presence of the amino rather than imino tautomer, the absence of a proton at N(10), and the aromatic bond lengths in the central ring are correlated with the stacking observed. In Table 4 are listed relevant dimensions of the acridine molecule for several derivatives illustrating these observations. The 1-nitro groups are each distorted from the plane of the acridine rings by approximately 60°, while the 2-nitro group, having fewer steric constraints, is coplanar with the ring system.

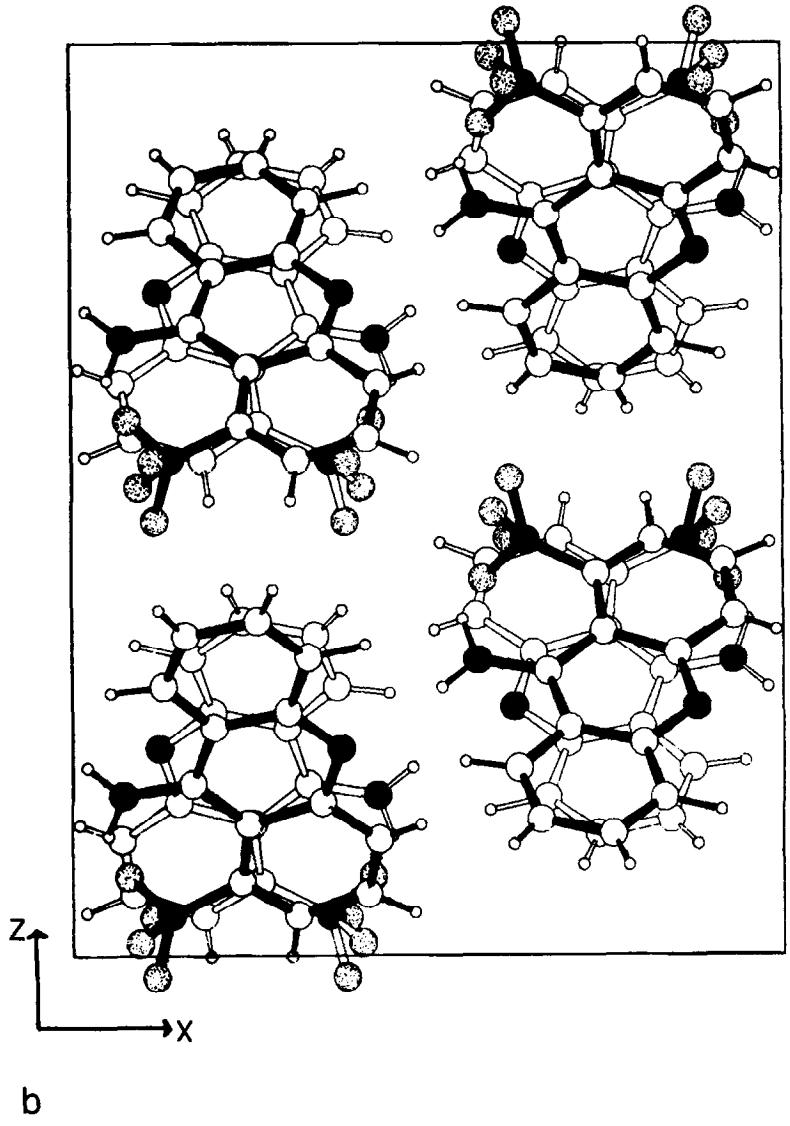


FIG. 4—(*Continued*).

The similarity in the packing of the two structures is of interest since the amino derivative can form an intermolecular hydrogen bond while the methyl derivative cannot. This hydrogen bond may be the cause of the 75°C higher melting point of the 9-amino derivative (we thank a referee for pointing this out).

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