STRUCTURE OF 1-DIMETHYLAMINO-4-CHLOROPHTHALAZINE

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The molecular-crystal structure of 1-dimethylamino-4-chlorophthalazine was investigated by means of x-ray diffraction analysis. The dimethylamino group is turned about the C_r—N bond at an angle of 33.4° from the position that is optimal for its conjugation with the ring, and the nitrogen atom has a flattened trigonal-pyramidal conformation (the sum of the angles is 346.9°); this is in agreement with NMR data on the low barrier to its rotation about the C_r—N bond.

The conformation of dimethylamino derivatives of azacycles has a substantial effect on the barrier to retarded rotation about the hetaryl—nitrogen bond and on the spectral characteristics. A great deal of attention has recently been devoted to these problems [1-7]. In molecules in which the dimethylamino group is coplanar with the ring, as, for example, in 1,5-dimethyl-4-dimethylamino-2-oxopyrimidine (I) [2] and 1-phenyl-3-dimethylamino-4-cyano-5-aminopyrazole (II) [3], it has a high degree of conjugation with the ring [4]. A high barrier to rotation about the C—N bond has been noted in similar molecules [1, 6]. In molecules for which a low barrier to rotation of the dimethylamino group is observed, as, for example, in 4-dimethylaminoquinazoline (III) [1] and 1-dimethylamino-4-chlorophthalazine (IV) [5], it is assumed that it rotates about the C—N bond (for amine III it is estimated at 25° [1]). The pyramidal character of the dimethylamino group in these compounds either has not been discussed [5] or it has been assumed that it is planar [1].

In order to determine the molecular structure of 1-dimethylamino-4-chlorophthalazine (IV) we subjected it to x-ray diffraction study. The geometry of the molecule and the bond lengths and angles in it are presented in Fig. 1.

The phthalazine system is planar within the limits of 0.09 Å, and the N_1 (0.090 Å), C_5 (—0.060 Å), C_7 (—0.044 Å), and C_8 (—0.070 Å) atoms have the greatest deviations from the mean square plane (P1). The Cl atom virtually lies in this plane (0.005 Å), but the N_3 (—0.105 Å), C_9 (0.0220 Å), and, particularly, C_{10} (—1.218 Å) atoms deviate from it, and upon the whole the molecule is not planar. The pyridazine (P2) and benzene (P3) rings are planar within the limits of 0.034 and 0.018 Å, respectively. The P2/P3 dihedral angle between the planes of these rings is 5.02° (P1/P2 2.67°, P1/P3 2.35°), which significantly exceeds the bending of the phthalazine system (1.43 and 1.59°) in salts of phthalazine derivatives that are protonated at the ring N_2 atom [8, 9].

The length of the C_1—Cl bond is closer to the average value of 1.737 Å in benzene derivatives [10] and to the length of the C—Cl bond in compounds with a chloroimine fragment [1.76 Å in benzoyl chloride phenylhydrazone [11] and 1.74 Å in 1,4-dichloro-1-(4-chlorophenyl)-4-dimethylamino-2,3-diazabutadiene (azine V [12]] than to the value of 1.717 Å in the more similarly constructed 3,6-dichloropyridazine [13].

The inequality of the N_1C_1Cl (115.4°), C_2C_1Cl (118.8°), $N_2C_8N_3$ (116.1°), and $C_7C_8N_3$ (121.5°) exocyclic bond angles is explained by the shortened Cl...H_3 [2.76(4) Å], Cl...C_3 [3.093(3) Å], N_3...C_6 [2.957(3) Å], C_6...C_{10} [3.122(9) Å], and N_2...C_9 [2.629(8) Å] intramolecular nonvalence contacts (the peri effect).

The deviations of the C_9 (0.260 Å) and C_{10} (—1.098 Å) atoms from the P2 plane (the N_3 atom deviates —0.030 Å) constitute evidence for rotation (θ) of the dimethylamine group about the C_8—N_3 bond from the position that is optimal for conjugation of the N_3 atom with the ring.

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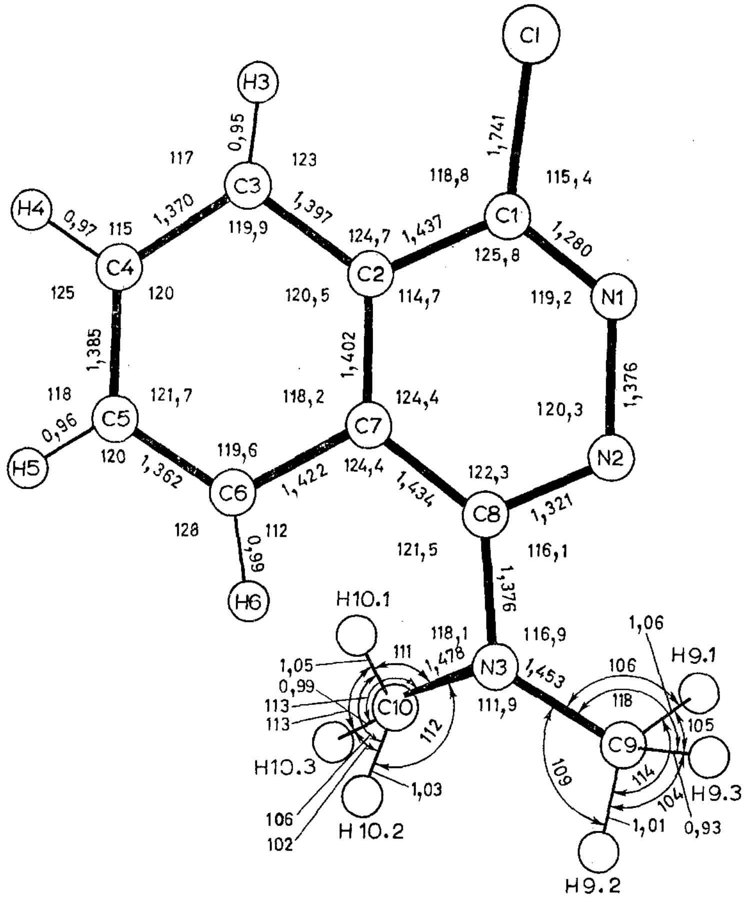

Fig. 1. General form and bond lengths (Å) and angles (deg) of amine IV.

The P4 plane drawn through the C_8 and N_3 atoms and the bisector of angle $C_9N_3C_{10}$ forms an angle of 56.6(2)° with the P2 plane, i.e., $\theta = -33.4(2)°$. The θ value can also be determined from the Newman projection along the N_3-C_8 bond (Fig. 2) using the values of the torsion angles $C_9N_3C_8N_2$ [12.1(7)°], $C_{10}N_3C_8N_2$ [−126.0(8)°], $C_9N_3C_8C_7$ [164.4(8)°], and $C_{10}N_3C_8C_7$ [−57.5(7)°] [$\theta = -34.8(7)°$] or the angles between the P2 plane and the P5 (13.0°) and P6 (−125.1°) planes drawn through $C_8N_3C_9$ and $C_8N_3C_{10}$ ($\theta = -33.9°$). The three methods for the determination of θ give close values. The N_3 atoms of the dimethylamino group has a flattened trigonal-pyrimidal conformation. The sum of the bond angles at N_3 is 346.9°, and this atom deviates 0.304 Å from the $C_8C_9C_{10}$ plane. The angles between the P5/P6 (138.1°), P5/P7 ($C_9N_3C_{10}$) (140.6°), P6/P7 (140.1°), P4/P5 (69.6°), P4/P6 (68.5°), and P4/P7 [90.0(1)°] planes constitute evidence for the symmetry of the pyramid of the dimethylamino group and the correctness of the drawing of plane P4. The P2/P7 dihedral angle is 133.4°.

For convenience in comparing the data (particularly in series of N, P, and As derivatives) one can assume that the degree of pyramidal character of the nitrogen atom in ammonia is unity (∠HNH 106.67° [14]; the sum of the angles is 320°) and that it is zero in molecules in which the tricoordinated sp^2-hybridized nitrogen atom has a planar conformation (the sum of the angles is 360°) the degree of pyramidal character of the nitrogen atom ($C^N{}_p$) can then be estimated from the empirical equation $C^N{}_p = 9 - 0.025 \cdot \Sigma$ (angles at the N atoms). In trimethylamine $C^N{}_p = 0.705$ (∠CNC 110.6° [15]), in triphenylamine $C^N{}_p = 0.30$ (∠CNC 116° [16]), in amine IV $C^N{}_p = 0.327$, in amine I $C^N{}_p = 0$, and in amine II $C^N{}_p = 0.07$.

Despite the substantial angle of rotation of the dimethylamino group and its pyramidal character, the C_8-N_3 bond in amine IV is only somewhat longer than in amines I and II [2, 3] [1.338(6) and 1.33(6),† 1.360(2) and 1.382(2) Å†] or in azine V [12] [1.338(4) and 1.339(4) Å†] and appreciably shorter than in dimethylamine VI [17] [1.43(2) Å]. Evaluation of the bond

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†With respect to two independent molecules in the cell [2, 3, 12].

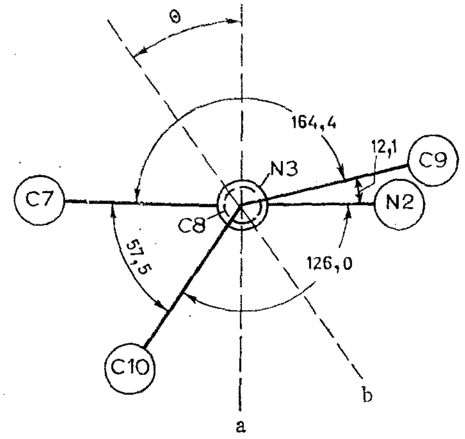

Fig. 2. Newman projection along the N_3–C_8 bond: a) bisector of angle $C_9N_3C_{10}$; b) bisector of angle $C_7C_8N_2$.

orders from the equation $p(C\text{–}N) = 7.68 - 4.54 \cdot l(C\text{–}N)$ [18] gives the following values: amines I 1.61 and 1.64,[†] II 1.51 and 1.41,[†] IV 1.43, and VI 1.19 and azine V 1.61 and 1.60.[†] This indicates considerable interaction of the electron systems of the dimethylamino group and the ring in amine IV. Evidence for this is provided by the angle of rotation and torsion angles $N_2C_8N_3C_9$ and $C_7C_8N_3C_{10}$, which could be considerably greater in the case of an increase in such short $N_2 \ldots C_9$ and $C_6 \ldots C_{10}$ intramolecular contacts, as well as by the redistribution of the bond lengths in the ring as compared with unsubstituted phthalazine [19], the values for which are presented in parentheses. Thus the N_2–C_8, C_1–C_2, C_2–C_7, and C_6–C_7 bonds [1.291(4), 1.407(4), 1.379(4), and 1.394(4) Å] are lengthened to 1.321(6), 1.437(7), 1.402(7), and 1.422(7) Å, respectively, and the N_1C_1 bond [1.297(4) Å] is shortened to 1.280(7) Å. The certain increase in the $N_1N_2C_8$ angle [118.5(3)° for phthalazine] and decrease to 122.3(4)° of the $N_2C_8C_7$ angle [126.1(4)°] should be noted. This sort of change in the adjacent endocyclic angles at the C and N angles is characteristic on passing from phthalazine [19] to its ring-protonated derivatives [8, 9] and from pyridazine [13] to its salt [20] or to pyridazones [21], when the ring nitrogen atom becomes tricoordinated.

The data obtained are in good agreement with the NMR spectral data on the low barrier to rotation of the dimethylamino group in amine IV and with the UV spectroscopic data; which constitute evidence for the low degree of conjugation of the dimethylamino group with the phthalazine ring and the absence of appreciable changes on passing from crystals of amine IV to solutions [5]. Thus only a slight increase in the intensity of the long-wave π–π^* band vis-à-vis a significant bathochromic shift is observed in the spectrum of amine IV [325 nm (ε 7000)] as compared with the spectra of phthalazine [262 nm (ε 3700)] and 1,4-dichlorophthalazines [275 nm (ε 5500)]. The same pattern is observed for naphthalene [285 nm (ε 4000)] and 1-dimethylaminonaphthalene [310 nm (ε 5000)] [22], while the transition from benzene [203 nm (ε 7300)] to dimethylaniline [251 nm (ε 14,000)] [23] is accompanied by a significant increase in the intensity of this band.

In conclusion, it may be assumed that resolution of the steric hindrance in dimethylaminoheterocycles occurs not only due to rotation of the dimethylamine group about the C–N bond [1] but also due to an increase in the degree of pyramidal character as a consequence of a decrease in the conjugation of the dimethylamino group with the heteroring.

EXPERIMENTAL

The crystals of amine IV ($C_{10}H_{10}N_3Cl$) were colorless needles from methanol with mp 101° and were monoclinic; at 20°C, a = 4.0008(2), b = 18.302(1), c = 13.342(1) Å, β = 94.129(8)°, d_{calc} = 1.42 g/cm^3, Z = 4, and space group $P2_1/c$.

The cell parameters and the intensities of 938 reflections with $F^2 > 3\sigma$ were measured with a Hilger–Watts four-circle diffractometer (λ CuK_α, graphite monochromator, $\theta/2\theta$ scan, $\theta \leqslant 66°$).

[†] With respect to two independent molecules in the cell [2, 3, 12].

TABLE 1. Coordinates of the Nonhydrogen ($\cdot 10^4$) and Hydrogen Atoms ($\cdot 10^3$)

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
Cl	4065 (4)	4271 (1)	2931 (1)	$C_{(9)}$	7482 (22)	863 (4)	3792 (6)
$N_{(1)}$	4775 (11)	2878 (2)	2924 (3)	$C_{(10)}$	6564 (18)	1193 (4)	5513 (5)
$N_{(2)}$	5542 (11)	2199 (2)	3318 (3)	$H_{(3)}$	716 (10)	455 (2)	481 (3)
$N_{(3)}$	7782 (11)	1435 (2)	4547 (3)	$H_{(4)}$	1004 (13)	448 (3)	628 (4)
$C_{(1)}$	5356 (12)	3444 (3)	3473 (4)	$H_{(5)}$	1190 (14)	332 (2)	694 (5)
$C_{(2)}$	7060 (11)	3449 (3)	4459 (3)	$H_{(6)}$	1070 (10)	222 (2)	594 (3)
$C_{(3)}$	7897 (12)	4079 (3)	5012 (4)	$H_{(9.1)}$	859 (15)	108 (3)	315 (5)
$C_{(4)}$	9717 (13)	4025 (3)	5919 (4)	$H_{(9.2)}$	860 (13)	40 (3)	407 (4)
$C_{(5)}$	10786 (13)	3348 (3)	6276 (4)	$H_{(9.3)}$	534 (17)	71 (3)	355 (5)
$C_{(6)}$	9989 (12)	2722 (3)	5761 (4)	$H_{(10.1)}$	626 (12)	164 (3)	599 (4)
$C_{(7)}$	8015 (11)	2758 (3)	4833 (3)	$H_{(10.2)}$	825 (16)	85 (3)	589 (5)
$C_{(8)}$	7037 (12)	2135 (3)	4229 (4)	$H_{(10.3)}$	455 (20)	88 (4)	543 (6)

The structure was decoded by a direct method by means of the MULTAN program and was refined by the method of least squares, initially within the isotropic approximation and then within the anisotropic approximation. All of the H atoms were revealed from differential synthesis and were refined isotropically to the final stage. The final values of the divergence factors were R = 0.054 and R_W = 0.063. All of the calculations were made with an Eclipse S/200 computer by means of EXTL programs modified in the laboratory of x-ray diffraction analysis of the A. N. Nesmeyanov Institute of Heteroorganic Compounds of the Academy of Sciences of the USSR by A. I. Yanovskii and R. G. Gerr.

The signs of the angle of rotation along the C_8-N_3 bond are presented from the condition that the fragment with the atom indicated first rotates relative to the fragment with the atom indicated second, which is arbitrarily assumed to be stationary.

The coordinates of the atoms are presented in Table 1. The accuracy in the bond angles without participation of the hydrogen atoms was ±0.04-0.05°, while the accuracy with participation of H was ±3°. The accuracy in the bond lengths without participation of hydrogen was ±0.006-0.008 Å, while the accuracy with participation of H was ±0.05-0.07 Å.

The UV spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer.

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SOME REACTIONS OF 4-AMINOPYRAZOLO[3,4-d]PYRIMIDINES

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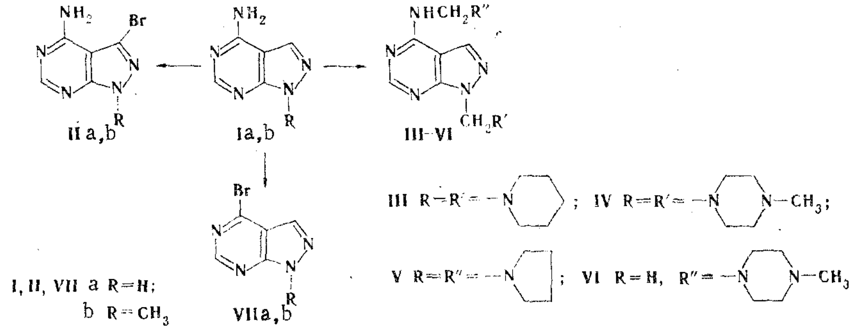
New 3-bromo and 1,4-diaminomethyl derivatives of 4-aminopyrazolo[3,4-d]pyrimidine were obtained by bromination and aminomethylation, respectively. 4-Bromopyrazolo[3,4-d]pyrimidines were synthesized for the first time by diazotization of 4-aminopyrazolo[3,4-d]pyrimidines.

We have previously studied the electrophilic substitution reactions of 4-hydroxypyrazolo[3,4-d]pyrimidines [1, 2]. It seemed of interest to extend them to 4-aminopyrazolo[3,4-d]pyrimidine (I) and substituted I. We found that the bromination of Ia, b also proceeds readily. 3-Bromo-substituted IIa, b were obtained in 50% yields when pyrazolopyrimidines Ia, b were heated with bromine in water on a water bath. The structures of these compounds were confirmed by the PMR spectra, in which, as compared with the starting substances, the signal of the proton attached to C_3 vanishes.



Under conditions similar to those in the aminomethylation of 4-hydroxypyrazolo[3,4-d]pyrimidine [2], Ia formed a Mannich base upon reaction with formalin and a secondary amine. Piperidine, methylpiperazine, and pyrrolidine were introduced into the reaction. On the basis of the results of elementary analysis and the PMR spectra it was concluded that bis(aminomethyl) derivatives III-V are obtained in this reaction. Mannich monobase VI was synthesized by the action of N-methylpiperazine on pyrazolopyrimidine Ib.

In contrast to 4-hydroxypyrazolo[3,4-d]pyrimidines, in the case of the 4-amino analogs one of the reaction centers is not the N_5 atom but rather the exocyclic amino group; this was demonstrated by means of the PMR spectra. The spectra of III and IV contain two signals of methylene protons: a singlet at 5.19 ppm and a doublet at stronger field (4.32 ppm). Splitting of the signal of the methylene protons by the proton attached to the exocyclic amino group is observed (Fig. 1). The assignment of the second reaction center to the N_1 atom was made on the basis of a comparison of the UV spectra of aminomethyl-substituted VI, i.e., with

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