Reaction of the Na salts of 2-amino-6-methyl-4-hydroxypyrimidine with bis(bromomethyl)phosphinic acid

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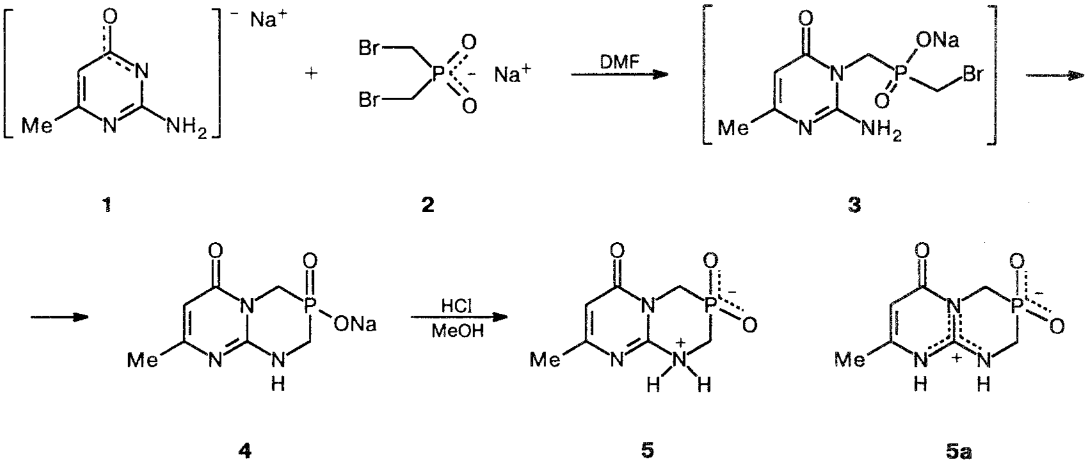
The reaction of the Na salts of 2-amino-6-methyl-4-hydroxypyrimidine and bis(bromomethyl)phosphinic acid gave 3,5-dioxo-1,2,3,4,5,8-hexahydro-7-methyl-1,8-diaza-4*a*-azonia-3-phosphanaphthalene-3-olate, whose structure was determined by X-ray diffraction study. The molecule has a bipolar structure, in which a positive charge is delocalized on the guanidine fragment and a negative charge is on the phosphinic acid fragment.

Key words: aminooxypyrimidines, phosphinic acids, oxopyrimidinyl-*N*-alkylphosphonic and phosphinic acids, X-ray diffraction analysis.

To develop methods for synthesizing *N*-alkylphosphonic and -phosphinic acids that may potentially be used as medicinals,$^{1-6}$ we studied the reaction of the Na salts of 2-amino-6-methyl-4-hydroxypyrimidine (**1**) with bis(bromomethyl)phosphinic acid (**2**). The reaction of **1** with **2** at 120—135 °C affords mainly the Na salt of 3,5-dioxo-3-hydroxy-7-methyl-1,3,4,5-tetrahydro-2*H*-1,4*a*,8-triaza-3-phosphanaphthalene (**4**) (Scheme 1).

At temperatures below 120 °C (refluxing in water or butanol), the reaction proceeds extremely slowly (the pH remains alkaline after 3 weeks) and ambiguously. At temperatures ≥140 °C, strong resinification was observed, especially when *N*-methylpyrrolidone was used as the solvent. When ethylene glycol was taken as the solvent, deamination of starting compound **1** with the formation of 6-methyluracil occurred. Dry DMF, which dissolves starting compounds **1** and **2** and precipitates the resulting bicyclic product **4**, is the most suitable solvent. The yield of compound **4** was 40—45 %, since the molecule of HBr, which is formed due to intramolecular cyclization of intermediate **3**, reacts with starting salt **1**, and thus 50 % of the latter is removed from the reaction. It is impossible to stop the process at the step of the formation of **3**. The interaction of **3** with **1** does not

Scheme 1



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occur even with an excess of compound **1** (with the ratio **1** : **2** = 2 : 1), *i.e.*, the rate of intramolecular cyclization of **3** into **4** is significantly higher than that of the reaction of **3** with **1**.

Treatment of the solution of salt **3** in MeOH with HCl afforded the corresponding base, which was assigned the structure betaine **5** (or **5a**). The IR spectrum of this compound contains a wide absorption band with a maximum at 2400 cm^{-1}, whose position is typical of $\nu(N^+H)$ or $\nu(N^+H_2)$, and a series of bands (3140, 3290, 3380, and 3500 cm^{-1}) that can be attributed to NH or OH groups capable of forming hydrogen bonds.

An X-ray diffraction study of the compound synthesized showed that its crystal structure is composed of bicyclic bipolar molecules and molecules of crystallization water. The pyrimidine cycle of the molecule (Fig. 1) is planar within 0.03 Å. The phosphorus-containing cycle has a semichair conformation, the C(6)N(1)C(2)N(3) fragment is planar within 0.013(2) Å, and deviations of the C(4) and P(5) atoms from this plane are oppositely directed and equal 0.268(2) and −0.655(1) Å, respectively.

The P atom has the usual distorted tetrahedral coordination. The bond lengths P(5)—O(1) (1.486(2) Å) and P(5)—O(2) (1.491(2) Å) are equal within the experimental error, which indicates delocalization of the negative charge on the OPO fragment. The lengths of the endocyclic P—C bonds (1.798(2) and 1.804(2) Å) are also equal within the experimental error. The C(4)—P(5)—C(6) endocyclic valence angle (97.2(1)°) is somewhat smaller than the angles usually observed in phosphorylanes with a tetracoordinated phosphorus atom (99.8—103.3°),[7] which have the chair conformation, and coincide with the value found in the structure of 1,3,5-dioxaphosphorylane with a "twisted" conformation of the ring (97.9°).[8]

The guanidine fragment N(1)C(2)N(2)N(3) of the molecule is planar (the sum of valence angles at the C(2) atom is 360°). The N atoms also have a planar-trigonal coordination. The H atoms are localized at the N(1) and N(2) atoms. The N(1)—C(2) bond (1.322(3) Å) is somewhat shorter than the N(2)—C(2) and N(3)—C(2) bonds (1.347(3) Å and 1.356(3) Å, respectively). These three distances are 0.12—0.16 Å longer than the C=N double bonds (1.208 Å)[9] and ~0.1 Å less than the C(sp^2)—N(sp^2) bonds in the absence of conjugation between these atoms (1.452 Å).[10] The calculation of the atomic charges carried out by the MNDO method (using the molecule geometry obtained from the X-ray diffraction study) brought us to the conclusion that the charges on the N atoms are practically identical (Fig. 2). Hence, one may conclude that the positive charge is delocalized on the guanidine fragment, and the whole molecule can be assigned structure **5a**.

The molecules of crystallization water in the crystal of **5a** form a complex three-dimensional framework of hydrogen bonds: N(1)—H(1)...O(W)′ (x, $-1/2-y$, $z-1/2$), N(1)...O(W)′ 2.811(3) Å, N(1)—H(1) 1.02(2) Å, $H^{N(1)}$...O(W)′ 1.96(2) Å, N(1)—H(1)...O(W)′ angle 140(1)°; N(2)—H(2)...O(2′), N(2)...O(2′) 2.592(3) Å,

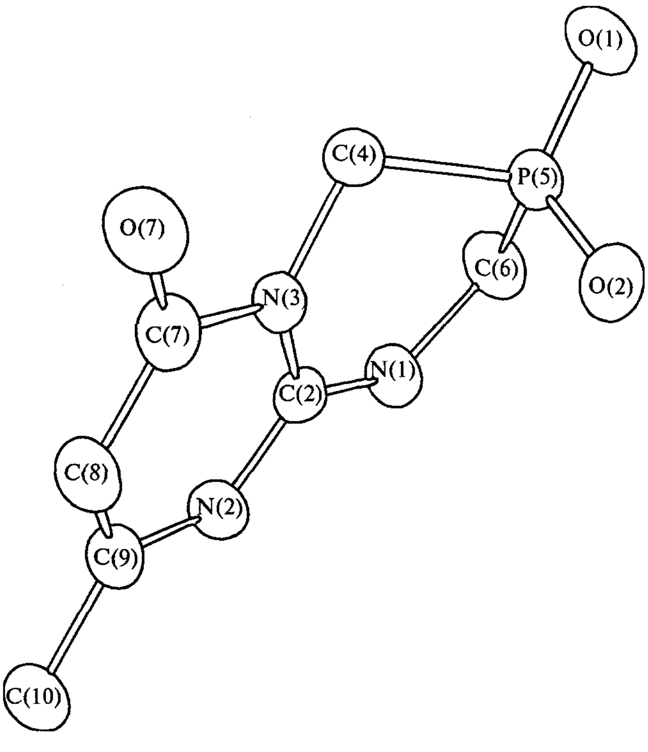

Fig. 1. Geometry of molecule **5a** in the crystal. The H atoms are not shown.

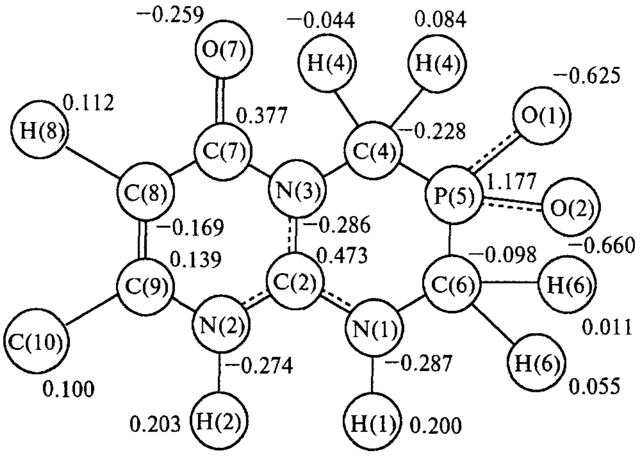

Fig. 2. Charges on the atoms of molecule **5a** according to an MNDO calculation.

N(2)—H(2) 0.92(2) Å, H(2)...O(2′) 1.67(2) Å, N(2)—H(2)...O(2′) angle 177(1)°; O(W)—H(1)...O(1′′) ($2-x$, $y-1/2$, $3/2-z$), O(W)...O(1′′) 2.722(3) Å, O(W)—H(1) 0.80(3) Å, H(1)...O(1′′) 1.93(3) Å, O(W)—H(1)...O(1′′) angle 174(1)°; O(W)—H(2)...O(1), O(W)...O(1) 2.875(3) Å, O(W)—H(2) 0.86(2) Å, H(2)...O(1) 2.11(2) Å, O(W)—H(2) angle 148(1)°.

Table 1. Coordinates of nonhydrogen atoms in structure **5a** and their equivalent isotropic temperature parameters $B_{\text{iso}}^{\text{eq}} = \sum_{i=1}^{3}\sum_{j=1}^{3}(\vec{a}_i\vec{a}_j)B(i,j)$ (Å^2)

Atom	x	y	z	B/Å^2
P(5)	0.83255(4)	0.1534(1)	0.55735(6)	2.69(1)
O(W)	0.9475(1)	−0.0478(4)	0.8091(2)	5.75(5)
O(1)	0.8931(1)	0.3025(3)	0.6322(2)	4.09(4)
O(2)	0.7732(1)	0.0187(3)	0.6276(2)	3.89(4)
O(7)	0.6138(1)	0.4094(3)	0.3462(2)	4.12(4)
N(1)	0.8286(1)	−0.1169(3)	0.3499(2)	2.76(4)
N(2)	0.7095(1)	−0.1554(3)	0.2161(2)	2.77(4)
N(3)	0.7210(1)	0.1556(3)	0.3499(2)	2.35(3)
C(2)	0.7544(1)	−0.0361(4)	0.3070(2)	2.32(4)
C(4)	0.7720(1)	0.3105(4)	0.4357(2)	2.78(4)
C(6)	0.8862(1)	−0.0263(4)	0.4533(2)	3.34(5)
C(7)	0.6385(1)	0.2299(5)	0.3065(2)	2.96(4)
C(8)	0.5928(1)	0.0827(5)	0.2178(3)	3.31(5)
C(9)	0.6283(1)	−0.1013(4)	0.1735(2)	2.80(4)
C(10)	0.5869(2)	−0.2585(5)	0.0767(3)	3.72(5)

Table 2. Bond lengths (d) and bond angles (ω) in molecule **5a**

Bond	d/Å	Angle	ω/deg
P(5)—C(1)	1.486(2)	O(1)—P(5)—C(2)	117.9(1)
P(5)—O(2)	1.491(2)	O(1)—P(5)—C(4)	111.0(1)
P(5)—C(4)	1.798(2)	O(1)—P(5)—C(6)	110.5(1)
P(5)—C(6)	1.804(3)	O(2)—P(5)—C(4)	107.8(1)
O(7)—C(7)	1.222(3)	O(2)—P(5)—C(6)	110.5(1)
N(1)—C(2)	1.322(3)	C(4)—P(5)—C(6)	97.2(1)
N(1)—C(6)	1.468(3)	C(2)—N(1)—C(6)	127.5(2)
N(2)—C(2)	1.347(3)	C(2)—N(2)—C(9)	122.7(2)
N(2)—C(9)	1.374(3)	C(2)—N(3)—C(4)	120.8(2)
N(3)—C(2)	1.356(3)	C(2)—N(3)—C(7)	122.0(2)
N(3)—C(4)	1.478(2)	C(4)—N(3)—C(7)	117.0(2)
N(3)—C(7)	1.427(3)	N(1)—C(2)—N(2)	117.4(2)
C(7)—C(8)	1.432(3)	N(1)—C(2)—N(3)	124.0(2)
C(8)—C(9)	1.333(3)	N(2)—C(2)—N(3)	118.6(2)
C(9)—C(10)	1.493(3)	P(5)—C(4)—N(3)	110.6(1)
		P(5)—C(6)—N(1)	111.5(1)
		O(7)—C(7)—N(3)	118.3(2)
		O(7)—C(7)—C(8)	126.3(2)
		N(3)—C(7)—C(8)	115.4(2)
		C(7)—C(8)—C(9)	121.2(2)
		N(2)—C(9)—C(8)	119.8(2)
		N(2)—C(9)—C(10)	115.3(2)
		C(8)—C(9)—C(10)	124.9(2)

Table 3. Torsion angles (τ) in molecule **5a**

Angle	τ/deg
N(1)—C(2)—N(3)—C(4)	9.6
C(2)—N(3)—C(4)—C(5)	−43.9
N(3)—C(4)—P(5)—C(6)	56.4
C(4)—P(5)—C(6)—N(1)	−45.0
P(5)—C(6)—N(1)—C(2)	20.5
C(6)—N(1)—C(2)—N(3)	3.4
N(3)—C(4)—P(5)—O(1)	171.6
N(3)—C(4)—P(5)—O(2)	−57.9
N(1)—C(6)—P(5)—O(1)	−160.6
N(1)—C(6)—P(5)—O(2)	67.1

Since the guanidine fragment of the molecule is symmetrical, the positive charge is delocalized, and the charges on the N(1) and N(2) atoms are practically identical, both N—H bonds are equivalent and possibly absorb at 2400 cm^{-1} in the IR spectrum, whereas the absorption bands at 3100—3500 cm^{-1} should be attributed to ν(OH) of the crystallization water, which is involved in hydrogen bonds with different energies.

Experimental

IR spectra were recorded on a Specord IR-75 spectrometer in Vaseline oil between KBr plates. UV spectra were obtained on a Specord M-40 spectrophotometer.

Na salt of 3,5-dioxo-3-hydroxy-7-methyl-1,3,4,5-tetrahydro-2*H*-1,4*a*,8-triaza-3-phosphanaphthalene (4). A solution of salt **1** (5.4 g) and salt **2** (10 g) in dry DMF was heated at 125—135 °C until pH 7 was attained. The precipitate that formed after cooling was filtered off and recrystallized from propanol to give 4.5 g (50 %) of salt **4**.

3,5-Dioxo-1,2,3,4,5,8-hexahydro-7-methyl-1,8-diaza-4*a*-azonia-3-phosphanaphthalene-3-olate (5a). A solution of salt **4** (4.5 g) in MeOH was acidified with HCl to pH 1. The precipitate formed was filtered off. Recrystallization from propanol gave 1.7 g (40 %) of compound **5a** · H_2O, m.p. 305—308 °C. Found (%): C, 35.65; H, 5.18; N, 18.22; P, 13.55. $C_7H_{10}N_3O_3P \cdot H_2O$. Calculated (%): C, 36.05; H, 5.18; N, 18.02; P, 13.30. UV (solvent, λ_{max}/nm(lgε)): 0.1 *N* HCl, 227 (3.81) and 266 (3.64); 0.1 *N* NaOH, 238 (3.78) and 293 (3.84).

X-Ray diffraction study. The crystals of **5a** · H_2O, $C_7H_{10}N_3O_3P \cdot H_2O$, are monoclinic. At 20 °C, $a = 16.024(4)$, $b = 5.920(1)$, $c = 10.576(3)$ Å, $\beta = 95.22(2)$°, $d_{calc} = 1.55$ g cm^{-3}, $Z = 4$, space group $P2_1/c$.

The cell parameters and intensities of 2313 independent reflections were measured on an Enraf-Nonius CAD-4 automatic four-circle diffractometer with K-geometry (λMo-K$_\alpha$), graphite monochromator, ω/2θ-scanning, θ ≤ 27°). The structure was solved by the direct method using a MULTAN program and was refined first in the isotropic and then in the anisotropic approximation. All hydrogen atoms were revealed from a differential row and refined isotropically at the final step. The final divergence factors were $R = 0.0368$, $R_w = 0.0535$ as calculated from 1430 reflections with $F^2 \geq 3\sigma$.

The coordinates of nonhydrogen atoms are given in Table 1, and the geometry of molecule **5a** is shown in Fig. 1. The main geometrical parameters are given in Tables 2 and 3.

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