New approach to the synthesis of azauracils and azaisocytosines*

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A new procedure was developed for the synthesis of 6-phenyltetrazolo[1,5-*b*]triazin-7-one. Aza analogs of uracil and isocytosine were prepared by the tetrazole ring cleavage. It was demonstrated that these transformations can be used in the synthesis of anomalous nucleosides.

Key words: tetrazolo[1,5-*b*]-1,2,4-triazine, azauracil, azaisocytosine, alkylation, azido-tetrazole rearrangement, destruction.

3,5-Dioxo-1,2,4-triazine derivatives (6-azauracils) have been widely described in the literature. For example, anomalous nucleosides and nucleotides based on azauracils have antiviral and antitumor activity.[1—3] The azauracil fragment is present in the structure, which is a promising ligand for positron emission tomography.[4] A glutamate receptor antagonist was designed based on 3,5-dioxo-1,2,4-triazines.[5] In addition, compounds having antiasthmatic activity were found among azauracils.[6,7] Hence, the development of new procedures for the synthesis of aza derivatives of pyrimidine bases is an important problem.

Earlier, we have described various procedures for partial destruction of azoloannelated pyrimidines and 1,2,4-triazines,[8—11] which were used as nontrivial synthetic approaches for the synthesis of substituted nonfused 1,2,4-triazines, including the synthesis of the antiepileptic drug lamotrigine.[11] The efficiency and advantages of this procedure over conventional synthesis methods were demonstrated.[11]

In the present study, we extended the scope of this synthetic approach and used it for introducing an alkyl substituent at the N(4) position of 3,5-dioxo- and 3-amino-5-oxo-1,2,4-triazines, which are aza analogs of uracil and isocytosine, respectively. This became possible due to the fact that *N*-alkylation of tetrazolo[1,5-*b*]-1,2,4-triazin-7-one (**1**) and subsequent cleavage of the tetrazole ring occur selectively. It should be noted that direct alkylation of 3,5-dioxo-1,2,4-triazines at the N(2) atom giving rise to *N*,*N*-dialkyl derivatives as by-products is generally used.[12,13] To synthesize alkylation products at the N(4) atom, it is necessary to initially acylate the starting triazine at the N(2) atom.[4,14]

The synthesis of 6-phenyltetrazolo[1,5-*b*]-1,2,4-triazin-7-one (**1**) by annulation of the tetrazole ring in the reaction of 3-hydrazino-5-oxo-6-phenyl-2,5-dihydro-1,2,4-triazine with nitric acid was documented.[15] We developed an alternative procedure for the synthesis of compound **1** based on the reaction of diazotetrazole **3** with ethyl phenyl(formyl)acetate **4** (Scheme 1).

We used formyl derivative **4** because ethyl phenylacetate is not involved in the azo-coupling reaction, whereas the introduction of the electron-withdrawing formyl group leads to an increase in CH-acidity. The reaction of diazotetrazole **3** with CH-active compound **4** produced hydrazone **5**, the azo-coupling reaction being accompanied by elimination of the formyl group. After further refluxing in acetic acid, compound **5** was transformed into 6-phenyltetrazolo[1,5-*b*]-1,2,4-triazinone (**1**). It should be noted that hydrazone **5** can undergo cyclization to give exclusively tetrazolo[5,1-*c*]-1,2,4-triazinone **6**, whose transformation into tetrazolo[1,5-*b*]-1,2,4-triazinone (**1**) can occur only with the involvement of the azido-tetrazole rearrangement, *i.e.*, through the formation of azide **7**.

The mass spectrum of compound **1** has a molecular ion peak (Table 1). The IR spectrum shows an absorption

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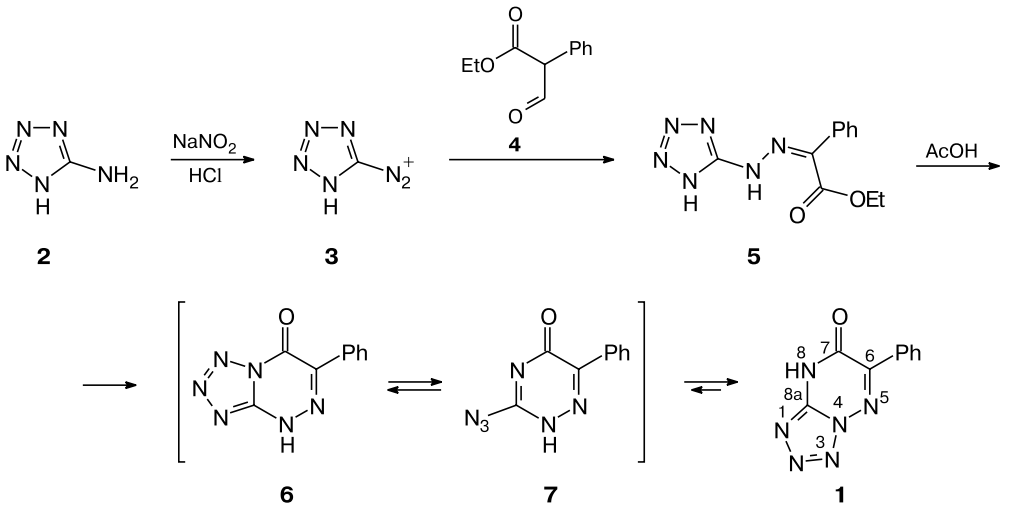
Scheme 1



band at 1711 cm^{-1} assigned to the carbonyl group. The absence of the signal of the azide group at 2210—2240 cm^{-1} in the IR spectrum of compound **1** indicates that this heterocycle has a bicyclic structure.

The ^1H NMR spectrum of heterocycle **1** shows signals for the protons of the phenyl substituent at δ 7.40—8.10 (Table 2).

Both the proton-coupled and proton-decoupled ^{13}C NMR spectra of compound **1** contain signals of the tetrazolotriazine system and the phenyl substituent at low field (Table 3).

However, all these data did not allow us to unambiguously conclude whether cyclization of hydrazone **5** is accompanied by the azido-tetrazole rearrangement. These data are insufficient to establish the mode of fusion of the tetrazole and triazine rings in compounds **1** and **6** (particularly, in solution). Although the structure of compound **1** was discussed in the literature, the proof of the mode of fusion of the azole and azine rings based on ^{13}C NMR spectroscopic data seems to be unconvincing.[15]

Hence, to solve this problem, we synthesized 5-aminotetrazole **2*** with the use of ^{15}N-labeled aminoguanidine bicarbonate **8*** (the isotope abundance was 87 %) (Scheme 2).

The position of the isotope label in aminoguanidine **8*** and the method used for the synthesis of compound **2*** enabled the introduction of the ^{15}N isotope at the N(2) position of the tetrazole ring. The subsequent use of amine **2*** in diazotization and azo-coupling reactions allowed us to prepare hydrazone **5***.

Scheme 2

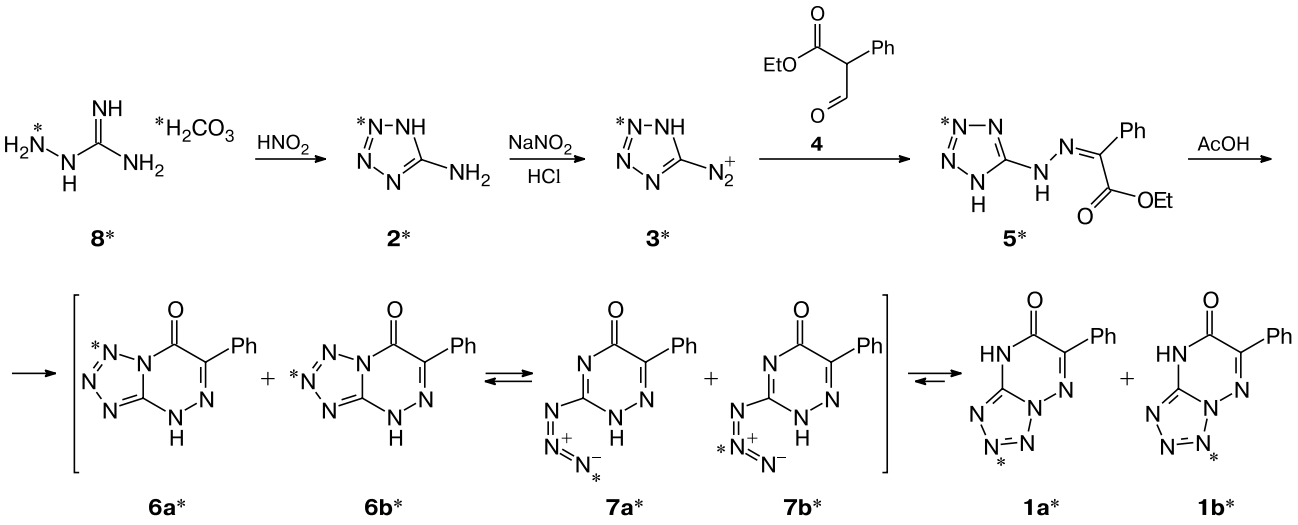


Table 1. Melting points, yields, molecular weights (mass-spectrometric data), and IR spectroscopic data for compounds **1**, **5**, **9, 10a—e**, **12a—d**, **13a—e**, and **14**

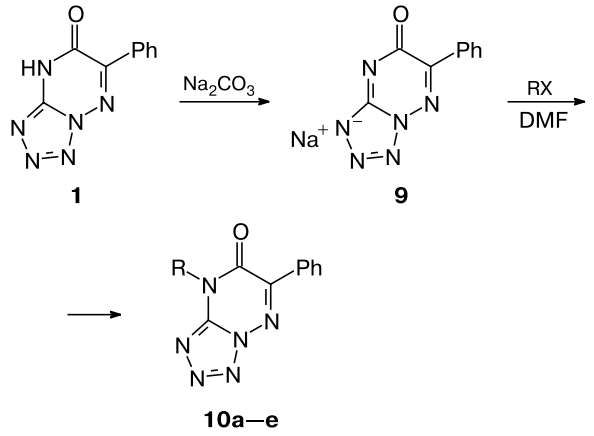
Compound	M.p.[a] /°C	Yield (%)	$[M]^+$, *m/z* (*I* (%))	IR, ν/cm^{-1}
1	225	80	214 (25.19)	1711 (CO)
5	172—174	86	260 (23.19)	1632 (CO)
9	311[b]	87	236 (1.44)	1630 (CO)
10a	182[c]	56	228 (18.54)	1730 (CO)
10b	159	45	242 (7.03)	1696 (CO)
10c	137[c]	50	256 (11.80)	1697 (CO)
10d	93	65	254 (7.88)	1700 (CO)
10e	67	40	328 (11.93)	1700 (CO)
				1750 (CO)
12a	265	35	202 (100.00)	1676 (CO)
				3340 (NH_2)
				3387 (NH_2)
12b	221	49	216 (56.21)	1679 (CO)
				3320 (NH_2)
				3393 (NH_2)
12c	149[d]	39	230 (40.95)	1684 (CO)
				3310 (NH_2)
				3399 (NH_2)
12d	165[e]	32	228 (100.00)	1679 (CO)
				3332 (NH_2)
				3421 (NH_2)
13a	199	49	203 (100.00)	1705 (CO)
				1722 (CO)
				3204 (NH)
13b	164	57	217 (75.90)	1697 (CO)
				1717 (CO)
				3200 (NH)
13c	154[c]	41	231 (44.73)	1676 (CO)
				1720 (CO)
				3196 (NH)
13d	149	39	229 (88.69)	1680 (CO)
				1715 (CO)
				3200 (NH)
13e	138	34	261 (30.49)	1670 (CO)
				1704 (CO)
				3160 (NH)
14	174	29	263 (9.59)	1666 (CO)
				1708 (CO)
				3200 (NH)

[a] After recrystallization from ethanol.
[b] After recrystallization from water.
[c] After recrystallization from isopropyl alcohol.
[d] After recrystallization from acetic acid
[e] After recrystallization from benzene.

Cyclization of compound **5*** afforded a mixture of two derivatives, whose structures differ only in the position of the isotope label. This was established by ^{13}C NMR spectroscopy. For example, the signal for the C(8a) bridgehead atom (δ 145.54) in the fully proton-decoupled ^{13}C NMR spectrum of this mixture (see Table 3) has a complex multiplet structure. This is indicative of several nonequivalent interactions between the carbon atom and the ^{15}N isotope, which can occur both in a mixture of compounds **6a*** and **6b*** and in a mixture of heterocycles **1a*** and **1b***. In this spectrum, the signal at δ 151.69 belonging to the C(6) atom has a simpler multiplet structure due to a long-range interaction with one ^{15}N atom, and a signal for the C(7) atom appears as a singlet because it does not interact with the ^{15}N isotope (see Table 3). This spectral pattern corresponds only to structure **1b***. We unambiguously established that compound **1** exists in solution as tetrazolo[1,5-*b*]-1,2,4-triazine, and its formation from hydrazone **5** occurs through the azido-tetrazole rearrangement involving bicyclic compound **6** and azide **7**.

8-Alkyl derivatives of compound **1** were synthesized with the use of the sodium salt of tetrazolotriazine **9**, which was prepared by the treatment of NH-heterocycle **1** with a sodium carbonate solution (Scheme 3). The reaction of compound **9** with various alkylating agents in DMF at 100 °C was completed in a few hours. The yields of alkyl derivatives **10a—e** were 40—65%.

Scheme 3



X = Br, I

10: R = Me (**a**), Et (**b**), Pr (**c**), CH_2—CH=CH_2 (**d**), CH_2—$(CH_2)_3$—OAc (**e**)

The structure of salt **9** ($Na^+[C_9H_5N_6O]^- \cdot 3H_2O$, Fig. 1) was established by single-crystal X-ray diffraction study of the product prepared by the reaction of heterocycle **1** with sodium carbonate. The geometric parameters of the organic ion are similar to those typical of tetrazolo[1,5-*b*]-1,2,4-triazines (Table 4).[16,11] The azole and azine rings form a virtually planar heterocyclic system, in which the phenyl substituent deviates from the conjugation system. The dihedral angle between the triazine ring and the phenyl group is 43.4°. The N(1) atom of the tetrazole ring is coordinated to the sodium ion, which, in turn, is surrounded by water molecules. The sodium ions are linked to each other through the oxygen bridges to

Table 2. ^{1}H NMR spectroscopic data for compounds **1**, **5**, **10a—e**, **12a—d**, **13a—e**, and **14**

Compound	δ
1	7.47—7.58 (m, 3 H, Ph); 8.05—8.09 (m, 2 H, Ph);
5	1.30 (t, 3 H, O—CH_2—$\underline{CH_3}$); 4.42 (q, 2 H, O—$\underline{CH_2}$—Me); 7.42—7.50 (m, 3 H, Ph); 7.74—7.77 (m, 2 H, Ph); 11.93 (br.s, 1 H, NH); 15.71 (br.s, 1 H, NH)
9	7.41—7.44 (m, 3 H, Ph); 8.14—8.18 (m, 2 H, Ph);
10a	3.62 (s, 3 H, N—Me); 7.48—7.59 (m, 3 H, Ph); 8.04—8.08 (m, 2 H, Ph)
10b	1.34 (t, 3 H, N—CH_2—$\underline{CH_3}$); 4.16 (q, 2 H, N—$\underline{CH_2}$—Me); 7.50—7.60 (m, 3 H, Ph); 8.05—8.09 (m, 2 H, Ph)
10c	0.97 (t, 3 H, N—CH_2—CH_2—$\underline{CH_3}$); 1.76—1.85 (m, 2 H, N—CH_2—$\underline{CH_2}$—Me); 4.08 (t, 2 H, N—$\underline{CH_2}$—CH_2—Me); 7.55—7.65 (m, 3 H, Ph); 8.00—8.04 (m, 2 H, Ph)
10d	4.47 (d, 2 H, N—$\underline{CH_2}$—CH=CH_2); 5.26, 5.46 (both dd, 1 H each, N—CH_2—CH=$\underline{CH_2}$); 5.90—5.97 (m, 1 H, N—CH_2—$\underline{CH}$=CH_2); 7.53—7.64 (m, 3 H, Ph); 8.00—8.04 (m, 2 H, Ph)
10e	1.64—1.74 (m, 2 H, CH_2—$\underline{CH_2}$—CH_2—O—CO—Me); 1.76—1.89 (m, 2 H, $\underline{CH_2}$—CH_2—CH_2—O—CO—Me); 1.96 (s, 3 H, CH_2—CH_2—CH_2—O—CO—$\underline{Me}$); 4.02 (t, 2 H, CH_2—CH_2—$\underline{CH_2}$—O—CO—Me); 4.16 (t, 2 H, N—$\underline{CH_2}$—CH_2); 7.48—7.63 (m, 3 H, Ph); 8.04—8.10 (m, 2 H, Ph)
12a	3.37 (s, 3 H, N—Me); 7.30—7.40 (m, 3 H, Ph and 2H, NH_2); 8.02—8.06 (m, 2 H, Ph)
12b	1.24 (t, 3 H, N—CH_2—$\underline{Me}$); 4.00 (q, 2 H, N—$\underline{CH_2}$—Me); 7.30—7.37 (m, 3 H, Ph + 2 H, NH_2); 8.01—8.06 (m, 2 H, Ph)
12c	0.96 (t, 3 H, N—CH_2—CH_2—$\underline{CH_3}$); 1.64—1.69 (m, 2 H, N—CH_2—$\underline{CH_2}$—Me); 3.90 (t, 2 H, N—$\underline{CH_2}$—CH_2—Me); 7.20—7.40 (m, 3 H, Ph and 2 H, NH_2); 8.00—8.06 (m, 2 H, Ph)
12d	4.59 (d, 2 H, N—$\underline{CH_2}$—CH=CH_2); 5.15, 5.18 (both dd, 1 H each, N—CH_2—CH=$\underline{CH_2}$); 5.82—5.91 (m, 1 H, N—CH_2—$\underline{CH}$=CH_2); 7.34—7.44 (m, 3 H, Ph and 2 H, NH_2); 8.00—8.04 (m, 2 H, Ph)
13a	3.27 (s, 3 H, N—Me); 7.37—7.42 (m, 3 H, Ph); 7.88—7.93 (m, 2 H, Ph); 12.60 (br.s, 1 H, NH)
13b	1.22 (t, 3 H, N—CH_2—$\underline{CH_3}$); 3.93 (q, 2 H, N—$\underline{CH_2}$—Me); 7.38—7.41 (m, 3 H, Ph); 7.87—7.92 (m, 2 H, Ph); 12.61 (br.s, 1 H, NH)
13c	0.95 (t, 3 H, N—CH_2—CH_2—$\underline{CH_3}$); 1.61—1.70 (m, 2 H, N—CH_2—$\underline{CH_2}$—Me); 3.83 (t, 2 H, N—$\underline{CH_2}$—CH_2—Me); 7.38—7.42 (m, 3 H, Ph); 7.87—7.92 (m, 2 H, Ph); 12.61 (br.s, 1 H, NH)
13d	4.47 (d, 2 H, N—$\underline{CH_2}$—CH=CH_2); 5.18, 5.24 (both dd, 1 H each, N—CH_2—CH=$\underline{CH_2}$); 5.81—5.89 (m, 1 H, N—CH_2—$\underline{CH}$=CH_2); 7.36—7.50 (m, 3 H, Ph); 7.80—7.92 (m, 2 H, Ph); 12.68 (br.s, 1 H, NH)
13e	1.46—1.54 (m, 2 H, CH_2—$\underline{CH_2}$—CH_2—OH); 1.61—1.73 (m, 2 H, $\underline{CH_2}$—CH_2—CH_2—OH); 3.44 (q, 2 H, CH_2—$\underline{CH_2}$—OH); 3.88 (t, 2 H, N—$\underline{CH_2}$—CH_2); 4.08 (t, 1 H, CH_2—$\underline{OH}$); 7.37—7.41 (m, 3 H, Ph); 7.88—7.93 (m, 2 H, Ph); 12.57 (br.s, 1 H, NH)
14	3.41 (t, 2 H, CH(OH)—$\underline{CH_2}$—OH); 3.76—3.91 (m, 2 H, N—$\underline{CH_2}$—CH(OH)); 4.00—4.06 (m, 1 H, N—CH_2—$\underline{CH}$(OH)); 4.27 (t, 1 H, CH_2—$\underline{OH}$); 4.52 (d, 1 H, CH—$\underline{OH}$); 7.38—7.41 (m, 3 H, Ph); 7.88—7.94 (m, 2 H, Ph); 12.65 (br.s, 1 H, NH)

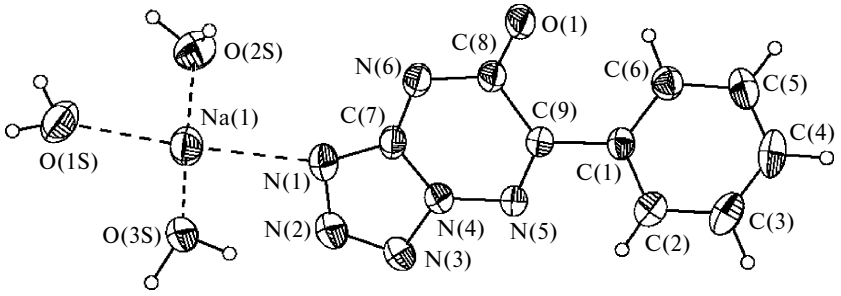


Fig. 1. Structure of the $Na^+[C_9H_5N_6O]^- \cdot 3H_2O$ salt (**9**).

form polymeric chains with an Na—Na distance of 3.765 Å (Fig. 2). As a result, sodium forms an octahedral complex, in which the metal ion is linked to one heterocyclic ligand and five water molecules (Table 5). This is a consequence of a weak π-π interaction and an extensive hydrogen bond network in the crystal structure (Table 6). The π-π overlap of the phenyl substituents is evident from the distance between the tetrazolotriazine ligands in the stacks (3.765 Å).[17]

The mass spectra of compounds **10a—e** have molecular ion peaks (see Table 1). In the IR spectra, the stretching vibrations in the 1690—1750 cm^{-1} region (see Table 1)

Table 3. ^{13}C NMR spectroscopic data for compound **1**, a mixture of **1a*** and **1b***, and compounds **10a—e**

Compound	δ (*J*/Hz)				
	C(6)	C(7)	C(8a)	Ph	R
1	151.66 (t, $^3J_{CH}$ = 3.8)	153.94 (s)	145.62 (s)	131.51, 130.87, 129.49, 128.26	
1a*, **1b***	151.69 (m)	153.94 (s)	145.54 (m)	131.53, 130.84, 129.50, 128.28	
10a	150.63 (t, $^3J_{CH}$ = 3.7)	152.95 (q, $^3J_{CH}$ = 2.9)	146.72 (q, $^3J_{CH}$ = 3.3)	131.73, 130.69, 129.51, 128.40	30.16 (q, $^1J_{CH}$ = 144.0)
10b	151.02 (t, $^3J_{CH}$ = 3.7)	152.41 (t, $^3J_{CH}$ = 3.8)	146.11 (t, $^3J_{CH}$ = 4.4)	131.65, 130.77, 129.56, 128.33	11.64 (qt, $^1J_{CH}$ = 128.6, $^3J_{CH}$ = 3.4); 38.28 (tq, $^1J_{CH}$ = 143.9, $^3J_{CH}$ = 4.6)
10c	150.97 (t, $^3J_{CH}$ = 4.0)	152.67 (t, $^3J_{CH}$ = 3.7)	146.45 (t, $^3J_{CH}$ = 4.3)	131.64, 130.79, 129.56, 128.31	11.11 (qm, $^1J_{CH}$ = 126.1); 19.79 (tm, $^1J_{CH}$ = 129.1); 45.68 (tm, $^1J_{CH}$ = 142.9)
10d	150.98 (t, $^3J_{CH}$ = 3.5)	152.37 (t, $^3J_{CH}$ = 3.7)	146.23 (t, $^3J_{CH}$ = 4.1)	131.71, 130.72, 129.58, 128.35	46.04 (tm, $^1J_{CH}$ = 143.6); 118.90 (ddt, $^1J_{CH}$ = 159.2, $^1J_{CH}$ = 156.1, $^3J_{CH}$ = 5.4); 129.60*
10e	150.99 (t, $^3J_{CH}$ = 3.7)	152.72 (t, $^3J_{CH}$ = 3.7)	146.23 (t, $^3J_{CH}$ = 4.3)	131.69, 130.78, 129.59, 129.35	20.67 (q, $^1J_{CH}$ = 129.3); 23.06 (dm, $^1J_{CH}$ = 133.5); 25.32 (tm, $^1J_{CH}$ = 127.7); 43.71 (tm, $^1J_{CH}$ = 143.6); 63.31 (tm, $^1J_{CH}$ = 147.0)

* The signal overlaps with the signal for the *ortho*-carbons of the phenyl substituent.

Table 4. Selected bond lengths and bond angles in the organic ion of the $Na^+[C_9H_5N_6O]^- \cdot 3H_2O$ salt (**9**)

Parameter	Value	Parameter	Value	Parameter	Value
Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
C(7)—N(1)	1.335(3)	C(8)—N(6)	1.350(2)	N(1)—N(2)	1.363(3)
C(7)—N(6)	1.344(3)	C(8)—C(9)	1.514(2)	N(2)—N(3)	1.293(3)
C(7)—N(4)	1.349(2)	C(9)—N(5)	1.302(3)	N(3)—N(4)	1.359(2)
C(8)—O(1)	1.241(3)	C(9)—C(1)	1.482(2)	N(4)—N(5)	1.356(2)
Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
N(1)—C(7)—N(6)	130.12(2)	N(5)—C(9)—C(1)	115.45(2)	C(7)—N(4)—N(5)	126.47(2)
N(1)—C(7)—N(4)	107.49(2)	N(5)—C(9)—C(8)	123.08(2)	C(7)—N(4)—N(3)	110.24(2)
N(6)—C(7)—N(4)	122.39(2)	C(1)—C(9)—C(8)	121.42(2)	N(5)—N(4)—N(3)	123.29(2)
O(1)—C(8)—N(6)	121.53(2)	C(7)—N(1)—N(2)	104.82(2)	C(9)—N(5)—N(4)	113.15(2)
O(1)—C(8)—C(9)	119.72(2)	N(3)—N(2)—N(1)	113.46(2)	C(7)—N(6)—C(8)	116.14(2)
N(6)—C(8)—C(9)	118.73(2)	N(2)—N(3)—N(4)	103.99(2)		

Table 5. Coordination environment of the sodium cation in the $Na^+[C_9H_5N_6O]^- \cdot 3H_2O$ salt (**9**)

Bond	*d*/Å	Angle	ω/deg	Angle	ω/deg
Na(1)—N(1)	2.513(2)	O(2SA)—Na(1)—O(3SA)	81.57(8)	N(1)—Na(1)—O(3SB)	95.14(7)
Na(1)—O(2SA)	2.464(3)	O(2SB)—Na(1)—O(3SB)	83.09(9)	N(1)—Na(1)—O(2SA)	83.80(8)
Na(1)—O(3SA)	2.502(2)	O(2SB)—Na(1)—O(3SB)	95.14(7)	N(1)—Na(1)—O(3SA)	79.94(7)
Na(1)—O(1S)	2.319(2)	O(3SA)—Na(1)—O(3SB)	100.20(7)	N(1)—Na(1)—O(3SB)	98.43(8)
Na(1)—O(2SB)	2.637(3)	N(1)—Na(1)—O(3SB)	95.10(8)	N(1)—Na(1)—Na(1)	80.02(6)
Na(1)—O(3SB)	2.405(2)	O(3SA)—Na(1)—O(3SB)	100.20(7)		

Table 6. Hydrogen bond parameters for the $Na^+[C_9H_5N_6O]^- \cdot 3H_2O$ salt (**9**)

D—H	*d*(D—H)	*d*(H..A)	*d*(D..A)	DHA Angle /deg	Atom	Transformation
	Å					
O(3S)—H(3SB)	0.918	2.045	2.840	144.05	N(2)	$(x-1, y, z)$
O(2S)—H(2SB)	0.957	1.928	2.861	164.31	N(6)	$(x+1/2, -y+1/2, -z)$
O(3S)—H(3SA)	1.022	1.871	2.802	149.79	O(1)	$(x, y-1, z)$
O(2S)—H(2SA)	0.833	2.343	3.079	147.67	O(2)S	$(x-1/2, -y+1/2, -z)$
O(1S)—H(1SA)	0.851	1.909	2.747	167.94	O(1)	$(x+1/2, -y+1/2, -z)$
O(1S)—H(1SB)	0.961	2.162	2.831	125.53	O(1)S	$(x-1/2, -y-1/2, -z)$

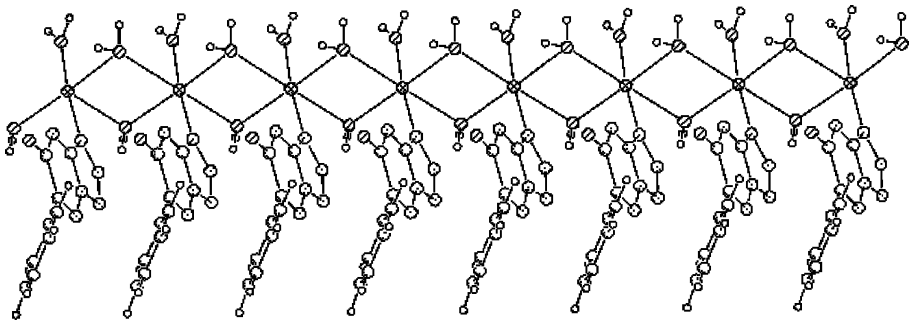


Fig. 2. Structure of the stack formed by the $Na^+[C_9H_5N_6O]^- \cdot 3H_2O$ salt (**9**).

are assigned to the carbonyl group. This is evidence of *N*-alkylation of salt **9**.

The ^{1}H NMR spectra of heterocycles **10a—e** show signals for both the protons of the phenyl substituent and the alkyl fragment (see Table 2).

To unambiguously determine the alkylation site and confirm the mode of fusion of the azole and azine rings in heterocycles **10a—e** in the solid phase, we studied the product of the reaction of sodium salt **9** with propyl bromide by X-ray diffraction. It was established that this reaction produces 6-phenyl-8-propyltetrazolo[1,5-*b*]-1,2,4-triazin-7-one (**10c**) (Fig. 3, Table 7).

The tetrazole and triazine rings in compound **10c** form a planar heterocyclic system, which is not conjugated with the phenyl substituent. The dihedral angle between the planes of the triazine and benzene rings is 30.4°. The dihedral angle between the planes of the propyl substituent and the triazine ring is 89.9°. The N(6)C(1)C(2)C(3) torsion angle is 176.4°.

The ^{13}C NMR spectra of compounds **10a—e** show signals of the tetrazolotriazine system, the phenyl substituent, and the alkyl fragment (see Table 3). The assignment of the signals was made based on the analysis of the fine structure of the signals for the carbon atoms in the

Table 7. Selected bond lengths and bond angles in compound **10c**

Bond	*d*/Å	Angle	ω/deg	Angle	ω/deg
O(1)—C(7)	1.208(2)	C(5)—N(1)—N(2)	104.3(1)	N(9)—C(8)—C(11)	116.2(1)
N(1)—N(2)	1.374(2)	N(3)—N(2)—N(1)	112.5(1)	N(9)—C(8)—C(7)	124.0(1)
N(1)—C(5)	1.306(2)	N(2)—N(3)—N(4)	104.9(1)	C(11)—C(8)—C(7)	119.6(1)
N(2)—N(3)	1.287(2)	C(5)—N(4)—N(3)	108.8(1)	C(8)—N(9)—N(4)	114.1(1)
N(3)—N(4)	1.352(2)	C(5)—N(4)—N(9)	127.6(1)	N(6)—C(1)—C(2)	112.5(1)
N(4)—N(9)	1.353(2)	N(3)—N(4)—N(9)	123.5(1)	C(1)—C(2)—C(3)	111.4(2)
N(4)—C(5)	1.343(2)	N(1)—C(5)—N(4)	109.4(1)	C(12)—C(11)—C(16)	118.7(1)
N(6)—C(1)	1.478(2)	N(1)—C(5)—N(6)	131.6(1)	C(12)—C(11)—C(8)	122.8(1)
N(6)—C(5)	1.354(2)	N(4)—C(5)—N(6)	119.0(1)	C(16)—C(11)—C(8)	118.4(1)
N(6)—C(7)	1.377(2)	C(5)—N(6)—C(7)	119.7(1)	C(13)—C(12)—C(11)	120.4(2)
C(7)—C(8)	1.507(2)	C(5)—N(6)—C(1)	119.9(1)	C(14)—C(13)—C(12)	120.1(2)
N(9)—C(8)	1.293(2)	C(7)—N(6)—C(1)	120.2(1)	C(15)—C(14)—C(13)	120.2(2)
C(8)—C(11)	1.481(2)	O(1)—C(7)—N(6)	121.2(1)	C(14)—C(15)—C(16)	120.2(2)
C(1)—C(2)	1.493(2)	O(1)—C(7)—C(8)	123.4(1)	C(15)—C(16)—C(11)	120.3(1)
C(2)—C(3)	1.505(3)	N(6)—C(7)—C(8)	115.5(1)		

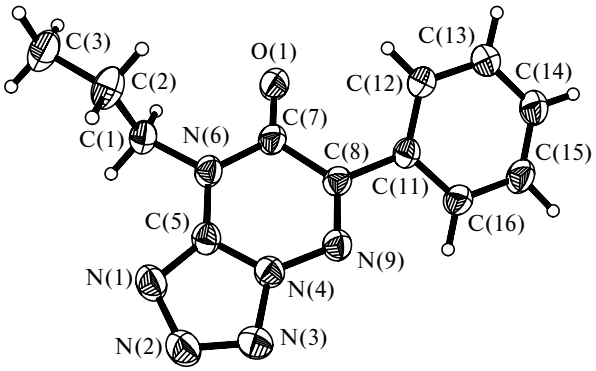


Fig. 3. Molecular structure of *N*-propyltetrazolotriazinone **10c**.

spectra recorded without suppression of the $^{13}C—^{1}H$ coupling constants. In the spectrum of *N*-methyl derivative **10a**, the signals for the C(7) and C(8a) atoms are observed as quartets ($^{3}J = 2.9$ Hz and $^{3}J = 3.3$ Hz, respectively). The signal for the C(6) atom appears as a triplet ($^{3}J = 3.7$ Hz).

For alkyl derivatives **10b—e**, all signals for the carbon atoms of the tetrazolo-1,2,4-triazine system in the spectra recorded without $^{13}C—^{1}H$ decoupling, appear as triplets due to the presence of the *N*-methylene fragment in the alkyl substituent. Hence, the assignment of the signals of the carbon atoms of the heterocyclic moiety in compounds **10b—e** was made based on a comparison of the chemical shifts with those for compound **10a**. The assignment of the signals in the ^{13}C NMR spectra of compounds **10a—e** was confirmed by correlation 2D HSQC and HMBC experiments for heterocycle **10e** and the ^{13}C NMR spectroscopic data for compounds **1a*** and **1b*** (see Table 3).

Study of destruction of tetrazolotriazines **10a—d** (Scheme 4) demonstrated that the treatment of these compounds with copper in acetic acid affords azaisocytosines **12a—d**. Most likely, the synthesis of amines **12a—d** proceeds through the formation of azides **11a—d**.

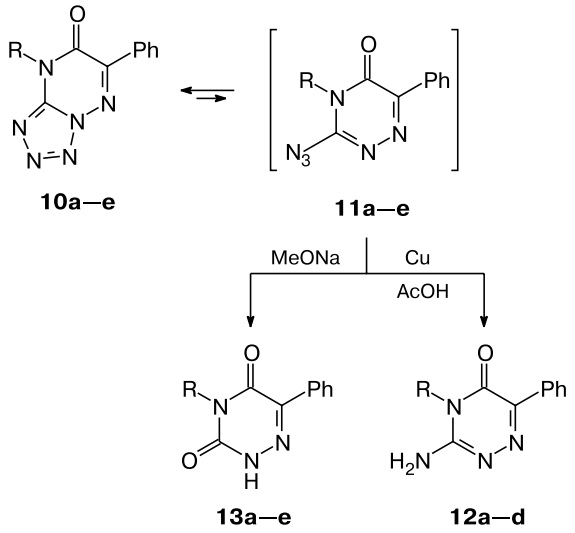
It should be noted that compounds **10a—e** are abnormally stable to acid hydrolysis. The formation of azauracils **13a—e** was observed only upon prolonged refluxing in a sodium methoxide solution. In the case of compound **10e**, cleavage of the tetrazole ring is accompanied by removal of the acyl protecting group to give anomalous nucleoside **13e**.

Oxidation of allyl derivative **13d** with iodine in the presence of silver acetate also afforded acyclic nucleoside **14** (Scheme 5).

Therefore, we synthesized azaisocytosine derivatives **12a—d** and azauracil derivatives **13a—e** and **14** containing the alkyl substituent at the N(4) atom of the 1,2,4-triazine ring.

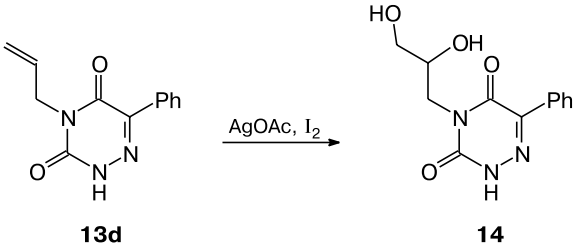
The ^{1}H NMR spectra of 1,2,4-triazine derivatives **12a—d**, **13a—e**, and **14** show signals for the protons of the phenyl fragment and the *N*-alkyl substituent (see Table 2).

Scheme 4



10—13: R = Me (**a**), Et (**b**), Pr (**c**), $CH_2—CH=CH_2$ (**d**), R = $CH_2—(CH_2)_3—OAc$ (**10e**, **11e**), $CH_2—(CH_2)_3—OH$ (**13e**)

Scheme 5



The IR spectra of triazinones **12a—d** show absorption bands in the 3310—3430 and 1670—1700 cm^{-1} regions, which is indicative of the presence of the amino and carboxy groups, respectively. The IR spectra of azauracils **13a—e** and **14** are characterized by the presence of two pronounced absorption bands in the 1660—1730 cm^{-1} region, which were assigned to stretching vibrations of the carbonyl groups. The appearance of the signals of the second carbonyl group for compounds **13a—e** and the detection of the amino group in heterocycles **12a—d** indicate that the tetrazole ring in azoloazines **10a—e** was cleaved (see Table 1).

The formation of 1,2,4-triazine derivatives **12a—d** and **13a—e** from annulated tetrazolotriazines **10a—e** is additionally confirmed by *m/z* for the molecular ion peaks in the mass spectra (see Table 1).

To summarize, a principally new procedure was developed for the synthesis of various derivatives of azauracils and azaisocytosines, including those with the desired position of the *N*-alkyl substituent, by destruction of the azole fragment in tetrazolo[1,5-*b*]-1,2,4-triazin-7-ones.

This synthetic methodology from "complex to simple" is more efficient than conventional approaches from "simple to complex" and can be used in the nucleoside synthesis.

Experimental

The IR spectra were recorded in KBr pellets on a Specord 75 IR spectrometer. The ^{1}H NMR spectra (in DMSO-d_6 + CCl_4) were measured on a Bruker WM -250 instrument with $SiMe_4$ as the internal standard. The ^{13}C 2D NMR spectra (100 MHz) were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6. The mass spectra were obtained on a Varian MAT-311A instrument; samples were introduced by a direct inlet system; the ionizing electron energy was 70 eV; the ionization chamber temperature was 100—300 °C. The melting points were determined on a Boetius apparatus. Thin-layer chromatography was carried out on Silufol UV-254 plates using ethyl acetate as the eluent; spots were visualized by exposing to UV radiation and iodine vapor. Column chromatography was performed on Kieseligel-60 silica gel (Merck, Germany).

5-Aminotetrazole, ethyl phenylacetate, and 60% sodium hydride in oil were purchased from Aldrich. All other reagents and solvents used in experiments were commercial Russian-made products.

The yields and solvents used for crystallization are listed in Table 1. The elemental analysis data are given in Table 8.

[^{15}N]-Aminoguanidine bicarbonate (8*) was prepared according to a procedure described earlier.[18]

6-Phenyltetrazolo[1,5-*b*]-1,2,4-triazin-7-one (1). A solution of hydrazone **5** (1 g) in acetic acid (7 mL) was refluxed for 2 h. After cooling, the precipitate that formed was filtered off and dried.

A mixture of [^{15}N]-labeled compounds 1a* and 1b*. Concentrated HCl (0.5 mL) was added to a solution of aminotetrazole **2*** (0.2 g, 2 mmol) in water (10 mL). After cooling of the reaction mixture to −2 °C, a solution of $NaNO_2$ (0.14 g, 2 mmol) in water (2 mL) was added dropwise with vigorous stirring. The reaction mixture was kept at −2 °C for 30 min. A mixture of ethyl phenyl(formyl)acetate (**4**) (2 mmol) and sodium carbonate (0.6 g) in water (3 mL) and ethanol (2 mL) was added to the resulting diazonium salt. The resulting mixture was stirred at room temperature for 2 h, concentrated HCl (1 mL) was added, and the mixture was filtered. The precipitate that formed was dissolved in acetic acid (2 mL). The solution was refluxed for 2 h, cooled, and filtered. A mixture of compounds **1a*** and **1b*** was obtained in a yield of 0.2 g (46 %), M^+ 215.

[2-^{15}N]-5-Aminotetrazole (2*). Aminoguanidine ^{15}N (**8***) (0.69 g) was stirred in 5 *N* nitric acid (2 mL). Then a 5 *N* $NaNO_2$ solution (1 mL) was added at a temperature no higher than 40 °C. Sodium acetate (1.4 g) was added to the resulting yellow solution. The mixture was refluxed for 5 min and then cooled. The precipitate that formed was filtered off. The yield was 0.43 g (88%), m.p. 200 °C, M^+ 86.

Ethyl α-formylphenylacetate (4). A 60% NaH oily suspension (6.60 g) was added to a mixture of anhydrous hexane (60 mL) and ethyl formate (8.8 mL, 0.11 mol), and the reaction mixture was stirred for 10 min. Then ethyl phenylacetate (15 mL, 0.1 mol) was added dropwise for 40 min. The precipitate was filtered off, washed with hexane (20 mL), dried, and dissolved in water (40 mL). Then HCl was added to the resulting solution to pH 2, and the mixture was treated with diethyl ether (4×15 mL). The organic layer was separated, dried with Na_2SO_4, and concentrated. The residue was distilled off *in vacuo*, and the fraction with 105—112 °C was collected at 5 Torr.

Ethyl α-(tetrazol-5-ylhydrazono)phenylacetate (5). Concentrated HCl (5 mL) was added to a solution of aminotetrazole (**2**) (2 g, 20 mmol) in water (100 mL). The reaction mixture was cooled to −2 °C, a solution of $NaNO_2$ (1.4 g, 20 mmol) in water (20 mL) was added dropwise with vigorous stirring, and the reaction mixture was kept at −2 °C for 30 min. A mixture of ethyl phenyl(formyl)acetate (**4**) (20 mmol) and sodium carbonate (6 g) in water (30 mL) and ethanol (15 mL) was added to the resulting diazonium salt. The reaction mixture was stirred at room temperature for 2 h, and concentrated HCl (5 mL) was added. The precipitate that formed was filtered off and recrystallized.

Table 8. Elemental analysis data for compounds **1**, **5**, **9**, **10a—e**, **12a—d**, **13a—e**, and **14**

Compound	Found / Calculated (%)			Molecular formula
	C	H	N	
1	50.44	2.72	39.27	$C_9H_6N_6O$
	50.47	2.82	39.24	
5	50.54	4.61	32.43	$C_{11}H_{12}N_6O_2$
	50.77	4.65	32.29	
9	41.71	2.94	32.35	$C_9H_5N_6NaO$
	41.07	3.06	31.94	$\cdot 1.5H_2O$
10a	52.54	3.54	36.75	$C_{10}H_8N_6O$
	52.63	3.53	36.83	
10b	54.40	4.13	34.63	$C_{11}H_{10}N_6O$
	54.54	4.16	34.69	
10c	56.00	4.68	32.80	$C_{12}H_{12}N_6O$
	56.24	4.72	32.79	
10d	56.49	3.79	33.15	$C_{12}H_{10}N_6O$
	56.69	3.96	33.05	
10e	54.89	4.97	25.34	$C_{15}H_{16}N_6O_3$
	54.87	4.91	25.60	
12a	59.37	5.14	27.59	$C_{10}H_{10}N_4O$
	59.40	4.98	27.71	
12b	61.05	5.63	25.99	$C_{11}H_{12}N_4O$
	61.10	5.59	25.91	
12c	62.61	6.51	24.26	$C_{12}H_{14}N_4O$
	62.59	6.13	24.33	
12d	63.00	5.30	24.38	$C_{12}H_{12}N_4O$
	63.15	5.30	24.55	
13a	59.05	4.45	20.49	$C_{10}H_9N_3O_2$
	59.11	4.46	20.68	
13b	60.63	5.15	19.18	$C_{11}H_{11}N_3O_2$
	60.82	5.10	19.34	
13c	62.32	5.84	18.16	$C_{12}H_{13}N_3O_2$
	62.33	5.67	18.17	
13d	62.74	4.72	17.99	$C_{12}H_{11}N_3O_2$
	62.87	4.84	18.33	
13e	59.50	5.84	16.09	$C_{13}H_{15}N_3O_3$
	59.76	5.79	16.08	
14	54.50	5.02	15.52	$C_{12}H_{13}N_3O_4$
	54.75	4.98	15.96	

Sodium salt of 7-oxo-6-phenyltetrazolo[1,5-*b*]-1,2,4-triazine (9). Tetrazolotriazine **1** (2.14 g, 10 mmol) was suspended in a 17% sodium carbonate solution (5 mL). The precipitate was filtered off and recrystallized.

8-Substituted 7-oxo-6-phenyltetrazolo[1,5-*b*]-1,2,4-triazines (10a—e). Sodium salt **9** (0.24 g, 1 mmol) was dissolved in DMF (5 mL), alkyl bromide or iodide (2 mmol) was added, and the mixture was heated on a water bath for 2 h. Water (40 mL) was added to the cooled reaction mixture. The precipitate that formed was filtered off and recrystallized.

4-Substituted 3-amino-5-oxo-6-phenyl-1,2,4-triazines (12a—d). A mixture of 8-R-6-phenyl-7-oxo-tetrazolo[1,5-*b*]-1,2,4-triazine **10a—d** (2 mmol) and a copper powder (0.252 g, 4 mmol) freshly prepared according to a known procedure[19] was refluxed in acetic acid (5 mL) for 2 h. Then the reaction mixture was cooled and aqueous (25%) ammonium (15 mL) was added. The precipitate that formed was filtered off, dried, and recrystallized.

4-Substituted 3,5-dioxo-6-phenyl-1,2,4-triazines (13a—d). Triazine **10a—d** (1 mmol) was added to a sodium methoxide solution, which was prepared from sodium (0.027 g, 1.2 mmol) and methanol (6 mL). The reaction mixture was refluxed for 2 h, cooled, and poured into water. Acetic acid was added to neutral pH. The precipitate that formed was filtered off and recrystallized.

4-(4-Hydroxybutyl)-3,5-dioxo-6-phenyl-1,2,4-triazine (13e). Triazine **10e** (0.33 g, 1 mmol) was added to a sodium methoxide solution, which was prepared from sodium (0.027 g, 1.2 mmol) and methanol (6 mL). The reaction mixture was refluxed for 2 h, cooled, and poured into water. Acetic acid was added to neutral pH, and the mixture was concentrated. The product was isolated by silica gel column chromatography using ethyl acetate as the eluent ($R_f = 0.3$).

4-(2,3-Dihydroxypropyl)-3,5-dioxo-6-phenyl-1,2,4-triazine (14). Water (0.03 mL) was added to a solution of dione **13d** (0.25 g, 1 mmol) in acetic acid (10 mL). Silver acetate (0.46 g, 2.75 mmol) and iodine (0.3 g, 1.2 mmol) were added portionwise to the reaction mixture. The resulting suspension was refluxed for 3 h, cooled, and filtered. The filtrate was concentrated *in vacuo*, the residue was dissolved in ethanol (10 mL), and acetyl chloride (0.5 mL) was added. The resulting solution was kept at room temperature for 48 h and then evaporated. The product was isolated by column chromatography in a 1 : 1 chloroform : ethyl acetate system ($R_f = 0.2$).

X-ray diffraction data sets for compounds **9** and **10c** were collected on an automated Xcalibur 3 diffractometer equipped with a CCD detector (**9**) and on an automated Enraf-Nonius CAD-4 diffractometer (**10c**) (ω/2θ-scanning technique, λMo-Kα radiation, graphite monochromator).

Both structures were solved by direct methods and refined by the least-squares method using the SHELXS-97[20] and SHELXL-97[21] program packages with anisotropic (isotropic for H atoms) displacement parameters.

Selected bond lengths and bond angles for the structures of **9** and **10c** are given in Tables 4 and 7, respectively. The geometric data for the coordination environment of the sodium cation in

Table 9. Crystallographic data and the X-ray data collection and refinement statistics

Parameter	**9**	**10c**
Molecular formula	$Na^+[C_9H_5N_6O]^- \cdot 3H_2O$	$C_{12}H_{12}N_6O$
Molecular weight	290.23	256.28
Crystal system	Orthorhombic	Monoclinic
Space group	*P*2(1)2(1)2(1)	*C*2/*c*
a/Å	3.7652(2)	16.026(2)
b/Å	9.8696(11)	6.992(1)
c/Å	33.529(4)	22.788(4)
α/deg	90	90
β/deg	90	93.43(3)
γ/deg	90	90
Z	4	8
λ/Å	0.71073	0.71073
U/Å	1246.0(2)	2548.9(7)
Ranges of measured indices	$-5 \le h \le 5$	$0 \le h \le 18$
	$-13 \le k \le 14$	$0 \le k \le 8$
	$-46 \le l \le 49$	$-27 \le l \le 27$
d_{calc}/g cm^{-3}	1.547	1.34
μ/mm^{-1}	0.152	0.093
Number of measured reflections	1968	2275
Number of independent reflections	2409	2192
Number of reflections with $I^2 > 4\sigma(I^2_0)$	1868	1770
R	0.0424	0.038
wR_2	0.1091	0.104
Number of parameters in refinement	225	221
GOOF	1.002	1.053
Residual electron density/e Å^{-3} (min/max)	−0.219/0.270	−0.134/0.163

the structure of **9** are given in Table 5. The hydrogen bond parameters are listed in Table 6. The results of X-ray diffraction study of compounds **9** and **10c** are presented in Table 9.

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