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INTERACTION OF AMINOAZOLES WITH MELDRUM'S ACID AND DIALKYL KETONES OR CYCLOHEXANONE

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Interaction of 3-amino-5-methylpyrazole, 3-amino-5-methylthio-, and 3,5-diamino-1,2,4-triazole with Meldrum's acid, acetone, ethyl methyl ketone, and cyclohexanone leads to alkyl-substituted pyrazolo[3,4-b]pyridin-6-ones and 1,2,4-triazolo[1,5-a]pyrimidin-7-ones respectively. The structure of 5,5-dimethyl-2-methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-a]pyrimidin-7-one was demonstrated by an X-ray structural investigation.

Keywords: 3-amino-5-methylpyrazole, 3-amino-5-methylthio-1,2,4-triazole, dialkyl ketones, 3,5-diamino-1,2,4-triazole, Meldrum's acid, pyrazolo[3,4-*b*]pyridin-6-ones, 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones, X-ray structural analysis.

The cyclocondensation of nitrogen-containing binucleophiles with arylmethylidene derivatives of Meldrum's acid or their synthetic precursors has given a broad scope to the synthesis of heterocycles [1-3]. Previously by the interaction of the indicated acid, aromatic aldehydes, 3-amino-1,2,4-triazole and 2-amino-benzimidazole, we obtained partially hydrogenated derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidin-5-one [4] or pyrimido[1,2-*a*]benzimidazol-2- or -4-one respectively [5]. It is known that ketones of the aliphatic and aromatic series are also capable of condensing with Meldrum's acid as carbonyl components [1, 6]. The alkylmethylidene and arylalkylmethylidene derivatives of isopropylidenemalonates, formed as a result of such an interaction, in their turn are of interest as synthons in the synthesis of azoloazine systems. The aim of the present investigation is to clarify the direction of formation of the azine ring in reactions of 3-amino-5-methylpyrazole (**1**), 3-amino-5-methylthio- (**2**) and 3,5-diamino-1,2,4-tetrazole (**3**) with Meldrum's acid (**4**) acetone (**5a**), ethyl methyl ketone (**5b**), and cyclohexanone (**5c**).

It was established that on boiling aminopyrazole **1** with an equimolar amount of 2,2-dimethyl-1,3-dioxane-4,6-dione (**4**) and ketones **5a-c**, both in methanol and in DMF, only the corresponding pyrazolo[3,4-b]pyridin-6-ones **6a-c** were formed. Products of the isomeric structure **7-9a-c** were not isolated.

The composition and structure of the obtained compounds **6a-c** were confirmed by the results of elemental analysis and spectral characteristics (see Experimental). In the IR spectra of compounds **6a-c** there was a set of absorption bands characteristic of cyclic amides in the regions 3400-2850 (ν NH), 1656-1652 (amide I), and 1524-1508 cm^{-1} (amide II). However these data do not permit an assignment to be made for structures to one of the two types of positional isomers **6** (**7**) or **8** (**9**).

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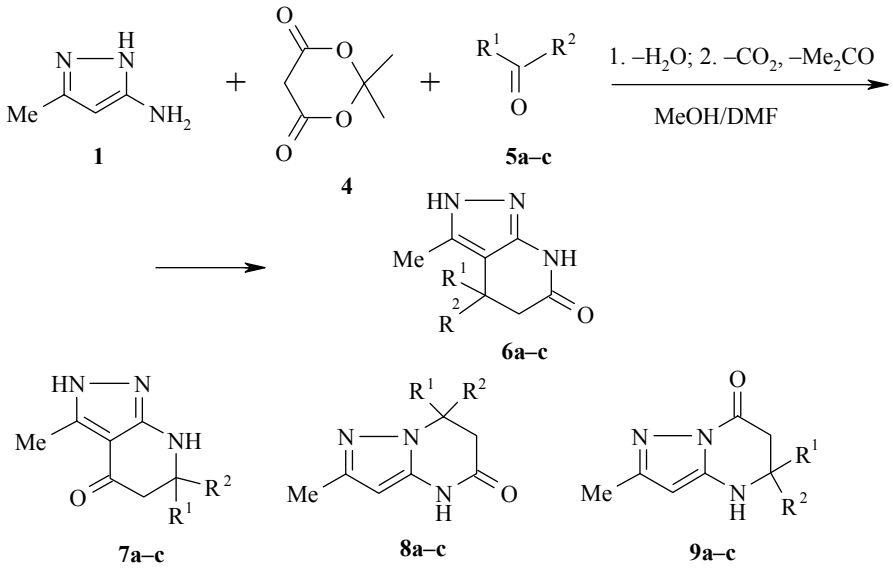
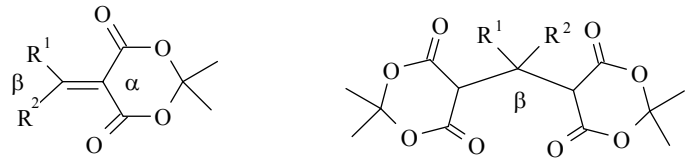


1 **4** **5a–c** **6a–c** **7a–c** **8a–c** **9a–c**

5–9 a $R^1 = R^2 = Me$, **b** $R^1 = Me$, $R^2 = Et$, **c** $R^1 + R^2 = –(CH_2)_5–$

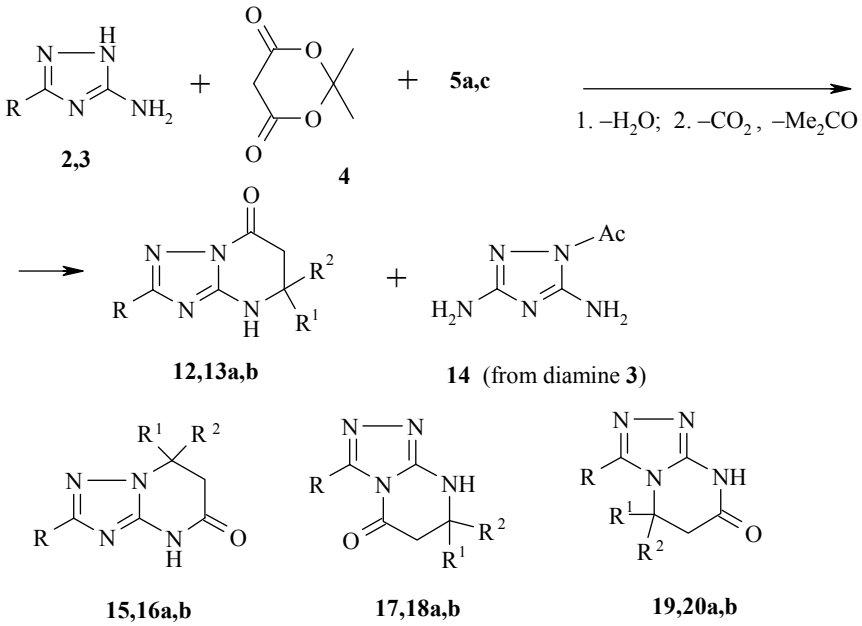
In the ^1H NMR spectra of compounds **6a-c** signals were present for protons of two NH groups, alkyl substituents, and a methylene group of a partially hydrogenated pyridine ring. In favor of assigning the obtained products to a pyrazolopyridine (**6** or **7**) and not a pyrimidine series (**8** or **9**) is the presence of two broadened singlet signals of NH groups at 11.71-11.69 and 10.65-10.10 ppm and the absence of a signal for the methine proton of a pyrazole ring. The choice in favor of isomers **6** was made on the basis of a nuclear Overhauser experiment carried out for compound **6c**. Irradiation of the protons of the CH_3 group at position 3 (2.20 ppm) causes a response at the proton of the NH group of the pyrazole ring (11.64 ppm) and at the protons of the spiro-linked cyclohexane fragment, which indicates their close spatial disposition.

The interaction of 3-amino-5-methylpyrazole (**1**) with 2,2-dimethyl-1,3-dioxane-4,6-dione (**4**) and ketones **5a-c** is therefore characterized by high regioselectivity and leads exclusively to the formation of the pyrazolo[3,4-*b*]-pyridin-6-one system **6**. Such a direction for the process corresponds to the interaction of the β-carbon atom of intermediates **10** or **11**, formed at the first stage from Meldrum's acid **4** and ketone **5** with the carbon nucleophilic center in the aminoazole molecule and the carbon atom of the C=O group with the exocyclic amino group.



10 **11**

The three-component condensation of 3-amino-5-methylthio-1,2,4-triazole (**2**) with 2,2-dimethyl-1,3-dioxane-4,6-dione (**4**) and acetone (**5a**) or cyclohexanone (**5c**) was carried out by us in ethyl acetate in the presence of catalytic amounts of pyridine. An excess of the appropriate ketone was used as solvent for the analogous reactions involving 3,5-diamino-1,2,4-triazole (**3**). In all cases tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones **12a,b** and **13a,b** were obtained. In the reaction of diamine **3**, triazolylacetamide **14** was isolated together with products **13a,b** [7].



The composition and structure of the previously undescribed compounds **12** and **13** were confirmed by results of elemental analysis and spectral characteristics (see experimental). In the IR spectra of products **12a,b** and **13a,b** there were absorption bands for a carbonyl group at 1712-1756 cm^{-1}, the position of which is typical of the similar 7-oxo isomers [8], but the amide I and amide II absorption bands characteristic of structures **15** (**16**) or **19** (**20**) were absent (see IR spectra of compounds **6a,c**). However the data presented do not permit a choice to be made between isomers **12** (**13**) and **17** (**18**).

The ^{1}H NMR spectra of the obtained products **12a,b 13a,b** contain signals of all the protons proposed for their structures. Finally a choice in favor of the latter was made on the basis of the results of X-ray structural analysis of compound **12a** (Fig. 1, Tables 1, 2).

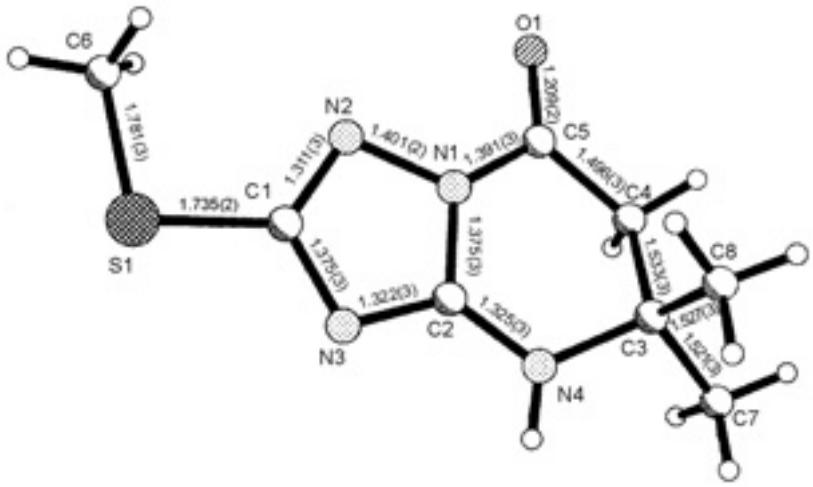


Fig. 1. Structure of the compound **12a** molecule.

TABLE 1. Bond Lengths (d) in Molecules A and B of Compound **12a**

Bond	*d*, Å		Bond	*d*, Å	
	A	**B**		**A**	**B**
S(1)–C(1)	1.735(2)	1.739(2)	N(3)–C(1)	1.375(3)	1.377(3)
S(1)–C(6)	1.781(3)	1.786(3)	N(4)–C(2)	1.325(3)	1.333(3)
O(1)–C(5)	1.209(2)	1.197(3)	N(4)–C(3)	1.474(3)	1.465(3)
N(1)–C(2)	1.375(3)	1.373(3)	C(3)–C(7)	1.521(3)	1.498(3)
N(1)–C(5)	1.391(3)	1.402(3)	C(3)–C(8)	1.527(3)	1.542(4)
N(1)–N(2)	1.401(2)	1.397(2)	C(3)–C(4)	1.533(3)	1.526(3)
N(2)–C(1)	1.311(3)	1.310(3)	C(4)–C(5)	1.496(3)	1.493(3)
N(3)–C(2)	1.322(3)	1.317(3)			

TABLE 2. Valence Angles (ω) in Molecules A and B of Compound **12a**

Angle	φ, deg		Angle	φ, deg.	
	A	**B**		**A**	**B**
C(1)–S(1)–C(6)	101.1(1)	101.2(1)	N(4)–C(2)–N(1)	121.5(2)	120.6(2)
C(2)–N(1)–C(5)	124.6(2)	125.0(2)	N(4)–C(3)–C(7)	107.8(2)	108.3(2)
C(2)–N(1)–N(2)	109.2(2)	109.3(2)	N(4)–C(3)–C(8)	109.5(2)	108.7(2)
C(5)–N(1)–N(2)	124.5(2)	124.5(2)	C(7)–C(3)–C(8)	110.5(2)	110.2(2)
C(1)–N(2)–N(1)	101.0(2)	100.9(2)	N(4)–C(3)–C(4)	108.0(2)	107.9(2)
C(2)–N(3)–C(1)	102.5(2)	102.3(2)	C(7)–C(3)–C(4)	109.2(2)	111.9(2)
C(2)–N(4)–C(3)	119.7(2)	119.9(2)	C(8)–C(3)–C(4)	111.7(2)	109.7(2)
N(2)–C(1)–N(3)	117.2(2)	117.2(2)	C(5)–C(4)–C(3)	116.8(2)	115.3(2)
N(2)–C(1)–S(1)	124.6(2)	123.5(2)	O(1)–C(5)–N(1)	121.5(2)	121.8(2)
N(3)–C(1)–S(1)	118.3(2)	119.3(2)	O(1)–C(5)–C(4)	125.6(2)	126.2(2)
N(3)–C(2)–N(4)	128.4(2)	129.1(2)	N(1)–C(5)–C(4)	112.7(2)	111.9(2)
N(3)–C(2)–N(1)	110.1(2)	120.6(2)			

In the symmetrically independent portion of the unit cell of the crystal of 5,5-dimethyl-2-methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one **12a** two molecules (**A** and **B**) were found which differed in the conformation of the six-membered ring. The tetrahydropyrimidine fragment has the distorted *half-chair* conformation (folding parameters $S = 0.58$ (**A**), 0.63 (**B**), $\theta = 50.03$ (**A**), 48.47 (**B**), $\Psi = 12.62$ (**A**), 20.93 (**B**) [9]). The deviation of the C(3) and C(4) atoms from the mean plane of the remaining ring atoms was 0.34 (**A**), 0.31 Å (**B**) and –0.25 (**A**) – 0.33 Å (**B**) respectively. The thiazole ring and the methylthio group atoms lie in one plane with a precision of 0.014 (**A**) and 0.028 Å (**B**). The configuration of the N(1) nitrogen atom was not absolutely planar, the sum of the valence angles centered on the atom was 358.3° in molecule **A** and 358.7° in molecule **B**. The C(7) and C(8) atoms have equatorial and axial orientations, respectively, relative to the six-membered ring [torsion angles C(7)-C(3)-C(4)-C(5) 162.6(2)° (**A**), -169.7(2)° (**B**), C(8)-C(3)-C(4)-C(5) –74.9(2) ° (**A**) and 67.7(3)° (**B**)],

Nonequivalence of the C(3)-C(7) and C(3)-C(8) bonds occurs in molecule **B**. The C(3)-C(7) bond at 1.498(3) Å (mean value 1.530 Å) [10] is significantly shorter, but the C(3)-C(8) bond at 1.542(4) Å is significantly lengthened. At the same time both bonds in molecule **A** have equal length [C(3)-C(7) 1.527(3) Å, C(3)-C(8) 1.521(3) Å]. Also observed was a shortening of the C(5)-N(2) bond at 1.391(3) (**A**), 1.402(3) Å (**B**) (1.346 Å) and of the C(2)-N(4) at 1.325(3) (**A**), 1.333(3) Å (**B**) (1.339 Å). In the crystal of the compound **12a** molecule dimers of the **AA** and **BB** type are formed as a result of hydrogen bonds N(4)-H(4)…N(3') (*-x,* 1-*y*, 1-*z* for **AA**, *-x*, 1-*y*, *-z* for **BB**), [H…N 2.23 Å (**AA**), 2.16 Å (**BB**), N-H…N 146° (**AA**), 172° (**BB**)]. Furthermore, there were also dimers of the **AB** type as a result of stacking interactions between the thiazole rings (distance between ring centers was 3.53 Å, angle between the planes of rings 8.4°).

The considered examples of the interaction of 3-amino-5-methylthio- and 3,5-diamino-1,2,4-triazole with Meldrum's acid and ketones **5a-c** indicate that the process proceeds regioselectively in all cases and leads to the formation of only one of the possible isomers, *viz.* 5-alkyl-substituted tetrahydro-1,2,4-triazolo[1,5-a]pyrimidin-7-one.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian 200 spectrometer (200 MHz) for solutions in DMSO-d_6. internal standard was $SiMe_4$. The IR spectra were described on a Specord M 82 instrument (KBr disks). Mass spectra of compounds **6b,c**, **12a,c**, and **13a,c** were obtained on a Finnigan MAT INCOS 50 instrument (70 eV) and of compound **6a** on a MSBC SELMI spectrometer (source was 10 μCi ^{252}Cf) for positive and negative ions with an accelerating voltage of ±20 kV. A check on the composition of reaction mixtures and the purity of the compounds obtained was effected by TLC on Silufol UV 254 plates, eluent was methanol–chloroform–dioxane, 3 : 3 : 4. Melting points were determined on a Kofler block.

3,4,4-Trimethyl-4,5,6,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (6a). A. A mixture of pyrazole **1** (0.19 g, 2 mmol), Meldrum's acid (4) (0.28 g, 2 mmol), and acetone (**5a**) (0.170 ml, 2 mmol) in methanol (5 ml) was boiled for 20-25 min. The reaction mixture was cooled, compound **6a** (0.14 g, 40%) was filtered off, and was purified by recrystallization from 2-propanol. Mp 245-247°C. IR spectrum, ν, cm^{-1}: 3400-2650, 1652, 1556, 1520. ^{1}H NMR spectrum, δ, ppm: 11.71 (1H, br. s, NH); 10.10 (1H, br. s, NH); 2,26 (2H, s, CH_2); 2.20 (3H, s, CH_3); 1.19 (6H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 180 [M+H], 178 [M-H]. Found, %: C 60.04; H 7.33; N 23.31. $C_9H_{13}N_3O$. Calculated, %: C 60.34; H 7.26; N 23.46.

B. DMF (1 ml) was used in place of methanol. The reaction mixture was boiled for 5-7 min, then cooled, 2-propanol (10 ml) was added, and compound **6a** (0.12 g, 34%) was filtered off, and was purified by recrystallization from 2-propanol. A mixing test with a sample obtained by method A gave no depression of melting point.

4-Ethyl-3,4-dimethyl-4,5,6,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one (6b) was obtained analogously to compound **6a** from ethyl methyl ketone **5b**. Yield was 46% (method A), 43% (method B); mp 226-228°C (from 2-propanol). IR spectrum, ν, cm^{-1}: 3200-2850, 1652, 1612, 1524. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.64 (1H, br. s, NH); 10.05 (1H, br. s, NH); 2.22 (2H, s, CH_2); 2.15 (3H, s, CH_3); 1.45 (2H, m, CH_2); 1.15 (3H, s, CH_3); 0.72 (3H, t, *J* = 8.0, CH_3). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 193 (42), 164 (100), 146 (32), 136 (23). Found, %: C 61.90; H 7.53; N 21.83. $C_{10}H_{15}N_3O$. Calculated, %: C 62.18; H 7.77; N 21.76.

3-Methyl-4,5,6,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-one-4-spirocyclohexane (6c) was obtained analogously to compound **6a** from cyclohexanone (**5c**). Yield was 52% (method A), 50% (method B); mp 272-275°C (from 2-propanol). IR spectrum, ν, cm^{-1}: 3400-2900, 1656, 1612, 1508. ^{1}H NMR spectrum, δ, ppm: 11.64 (1H, br. s, NH); 10.67 (1H, br. s, NH); 2.43 (2H, s, CH_2); 2.20 (3H, s, CH_3); 1.62-1.36 (10H, m, CH_2); Mass spectrum, *m/z* (I_{rel}, %): 219 (93), 176 (100), 164 (86), 150 (40), 134 (56). Found, %: C 66.02; H 7.63; N 19.21. $C_{12}H_{17}N_3O$. Calculated, %: C 65.75; H 7.76; N 19.18.

5,5-Dimethyl-2-methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one (12a). A mixture of amine **2** (0.2 g, 1.5 mmol), Meldrum's acid (0.22 g, 1.5 mmol), and acetone (**5a**) (0.13 ml, 1.5 mmol) in ethyl acetate (5 ml) was boiled for 2 h in the presence of a catalytic amount of pyridine. The reaction mixture was cooled, compound **12a** (0.17 g, 54%) was filtered off, and was recrystallized from acetone, mp 222-224°C. IR spectrum, ν, cm^{-1}: 3180-2892, 1752, 1636. ^{1}H NMR spectrum, δ, ppm: 8.50 (1H, br. s, NH); 2.75 (2H, s, CH_2); 2.46 (3H, s, CH_3S); 1.26 (6H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 212 (100), 197 (21), 170 (87), 83 (83), 42 (30). Found, %: C 45.40; H 5.74; N 26.37; S 14.89. $C_8H_{12}N_4OS$. Calculated, %: C 45.28; H 5.66; N 26.42; S 15.09.

2-Methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one-5-spirocyclohexane (12b) was obtained analogously to compound **12a**, using cyclohexanone in place of acetone. Yield was 48%; mp 228-231°C (from 2-propanol). IR spectrum, ν, cm^{-1}: 3252-2812, 1756, 1640. ^{1}H NMR spectrum, δ, ppm: 8.50 (1H, br. s, NH);

2.79 (2H, s, CH_2); 2.46 (3H, s, CH_3S); 1.26-1.58 (10H, m, $5CH_2$). Mass spectrum, *m/z* (I_{rel}, %): 252 (95), 209 (53), 123 (100), 85 (39), 55 (36). Found, %: C 53.00; H 6.28; N 22.32; S 12.75. $C_{11}H_{16}N_4OS$. Calculated, %: C 52.80; H 6.40; N 22.40; S 12.80.

2-Amino-5,5-dimethyl-4,5,6,7-tetrahydrotriazolo[1,5-*a*]pyrimidin-7-one (13a) and 1-Acetyl-3,5-diamino-1,2,4-triazole (14). A mixture of diamine **3** (0.2 g, 2 mmol) and Meldrum's acid **4** (0.28 g, 2 mmol) in acetone (5 ml) was boiled for 2 h in the presence of a catalytic amount of pyridine, then cooled, and compound **13a** (0.08 g, 22%) was filtered off, and recrystallized from methanol, mp 248-250°C. IR spectrum, ν, cm^{-1}: 3360-2800, 1716, 1636. ^{1}H NMR spectrum, δ, ppm: 8.07 (1H, br. s, NH); 5.70 (2H, br s, NH_2); 2.60 (2H, s, CH_2); 1.21 (6H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 181 (100). 166 (26), 139 (53), 99 (73), 83 (86), 42 (52). Found, %: C 46.50; H 6.08; N 38.75. $C_7H_{11}N_5O$. Calculated, %: C 46.41; H 6.08; N 38.67.

The filtrate was evaporated to dryness, 2-propanol (3 ml) was added to the residue, and diamine **14** (0.11 g, 39%) was filtered off, mp 198-200°C. IR spectrum, ν, cm^{-1}: 3392, 3296, 3228, 3140, 1712, 1644, 1572. ^{1}H NMR spectrum, δ, ppm: 7.32 (2H, br. s, NH_2); 5.62 (2H, br. s, NH_2); 2.32 (3H, s, CH_3) [7].

2-Amino-4,5,6,7-tetrahydrotriazolo[1,5-*a*]pyrimidin-7-one-5-spirocyclohexane (**13b**) was obtained analogously to compound **13a** using cyclohexanone **5c** in place of acetone. The product **13b** was purified from amide **14** by recrystallization from a DMF–2-propanol (1 : 2) mixture. Yield was 23%; mp 258-259°C. IR spectrum, ν, cm^{-1}: 3352-2848, 1720, 1628. ^{1}H NMR spectrum, δ, ppm: 8.17 (1H, br. s, NH); 5.72 (2H, br. s, NH_2); 2.66 (2H, s, CH_2); 1.54-1.22 (10H, s, CH_2). Mass spectrum, *m/z*, (I_{rel}, %): 221 (100), 178 (34), 123 (81), 99 (26), 83 (34). Found, %: C 54.51; H 7.00; N 31.58. $C_{10}H_{15}N_5O$. Calculated, %: C 54.30; H 6.79; N 31.67.

X-ray Structural Investigation of Compound 12a. Crystals of compound **12a** were triclinic, $C_8H_{12}N_4OS$, at 20°C a = 8.371(2), b = 9.810(2), c = 13.520(4) Å, α = 70.41(2), β = 82.51(2), γ = 81.93(2)°, V = 1031.4(5) $Å^3$, M_r = 212.28, Z = 4, space group $P1$, d_{calc} = 1.367 g/cm^3, μ(MoKα) = 0.288 mm^{-1}, F(000) = 448. The parameters of the unit cell and the intensities of 3901 reflections (3632 independent, R_{int} = 0.035) were measured on a Siemens P3/PC automatic four-circle diffractometer (MoKα, graphite monochromator, 2θ/θ scanning, $2\theta_{max}$ = 50°).

The structure was solved by the direct method with the SHELXTL set of programs [11]. The positions of the hydrogen atoms were made apparent from an electron density difference synthesis and were refined by the rider model with nonfixed U_{iso}. The structure was refined on F^2 by the full matrix least squares method in an anisotropic approximation for the nonhydrogen atoms to wR_2 = 0.073 for 3632 reflections [R_1 = 0.042 for 2650 reflections with $F > 4\sigma(F)$, S = 1.18].

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