2-Acetylimino-5-benzylideneselenazolidinone-4 (I). To a mixture of 0.01 mole of 2-acetyliminoselenazolidinone-4 and 0.01 mole of benzaldehyde in 5 ml of acetic acid was added 3 drops of a 25% aqueous solution of methylamine and this was then heated on an oil bath at 130-140° for 4-5 min. The crystals which separated on cooling were filtered off and washed with ether, and recrystallized from glacial acetic acid. Data for these compounds are given in Table 1. Melting points did not differ from those of known compounds, obtained by other methods [2, 7].

Other 5-R-ylidene derivatives of 2-acetyliminoselenazolidinone-4 were prepared by similar methods.

EXPERIMENTAL BIOLOGICAL SECTION

The bacteriostatic action of the compounds against *Staphylococcus aureus* 209P and *E. coli* 675 in Hottinger's broth (pH 7.2-7.4, containing 135 mg/liter of amine nitrogen) was determined. In several cases the minimum bacteriostatic concentrations effective against other types of gram-positive bacteria — *C. diphtheriae* PW8, *Diplococcus pneumoniae*, and *Bac. anthracoides* 1312 — were also determined. The mycostatic activity against *Microsporum canis* was studied using Sabouraud's medium. The standard method of serial dilution [8] was used for these determinations.

LITERATURE CITED

1. A. A. Tsurkan, Third All-Union Symposium on the Chemistry and Technology of Heterocyclic Compounds for Fossil Fuels, Donets (1978), p. 114.
2. O. O. Tsurkan and V. V. Groshev, Farm. Zh., No. 1, 82-84 (1978).
3. D. Cram, Fundamentals of Carbanion Chemistry, Academic Press (1965).
4. W. J. Crowell, Lo-Chien-Pen, and E. Y. Shropshire, J. Am. Chem. Soc., 75, 5419 (1953).
5. M. Girard, Ann. Chim., 16, 326-344 (1941)
6. L. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], Moscow (1963).
7. A. M. Comrie, D. Dingwall, and J. B. Stenlake, J. Chem. Soc., 5713-5717 (1963).
8. G. N. Pershin (editor), Methods of Experimental Chemotherapy [in Russian], 2nd edn., Moscow (1971).

SYNTHESIS AND ANTITUMOR ACTIVITY OF SOME 5,7-SUBSTITUTED s-TRIAZOLO[1,5-a]-PYRIMIDINES

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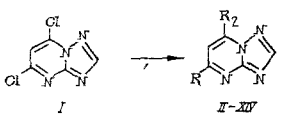
UDC 615.277.3:547.853

Derivatives of s-triazolo[1,5-a]pyrimidine (I-XIV) can be regarded as "isopurines." A number of purine isomers (pyrazolopyrimidines, pyrazolopyridines) are known to be effective antitumor agents [1], and some 6- and 7-halogen substituted s-triazolo[1,5-a]pyrimidines are also reported to display antitumor activity [2, 3]. Hence it was of interest to continue the search for antitumor agents among the s-triazolo[1,5-a]pyrimidine derivatives (I-XIV).

We synthesized the 5,7-disubstituted s-triazolo[1,5-a]pyrimidines (I-XIV), which have a halogen, and also a hydrazino, amino, benzylamino, morpholino, or mercapto group in the molecule, and studied the antitumor properties of these compounds. The starting material for the preparation of II-XIV was 5,7-dichloro-s-triazolo[1,5-a]pyrimidine (I), and this was prepared by the method given in [4]:



I *II-XIV*

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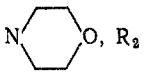
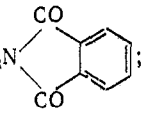
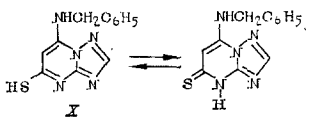
II: $R_1 = Cl$, $R_2 = NHNH_2$; III: $R_1 = R_2 = NHNH_2$; IV: $R_1 = Cl$, $R_2 = NHNCH(CHOH)_4CH_2OH$; V: $R_1 = R_2 = NHNCH(CHOH)_4CH_2OH$; VI: $R_1 = NHNH_2$, $R_2 = NHCH_2C_6H_5$; VII: $R_1 = Cl$, $R_2 = NHCH_2C_6H_5$; VIII: $R_1 = NH_2$, $R_2 = NHCH_2C_6H_5$; IX: $R_1 =$  , $R_2 = NHCH_2C_6H_5$; X: $R_1 = SH$, $R_2 = NHCH_2C_6H_4$; XI: $R_1 = R_2 =$  ; XII: $R_1 = R_2 = SCH_2CH_2NH_2 \cdot HBr$; XIII: $R_1 = R_2 = SH$; XIV: $R_1 = Cl$; $R_2 = N_3$.

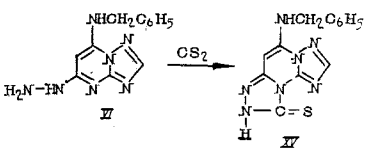
The chlorine atom at C-7 of s-triazolo[1,5-a]pyrimidine is more reactive to nucleophilic substitution than the chlorine at C-5 [14]. The substitution of $Cl_{(7)}$ by a hydrazine group (II) proceeds vigorously with the evolution of much heat, but the reaction goes more quickly in solution, for example, in water. Replacement of the chlorine at C-5 was accomplished by heating for 3-5 h (III, VI, and IX). The 2-amino-7-benzylamino derivative VIII was prepared by heating the chloro derivative VII with ammonia in a sealed tube at 160°. The 5-mercapto derivative X was prepared by heating equimolar quantities of VII and thiourea in DMF. In the crystalline state, X exists in the tautomeric thioamide form, as shown by the absence of bands characteristic of the mercapto group at 2650-2550 cm^{-1}.



X

5,7-Di(aminoethylthio)-s-triazolopyrimidine (XII) was obtained from the potassium salt of the 5,7-dimercapto derivative of XIII [4] and β-bromoethylphthalimide, with subsequent hydrolysis of the diphthalimide derivative of XI in acid solution.

Diazotization of the 5-chloro-7-hydrazino derivative II gave the azide XIV, confirmed by the presence of strong absorption bands at 2157-2130 cm^{-1} in the IR spectrum of the compound. When the 5-hydrazino-7-benzylamino derivative VI was heated with carbon disulfide in the presence of triethylamine, the hydrazine group was cyclized to the triazolthione XV:



VI XV

The NMR spectrum of XV in DMSO has a signal at 14 ppm, from the thioamide NH proton, which disappears on addition of deuterated alcohol CD_3OD. The IR spectrum of crystals of this compound shows no absorption corresponding the mercapto group. Between 3400 and 3100 cm^{-1} are two bands: at 3368 cm^{-1} (benzyl group) and a broad band at 3140-3120 cm^{-1} (thioamide group).

The 5-chloro-s-triazolo[1,5-a]pyrimidines II, IV, and VIII, which have a basic group in the 7 position, have two UV absorption maxima at 220 and 295 nm. For compounds III-IX, which have two basic groups at positions 5 and 7, the absorption maxima are at 230 and 265-270 nm, in agreement with literature values [4, 5].

The 5,7-disubstituted s-triazolo[1,5-a]pyrimidines are colorless or pale yellow crystalline substances, insoluble in water, and soluble in ethanol and DMF. Analytical and physical data for these compounds are given in Table 1.

EXPERIMENTAL

NMR spectra were taken on a Perkin-Elmer R-12B instrument (England) using trifluoracetic acid or DMSO as solvent, internal standard hexamethyldisiloxane. Infrared spectra were taken on a UR-20 spectrophotometer (GDR) in perfluorohydrocarbons. Ultraviolet spectra were taken on a Specord instrument (GDR) ($1 \cdot 10^{-3}$ moles/liter in ethanol). Chromatography was carried out on Silufol UV-254 plates in chloroform–ethanol (17:3); R_{f_1}, ethanol–concentrated ammonia (100:1); R_{f_2}, chloroform–ethanol–concentrated ammonia (60:20:1); R_{f_3}.

TABLE 1. Physicochemical Characteristics of the 5,7-Substituted s-Triazolo[1,5-a]pyrimidines

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			λ_{max}, nm, ($\varepsilon \cdot 10^4$)
			C	H	N		C	H	N	
II	95	360	32,5	2,9	45,4	$C_5H_5N_6Cl$	32,5	2,7	45,5	220 (2,7) 294 (1,2)
III	65	240—1	33,6	4,5	61,9	$C_5H_8N_8$	33,3	4,4	62,5	228 (3,5) 280 (1,5)
IIIa	95	222—4	23,8	3,9	44,7	$C_5H_{10}N_8Cl_2$*	23,7	3,9	44,3	226 (3,0) 275 (1,2)
IV	64	168—70	38,2	4,7	24,1	$C_{11}H_{15}N_6O_5Cl$	38,1	4,3	24,2	222 (268) 292 (1,3)
V	80	174—6	40,3	4,9	22,4	$C_{17}H_{28}N_8O_{10}$	40,3	5,2	22,1	230 (2,9) 276 sh. 350 (0,8)
VI	98	185—6	56,3	5,1	38,4	$C_{12}H_{13}N_7$	56,4	5,1	38,4	236 (4,3) 265 (2,9)
VIa	98	225—7	49,8	5,0	33,5	$C_{12}H_{14}N_7Cl$ †	49,4	4,8	33,6	230 (3,4) 276 (1,4)
VIII	45	207—9	59,7	5,0	34,9	$C_{12}H_{12}N_6$	59,9	5,0	34,9	232 (4,9) 265 (1,3)
IX	85	208—9	61,5	5,8	27,9	$C_{16}H_{18}N_6O$	61,9	5,8	27,1	244 (5,3) 270 (1,7)
X	70	257—8	56,0	4,4	27,2	$C_{12}H_{11}N_5S$	56,0	4,3	27,2	232 (4,9) 265 (1,3)
XI	50	280	56,8	3,3	16,1	$C_{25}H_{18}N_6S_2O_4$ ‡	56,6	3,4	15,8	not det.
XII	55	228—9	25,4	3,9	19,3	$C_9H_{16}N_6S_2Br_2$ ‡	25,0	3,7	19,4	250 (2,6) 303 (1,9)
XIV	20	148—50	31,1	1,5	18,0	$C_5H_2N_7Cl$	30,7	1,0	18,1	222 (2,1) 300 (1,1)

*Found, %: Cl 27.7. Calculated, %: Cl 28.0.
†Found, %: Cl 12.2. Calculated, %: Cl 12.2.
‡Found, %: S 14.0. Calculated, %: S 14.8.

5,7-Dichloro-s-triazolo[1,5-a]pyrimidine (I). This was prepared by the method described in [4]; mp 127-129°C, literature value 131-132°C.

5-Chloro-7-hydrazino-s-triazolo[1,5-a]pyrimidine (II). A mixture of 3 g of the 5,7-dichloro derivative of I and 3 ml of water was cooled and 4.5 ml of hydrazine hydrate added dropwise. After 3 h at room temperature, the precipitate was filtered off and washed with water to give a product with R_f 0.74. NMR spectrum, ppm: $\delta_{H(2)}$ 8.7; $\delta_{H(6)}$ 6.78.

5,7-Dihydrazino-s-triazolo[1,5-a]pyrimidine (III). Compound I (0.95g) was cooled, mixed with 3 ml of hydrazine hydrate, and heated on the water bath for 3 h. This was then diluted with water and the precipitated material filtered off and recrystallized from water. The product has an R_{f_2} of 0.7.

Dihydrochloride of III (IIIa). A solution of 0.5 g of III in 10 ml of 3N hydrochloric acid was evaporated to dryness on the water bath and the residue recrystallized from a mixture of 2 N hydrochloric acid and ethanol (1:2). The product had an R_{f_2} of 0.7. The dihydrochloride VIa was prepared in the same way.

Glucose-s-triazolo[1,5-a] pyrimidine-5-chloro-7-hydrazone (IV). A mixture of 0.5 g of the 5-chloro-7-hydrazine derivative II and 0.49 g of glucose in 10 ml of dilute acetic acid (1:1) was heated on the water bath for 30 min, the solvent evaporated in vacuum, and the residue treated with ether. The product was recrystallized from absolute ethanol.

Glucose-s-triazolo[1,5-a]pyrimidine-5,7-hydrazone (V). This was prepared in the same way as IV from 0.5 g of III and 1 g of glucose. It was purified by precipitation from DMF with absolute alcohol.

5-Hydrazino-7-benzylamino-s-triazolo[1,5-a]pyrimidine (VI). This was prepared in the same way as III from 0.5 g of the 5-chloro-7-benzylamino derivative of VII and 2 ml of hydrazine hydrate. After recrystallization from ethanol the product had an R_f of 0.67. NMR spectrum, ppm: δ_{CH_2} 4.8; 4.9; $\delta_{H(2)}$ 8.68; $\delta_{H(6)}$ 6.36.

5-Chloro-7-benzylamino-s-triazolo[1,5-a]pyrimidine (VII). This was obtained as described in [6], mp 176-179°C, literature value, mp 178°C. NMR spectrum, ppm: δ_{CH_2} 4.55; 4.45; $\delta_{(H_2)}$ 8.58; $\delta_{H(6)}$ 6.6.

5-Amino-7-benzylamino-s-triazolo [1,5-a]pyrimidine (VIII). A mixture of 1.0 g of VII, 10 ml of concentrated ammonia, and 10 ml of ethanol was heated in a sealed tube for 8 h at 160°C. The reaction mixture was evaporated to dryness, and the residue was precipitated from ethanol with water and recrystallized from aqueous ethanol. R_{f_1} of product 0.75. NMR spectrum, ppm: $\delta_{H(2)}$ 8.58; $\delta_{H(6)}$ 6.75.

5-Morpholino-7-benzylamino-s-triazolo[1,5-a]pyrimidine (IX). This was obtained from 5.0 g VII and 2.2 g of morpholine in 50 ml of butanol. The mixture was refluxed for 5 h and the precipitate obtained on cooling recrystallized from aqueous ethanol.

5-Mercapto-7-benzylamino-s-triazolo[1,5-a]pyrimidine (X). A mixture of 1.3 g of VII and 0.46 g of thiourea in 20 ml of DMF was refluxed for 4 h. The product was precipitated from the cooled solution by the addition of water and recrystallized from DMF.

5,7-Diphthalimidoethylthio-s-triazolo[1,5-a]pyrimidine (XI). Solutions of 5.3 g of β-bromoethylphthalimide in 25 ml of ethanol and 3.1 g of the potassium salt of the dimercapto derivative XIII in 10 ml of water were mixed and refluxed for 3 h. The yellow precipitated material was recrystallized from DMSO.

5,7-Bis-(β-aminoethylthio)-s-triazolo[1,5-a]pyrimidine Dihydrobromide (XII). This was obtained from 2.65 g of XI by refluxing on a water bath in a mixture of 10 ml of glacial acetic acid and 10 ml of concentrated hydrobromic acid for 40 h. The solution was filtered hot and evaporated in vacuum to small volume. The material which precipitated on cooling was filtered and washed on the filter with hot absolute ethanol. The product was hygroscopic.

5,7-Dimercapto-s-triazolo[1,5-a]pyrimidine (XIII). This was obtained by the method given in [4]: mp 320°C, literature value, mp 320°C. Found, %: C 32.23; H 2.37; N 30.63. $C_5H_4N_4S_2$. Calculated, %: C 32.6; H 2.2; N 30.4.

5-Chloro-7-azido-s-triazolo[1,5-a]pyrimidine (XIV). A suspension of 0.93 g of II in 4 ml of water was mixed with 5 ml of concentrated hydrochloric acid, cooled to 0-3°C, and a concentrated aqueous solution containing 0.35 g of sodium nitrite added. This was kept in an ice-bath for 30 min and the solution extracted with chloroform. The extract was evaporated under low vacuum, and the residue dried over calcium chloride. IR spectrum, ν, cm^{-1}: 2157-2130 cm^{-1}.

Cyclization of 5-Hydrazino-7-benzylamino-s-triazolo[1,5-a]pyrimidine with Carbon Disulfide. A mixture of 0.5 g of VI, 10 ml of ethanol, and 1.3 g of carbon disulfide containing 1-2 drops of triethylamine was heated on the water bath for 5 h. The cyclization product XV which separated was twice precipitated from DMF with water, giving 0.4 g (67%) of product mp 260°C, R_{f_3} 0.8. Yield 0.4 g (67%), mp 260°C. Found, %: C 52.1; H 3.8; N 32.6; S 11.3. $C_{13}H_{11}N_7S$. Calculated, %: C 52.5; H 3.7; N 32.9; S 10.8. NMR spectrum, ppm: 4.47-4.58; 5.7; 7.2-7.6; 8.5; 14.0. IR spectrum, ν, cm^{-1}: 3140-3120; 3368.

EXPERIMENTAL BIOLOGICAL SECTION

The 5,7-substituted s-triazolo[1,5-a]pyrimidines were tested on transplanted tumors in nonpedigree mice and $C_{52}Bl_6$ × Braun hybrid mice. The experiments used: mammary gland adenocarcinoma (AK-755), Lewis light tumor, sarcoma 37, and sarcoma 180. The compounds were administered intraperitoneally 48 h after transplantation 5 times in 24 h. Seven days after the last injection, the animals were killed, the tumors weighed, and the percentage inhibition of tumor growth (T, %) calculated from the formula:

$$T, \% = \frac{P_k - P_0}{P_k} \times 100\ \%,$$

where P_k is the mean weight of the tumors in the control and P_0 is the mean weight in the test.

Initial results of the study of antitumor activity did not show any very effective compounds among the 5,7-substituted s-triazolo[1,5-a]pyrimidines. Compound VI showed some inhibition of tumor growth (40-50%) on AK-755, IX on sarcoma 37, and XI on Lewis light tumor. The 5,7-dimercapto and 5,7-dichloro derivatives, and also compound II, which has a chlorine in the 5 position, did not show any antitumor activity.

LITERATURE CITED

1. N. N. Blokhina (editor), Chemotherapy of Malignant Tumors [in Russian], Moscow (1977), pp. 61-119.
2. Ya. Makisumi, H. Kano, and Sh. Takahashi, Japanese Patent No. 5271 (1959); Chem. Abstr., 54, No. 142828 (1960).
3. Ya. Makisumi and H. Kano, Japanese Patent No. 9498 (1962); Chem. Abstr., 59, No. 51781 (1963).
4. Ya. Makisumi, Chem. Pharm. Bull., 9, 801-808 (1961); Chem. Abstr., 57, No. 16606B (1962).
5. M. A. Hill, G. A. Reynolds, J. E. Tinker, et al., J. Org. Chem., 26, 3834 (1961).
6. E. Tenor and H. Füller, German Patent No. 61269 (1968).

SYNTHESIS AND BIOLOGICAL ACTIVITY OF ALKYLAMIDES OF 2-ARYLAMINO-6-METHYLNICOTINIC ACIDS

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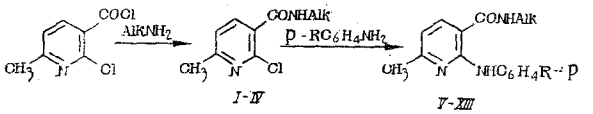
UDC 615.213:547.826.1

In continuation of our investigations into the synthesis of antispasmodic derivatives of the amides of substituted nicotinic acids [1], and to study the effect of the length of the alkyl chain attached to the amide moiety of the molecule, and of the nature and position of the radical in the benzene ring attached to the amino group, we have obtained the previously unknown alkylamides of the 2-arylamino-6-methylnicotinic acids (V-XIII).



The synthesis of the starting 2-chloro-6-methylnicotinic acid alkylamides (I-IV) was accomplished by reaction of the acid chloride [2] with the alkylamines in solution in anhydrous ether in the presence of triethylamine. The alkylamides I-IV were reacted with the arylamines by boiling in 50% acetic acid, yields of 40-61% of the 2-arylamino-6-methylnicotinic acid alkylamides being obtained (V-XIII; Table 1) as colorless crystalline substances, insoluble in water, but soluble in alcohol, ether, and acetone. Compounds V-XII possess basic properties, and give water-soluble hydrochlorides.

The compositions and structures of V-XIII were confirmed by the elemental analyses and IR spectra, which displayed bands for ν_{CO} at 1655 cm^{-1}, and ν_{NH} at 3475 cm^{-1}.

EXPERIMENTAL PHARMACOLOGICAL SECTION

Pharmacological investigations of compounds V-XIII were carried out using 700 mice of both sexes weighing 18-22 g. The compounds were administered intraperitoneally in a 2% starch mucilage. Experimental data were treated statistically by the Litchfield and Wilkinson method for P = 0.05 [3].

The acute toxicity [4], antispasmodic activity (ASA) by the maximum electroshock test (MET) [5] and the corazole test, and the antitremor activity by the nicotine and arecoline tests were studied. Inhibitory and excitatory effects were assessed visually. The specific breadth of pharmacological activity (the ratio LD_{50}/ED_{50}) was calculated.

Antimicrobial activity was measured by the serial dilution method towards *Staphylococcus aureus* and *E. coli*. The effective dose was taken as the least concentration which retarded the growth of bacterial cultures [4]. The results of the investigations are shown in Table 2.

The most active compound in the MET was VII, the difference in the ED_{50} for this compound and the known antispasmodic drug chloracon being statistically insignificant. The ac-

Perm Pharmaceutical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 4, pp. 35-38, April, 1981. Original article submitted June 4, 1980.