SEQUENCE OF THE CONVERSION OF PYRIMIDO [5,4-e]-1,2,4-TRIAZINEDIONES TO IMIDAZO[4,5-e]-1,2,4-TRIAZINONES

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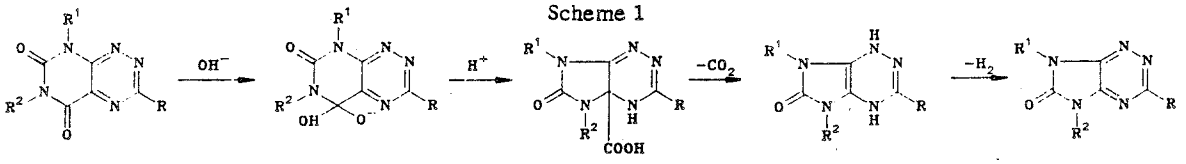
The conversion of pyrimido[5,4-e]-1,2,4-triazinediones to imidazo[4,5-e]-1,2,4-triazinones is a multistage process including the hydrolysis of the $C_{(5)}$-$N_{(6)}$ amide bond, the closure of the ureido group to the imidazolidinone ring, decarboxylation, acid oxidation.

The pyrimido[5,4-e]-1,2,4-triazinediones (7-azalumazines), to which are related the antineoplastic antibiotics reumicin (Ia), fervenulin (Ib), and xanthothricin (VIII), are the objects of detailed chemical study [1, 2]. The heterocycles of this series, possessing a π-deficiency, are very sensitive to the action of nucleophilic agents [3-8]. Thus, the treatment of the 3-aryl-substituted (Ia, b) and (VIII) [4-6] and their $N_{(4)}$-oxides [7, 8] with aqueous-alcoholic alkalis leads to the formation of imidazo[4,5-e]-1,2,4-triazinones. The authors explained the observed conversion by the mechanism of the type of benzilic rearrangement [4-7], presented in the Schee 1, without additional experimental confirmation. The detailed study of this reaction by the method of PMR spectroscopy under controlled conditions (temperature, pH value) shows that the mechanism of the conversions (Scheme), proposed by the authors [4-6], is unfounded.

Thus, we previously showed [9-11] that the treatment of the pyrimidotriazinedione (Ia) with aqueous alkali leads to the formation of the stable compound (IIIa) (Scheme 2) — the product of the hydrolysis of (Ia) at the $C_{(5)}$-$N_{(6)}$ bond; this wave not proposed in the framework of the suggested reaction mechanism (Scheme 1). At the same time, the formation of the product with the ring-opening of uracil [10, 16] at the first stage of the process does not contradict the literature data on uracilimidazolidinone conversions [12-15].

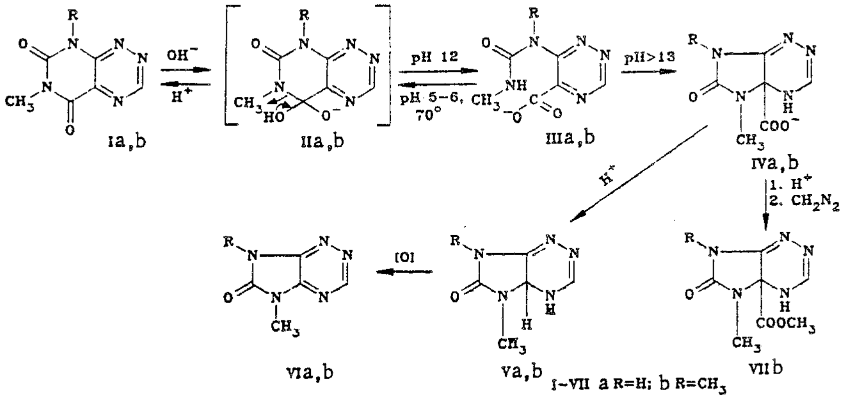
Scheme 1



R=Ar, R^1=Alk, R^2=Alk

The multistage character of the process of the conversion of pyrimido [5,4-e]-1,2,4-triazinediones to imidazo [4,5-e]-1,2,4-triazinones, including the formation of a series of stable intermediate compounds, was demonstrated experimentally in the present work. The reaction sequence and the structure of the intermediate compounds are presented in the Scheme 2.

Scheme 2



I-VII a R=H; b R=CH_3

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TABLE 1. Characteristics of the Compounds (I) and (III)-(VII)

Compound	T_{mp}, °C[a]	UV spectrum (in water), λ_{max}, nm (log ε)[b]	PMR spectrum (D_2O), ppm			m/z[c]
			3-H	$N_{(5)}CH_3$	other	
Ia	243—244	235 (4,22), 267 (sh 3,33), 338 (3,69), 400 (2,59)	9,67	3,34[d]		179, M+
Ib	175—176	238 (4,22), 275 (3,22), 345 (3,61)	9,69	3,39[d]	3,71	193, M+
IIIa	219—221	240 (3.87), 314 (3,18), 382 (sh 2,27)	9,23	2,81		198, [M+H]+
IVa	184—187	211 (sh,3,83), 272 (3,24)	7,51	2,81		198, [M+H]+
IVб	125—130	213 (sh,3,98), 277 (3,37)	7,55	2,83	2,94[e]	212, [M+H]+
Va	193—195	224 (3,69), 272 (3,19)	7,46[f]	2,94	4,58[g]	154, [M+H]+
Vб	133—137	222 (3,89), 271 (3,38)	7,42[h]	2,92	4,52[i] 2,96[e]	168, [M+H]+
VIa	231,5—233	229 (sh,3,57), 283 (3,84)	8,87	3,33		151, M+
VIб	146,5—147,5	214 (sh,3,81), 283 (4,06)	8,88	3,36	3,42[e]	165, M+
VII	182—183	212 (4,00), 276 (3,46)	7,62	2,89	2,97[e], 3,67[j]	226, [M+H]+

Tyltin,

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[a] Compounds (Ia, b) and (IIIa) were crystallized from ethanol; the remaining compounds were crystallized from water.
[b] Compounds (Ia, b) were in ethanol; sh indicates shoulder.
[c] Compounds (Ia, b) and (VIa, b) were analyzed by mass spectrometry with FAB. [d] $N_{(6)}CH_3$ [e] $N_{(7)}CH_3$. [f] d, $J_{3,4a}$ = 2.1 Hz. [g] d, $J_{4a,3}$ = 2.1 Hz, 4a-H. [h] d, $J_{3,4a}$ = 1.6 Hz. [i] d, $J_{4a,3}$ = 1.6 Hz, 4a-H. [j] $COOCH_3$.

The nucleophilic attack of the hydroxyl ion at the $C_{(5)}$ carbon atom with the formation of the unstable hypothetical intermediate (IIa) precedes the opening of the uracil ring of compound (Ia) when it is acted on by an aqueous solution of alkali. The breaking of the $C_{(5)}$-$N_{(6)}$ amide bond leads to the formation of the salt of 6-(3-methylureido)-1,2,4-triazine-5-carboxylic acid (IIIa) [16]. The conversion of the pyrimidotriazinedione (Ia) to the salt (IIIa), which was evaluated from the integral intensities of the PMR signals, comprises 40-50% at the pH 12 after 5-6 h at 20°C. The structure of the carboxylic acid (IIIa) isolated from the reaction mixture was determined on the basis of the data of mass spectrometry and the ^1H and ^{13}C NMR spectra. The molecular mass of the acid (IIIa), which equals 197 amu and corresponds to the formula $C_6H_7N_5O_3$, was determined by the method of fast atom bombardment (FAB) [17]; it had the m/z 1988 for $[M + H]^+$. It should be noted that the peak of the molecular ion is not successfully registered when the molecules of the carboxylic acid (IIIa) are ionized by electron impact. The chemical transformation of the uracil ring and the preservation of the triazine ring [9] during the conversion of reumicin (Ia) to the acid (IIIa) is indicated by the PMR spectral data of these compounds (Table 1). Thus, two singlet signals of the N-methyl and methine protons are registered in the spectrum of the solution of compound (IIIa) in D_2O. The first signal is thereby shifted by 0.53 ppm to high field by comparison with the corresponding signal of the initial (Ia), whereas the osition of the 3-H methine proton changes insignificantly. The presence of the 3-methylureido fragment in the molecule of the carboxylic acid (IIIa) is confirmed by the doublet structure of the signal of the methylamine protons in the PMR spectrum in DMSO-D_6, on account of the spin-spin coupling (SSC) with the vicinal proton at the nitrogen atom (J = 4.5 Hz). The signal of the carbon of the carboxyl group with the characteristic CS value of 168.6 ppm is registered in ^{13}C NMR spectrum of the acid (IIIa) (Table 2). The signals of the carbonyl carbon atoms of the amide groups in reumicin (Ia) are observed at higher field. The process of the conversion of the pyrimidotriazinedione (Ia) to the compound (IIIa) is evidently reversible under the conditions indicated. Thus, the heating of the weakly acidic (pH 5-6) aqueous solution of the carboxylic acid (IIIa) at 70°C for 3 h leads to the cyclization of this substance to the initial reumicin (Ia).

With high concentrations of alkali (pH > 13), compound (IIIa) (monitoring by the PMR spectra [16]) as well as reumicin (Ia) are converted to the salt of 4,4a-dihydro-5-methyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one-4a-carboxylic acid (IVa). As is also noted in the case of the acid (IIIa), the molecular mass of compound (IVa) (m/z 198, [M + H], corresponding to the formula $C_6H_7N_5O_3$, can be registered in the mass spectra obtained by the method of FAB. The structure of compound (IVa) was established on the basis of the data of the ^1H and ^{13}C NMR spectra and the UV spectrum. The ^{13}C NMR spectrum of the salt (IVa) (Table 2) registered six signals including the signals with the CSs of 171.9 and 76.8 ppm which are

TABLE 2. The ^{13}C NMR Spectra of the Compounds (I) and (III)-(VII)[a]

Compound	Solvent	Chemical shift, ppm (multiplicity), SSCC, Hz						
		$C_{(3)}$	$C_{(4a)}$	$C_{(6)}$	$C_{(7a)}$	COO	$N_{(5)}CH_3$	$N_{(7)}CH_3$
Ia	DMSO-D_6	155,1 (d), ^{1}J=213,3	133,5 (d), ^{3}J=8,8^{b}	150,8 (q), ^{3}J=2,9^{c}	152,9 (s)	161,8 (q), ^{3}J=2,9^{d}	29,0 (q), ^{1}J=142,7	—
Ib	DMSO-D_6	154,7 (d), ^{1}J=212,5	134,3 (d), ^{3}J=8,1^{b}	151,0 (m)	152,6 (m)	160,9 (q), ^{3}J=3,0^{d}	29,7 (q), ^{1}J=142,6	30,2 (q), ^{1}J=142,7
IIIa	D_2O/H_2O, 1 : 1	152,6 (d), ^{1}J=203,0	142,0 (m)	157,0 (q), ^{3}J=3,8^{c}	153,9 (s)	168,6 (s)	27,2 (q), ^{1}J=139,0	—
IVa	D_2O (pH 12)	146,5 (d), ^{1}J=200,4	76,8 (d,q), ^{3}J=9,7^{b}, ^{3}J=3,1^{e}	166,2 (q), ^{3}J=2,7^{c}	151,8 (s)	171,9 (s)	26,8 (q), ^{1}J=139,2	—
IVb	D_2O (pH 12)	146,8 (d), ^{1}J=201,9	74,4 (m)	159,5 (q,q) ^{3}J=^{3}J=3,2$^{c, f}$	145,0 (q,d), ^{3}J=2,7^{g}, ^{4}J=0,9^{h}	170,9 (s)	26,9 (q), ^{1}J=140,1	27,2 (q), ^{1}J=141,4
Va	DMF-D_7	146,4 (d,d), ^{1}J=198,7; ^{3}J=2,5^{i}	66,8 (d,d,q), ^{1}J=158,9; ^{3}J=10,9^{b}, ^{3}J=2,8^{e}	157,6 (d,q), ^{3}J=4,3^{j}; ^{3}J=1,8^{c}	141,4 (h), ^{2}J=3,5^{e}	—	27,5 (d,q), ^{1}J=138,2, ^{3}J=1,5^{m}	—
Vb	DMF-D_7	146,5 (d,d), ^{1}J=199,3; ^{3}J=2,5^{i}	65,6 (d,d,q), ^{1}J=160,4; ^{3}J=10,6^{b}; ^{3}J=3,0^{d}	157,2 (m)	142,0 (d,q) ^{2}J=^{3}J=2,0^{k,g}	—	28,0 (q,d), ^{1}J=138,7, ^{3}J=1,5^{m}	26,3 (q), ^{1}J=140,2
VIa	DMSO-D_6	151,2 (d), ^{1}J=206,1	144,4 (m)	153,0 (m)	145,9 (s)	—	25,2 (q), ^{1}J=141,9	—
VIb	DMSO-D_6	151,4 (d), ^{1}J=207,5	144,0 (d,q), ^{3}J=9,3^{b}, ^{3}J=3,4^{e}	152,9 (q,q); ^{3}J=^{3}J=3,4^{c,f}	145,3 (m)	—	25,61 (q), ^{1}J=142,1	26,0 (q), ^{1}J=141,6
VIIb[m]	CD_3OD	147,5	72,6	^{p} 152,8	146,1	167,3	26,3	26,8

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[a] For the compounds (Ia, b), the designations of the $C_{(6)}$, $C_{(7a)}$, COO, $N_{(5)}CH_3$, and $N_{(7)}CH_3$ correspond to $C_{(7)}$, $C_{(8a)}$, $C_{(5)}$, $N_{(6)}CH_3$, and $N_{(8)}CH_3$. [b] $^{3}JC_{(3a)}$-3H. [c] $^{3}JC_{(6)}$-$_{(5)}CH_3$. [d] $^{3}JC_{(5)}$-$N_{(6)}CH_3$. [e] $^{3}JC_{(4a)}$-$N_{(5)}CH_3$. [f] $^{3}J_{(6)}$-$N_{(7)}CH_3$. [g] $^{3}JC_{(7a)}$-$N_{(7)}CH_3$. [h] $^{4}JC_{(7a)}$-3H. [i] $^{3}JC_{(3)}$-4aH. [j] $^{3}JC_{(6)}$-4aH. [k] $^{2}JC_{(7a)}$-4aH. [ℓ] $^{3}J_{CH_3}$-4aH. [m] $\delta COOCH_3$ 53.8 ppm.

characteristic of the carbon nuclei of carboxylate group anions and carbon atoms with sp^3-hybridization [$C_{(4a)}$], connected with two electronegative nitrogen atoms. The PMR spectrum of the solution of the acid (IVa) in D_2O (Table 1) contains two singlet signals of the N-methyl and methine protons with the CSs of 2.81 and 7.51 ppm respectively. The shift of the signal of the 3-H proton of the triazine ring by more than 1 ppm to high field by comparison with the position of this signal in the spectra of reumicin (Ia) and the carboxylic acid (IIIa) indicate the loss of the aromaticity of the triazine ring on account of the nucleophilic addition of the NH of the ureide group at the $N_{(4)} = C_{(5)}$ bond of the triazine. In the UV spectrum, the transition from the structures (Ia) and (IIIa) to (IVa) is shown by the shift of the absorption maxima to the hypsochromic region (Table 1). Therefore, in contrast to the previously proposed mechanism of the conversion of pyrimido[5,4-e]-1,2,4-triazinediones to imidazo[4,5-e]-1,2,4-triazinones [4-6] (Scheme 1) which assumed only the formation of the intermediate with the tetrahedral $C_{(4)}$ carbon atom in alkaline media, the experimental data obtained in the present work indicate that the reaction is completed by the cyclization of the ureidotriazine (IIIa) to the imidazotriazinone (IVa) in the presence of alkali. The analysis of the conditions of the experiments in the works [4-8] permits the proposition that the decarboxylation and oxidation by the oxygen of the air (cf. Scheme 1) proceed during the acidification of the reaction mixtures with acetic acid and the subsequent evaporation. This proposition is fully confirmed by experimetns to study the stability of the imidazotriazinonecarboxylic acid (IVa) in different solvents. It was shown that the anionic form of compound (IVa) is stable in aqueous solutions ($pH > 7$). The acidification of the solutions of (IVa) in the presence of oxygen in the air leads to the formation of a mixture of products, the main product being 5-methyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one (VIa). When the acid (IVa) is dissolved in polar aprotic solvents such as DMF and DMSO, 4,4a-dihydro-5-methyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one (Va) and its oxidation product (VIa) are formed. Compound (Va) was obtained preparatively by the brief heating (30 min) of the solution of the acid (IVa) at 60°C in degassed DMF in vacuo. The $[M + H]^+$ ion with the m/z 154, corresponding to the molecular mass of the substance (Va) (153 amu) of the composition $C_5H_7N_5O_1$, registers in the mass spectrum of the compound (Va) obtained by the FAB method. According to the data of the PMR (Table 1, Experimental) and ^{13}C NMR (Table 2) spectra, this compound is 4,4a-dihydroimidazotriazinone (Va). Three sharp signals with CSs of 7.50 ppm (1H, d, J = 2.2 Hz), 4.53 ppm (1H, d, J = 2.2 Hz), and 3.00 ppm (3H, s), which pertain to the protons of the $C_{(3)}H$ and $C_{(4a)}H$ methine groups and the $N_{(5)}CH_3$ N-methyl groups, are registered in the PMR spectrum of the solution of compound (Va) in DMF-D_7. The structure of compound (Va) is confirmed by the ^{13}C NMR spectra recorded in the regimes of complete suppression and without the suppression of the SSC of the protons, as well as by the correlation of the ^3C NMR spectrum with the PMR spectrum performed on the basis of experiments on the selective uncoupling of the SSCs of the protons of individual groups. Thus, the doublet-doublet-quartet signal of the $C_{(4a)}$ atom ($^1J = 158.9$ Hz, $^3J_{C(4a),3H} = 10.9$ Hz, $^3J_{C(4a),N(5)CH_3} = 2.8$ Hz) with the CS of 66.8 ppm is converted to a narrow multiplet with the residual distant SSCCs ($^3J_{res}$) with the double resonance for the 4a-H proton at 4.53 ppm. The selective uncoupling of the SSC of the $C_{(3)}$ carbon atom with the 3-H proton at 7.50 ppm leads to the conversion fo the doublet-doublet signal of this carbon atom ($^1J = 198.7$ Hz, $^3J_{C(3),4aH} = 2.5$ Hz) with the CS 146.4 ppm to the doublet with the residual constant of the distant SSC ($^3J_{res}$).

The oxidation of compound (Va), as well as the decarboxylation with the subsequent oxidation of the carboxylic acid (IVa) with a 1.5% aqueous solution of $KMnO_4$, leads to the aromatization (VIa) — an analog of the previously described [4-7] 3-aryl-substituted imidazotriazinones (6-azapurines). The physicochemical characteristics of compound (VIa) are presented in Tables 1 and 2.

The analogous sequence of reactions, leading to the contraction of the uracil ring, is also observed in the case of the $N_{(8)}$-methyl derivative of reumicin —fervenulin (Ib), but at lower concentrations of the alkali, pH ~ 9 [9]. It is characteristic that the formation of the intermediate compound — the ureidotriazine-5-carboxylic acid (IIIb) — cannot be detected by the method of PMR spectroscopy in the conditions under which the reaction is usually performed. This is associated with the high lability of the intermediate (IIIb) in alkaline media at temperatures of 20-30°C. When the temperature decreases to −50°C (aqueous methanol solution), the weak signal of the 3-H proton of the intermediate compound (IIIb) can be registered in the PMR spectra; it has the CS 9.37 ppm, and is shifted to high field by comparison with the signal of the analogous methine proton in the initial fervenulin (Ib) at 9.79 ppm. It is not possible to perform the reliable identification of the signals of the protons of the N—methyl groups in compound (IIIb) in these spectra, since this region is superimposed by the strong signal of the residual protons of the solvent deuteromethanol. The higher stability of compound (IIIa), in contrast to the intermediate (IIIb), in the alkaline medium is explained by the delocalization of the negative charge of the $N_{(8)}$ nitrogen atom of the anion (IIIa) along the triazine ring; this decreases the electrophilicity of the $C_{(4a)}$ carbon atom and the probability of the nucleophilic attack there by the nitrogen atom of the ureide group. In consequence of this, the tendency of this part of the anion of (IIIa) to cyclize to the imidazolidinone ring also decreases. The structure of the carboxylic acid (IVb) was established from the data of mass spectrometry with FAB, ^{13}C and ^{1}H NMR, and UV spectroscopy (Tables 1, 2) by analogy with the compound (IVa). The presence of the carboxyl function in compound (IVb) was confirmed chemically; this was done by the isolation of the methyl imidazotriazinone-4a-carboxylate (VIIb) after the methylation of the acid (IVb) by an ether-methanol solution of diazomethane. It should be noted that the $N_{(4)}H$ group is not methylated under the given conditions. The molecular mass of the methyl ester (VIIb), 225 amu, was obtained from the mass spectrum taken with the FAB method (m/z 226, $[M + H]^+$, and corresponds to the formula $C_8H_{11}N_5O_3$. The structure of this substance was confirmed by the data of the PMR (Table 1) and ^{13}C NMR spectra with the complete suppression of the SSCs of the protons (Table 2). The PMR spectrum of the solution of the methyl ester (VIIb) in deuterochloroform (cf. Experimental) contains a singlet signal of the methoxycarbonyl protons with the CS 3.74 ppm, two singlets of the N-methyl protons at 3.08 and 3.05 ppm, two singlets of the N-methyl protons at 3.08 and 3.05 ppm, the doublet of the 3-H methine proton at 7.58 ppm (J = 2.3 Hz), and the broad signal of the 4-H proton, connected with the nitrogen atom, at 8.11 ppm. The presence of the available proton at the $N_{(4)}$ nitrogen atom was confirmed by the deuterium exchange or registering the PMR spectra of the methyl ester (VIIb) in D_2O and deuteromethanol. The signal fo the 3-H proton appears in the form of a singlet under these conditions.

The dihydroimidazotriazinone (Vb) is formed by the decarboxylation of the carboxylic acid (IVb) in the solution of degassed DMF analogously to the triazinone (Va). The structure of (Vb) is confirmed by the physicochemical data in the comparison with the analogous characteristics of the compound (Va) (Tables 1, 2). Together with the singlet signals of the N-methyl protons in the PMR spectrum of the solution of (Vb) in $CDCl_3$ (cf. Experimental), the following three groups of signals are observed: the broad signal of the proton connected to $N_{(4)}$ (7.83 ppm), the triplet of the 3-H proton (7.40 ppm, $^4J_{3,4a} = {}^3H_{3,4} = 2.3$ Hz), and the doublet of 4a-H (4.44 ppm, $^4J_{3,4a} = 2.3$ Hz). The SSC of the 3-H, 4-H, and 4a-H protons was confirmed by experiments employing double resonance. As in the case of compound (Va), the 3-H and 4a-H protons appear as doublets with the constant $^4J_{3,4a} = 1.9$ Hz in the PMR spectra of compound (Vb) in D_2O (Table 1) and DMF-D_7 (Experimental). The SSC of the 3-H and 4-H protons is absent due to the exchange of the latter with the deuterium in D_2O and the rapid exchange in DMF-D_7.

The oxidation of the dihydroimidaztotriazinone (Vb) and decarboxylation, with the subsequent oxidation of the imidazotriazinonecarboxylic acid (IVb) with an aqueous solution of $KMnO_4$ (equivalent amounts), leads to the aromatization of the triazine ring and the formation of the previously described dimethylimidazotriazinone (VIb) (mp 146-147°C [8]), the physicochemical characteristics of which are presented in Tables 1, 2.

Therefore, in contrast to the previously proposed mechanism of the conversion (Scheme 1) of the pyrimido[5,4-e]-1,2,4-triazinediones to imidazo[4,5-e]-1,2,4-triazinones [4-6], this process proceeds by a series of sequential reactions including the hydrolysis of the $C_{(5)}$-$N_{(6)}$ amide bond and the cyclization of the ureido group to the imidiazolidinone ring in an alkaline medium. The main mechanism of the first stages of the process, which proceed in alkaline media, is the uracil-imidazolidinone conversion [10, 12-16]. Decarboxylation proceeds in an acid medium, whereby, in contrast to the Scheme 1, this reaction leads to the formation of the 4,4a-dihydroimidazotriazinones (Va, b); the oxidation of (Va, b) also gives the imidazotriazinones (6-azapurines) (VIa, b).

In conclusion, the authors express their thanks to V. S. Soifer for his help in the separation and chromatographic purification of the investigated substances.

EXPERIMETNAL

The ^{1}H and ^{13}C NMR spectra were registered on a WH-90 (Brucker) spectrometer [90 MHz (^{1}H) and 22.62 MHz (^{13}C)] at 30°C. The CSs were measured on the scaler relative to the internal standard of dioxane: δ (^{1}H) 3.65 ppm and δ(^{13}C) 67.4 ppm. The accuracy of the measurements of the CS, determined by numerical resolution, comprised 0.005 ppm (for the ^{1}H nuclei) and 0.02 ppm (for ^{13}C). The experiments on the selective uncoupling of the SSCs of the protons with the carbon atoms in the ^{13}C NMR spectra were performed using the decoupling apparatus $\gamma H_2/2\pi$ at 550-600 Hz. The mass spectra were obtained on the MAT-311A spectrometer by the method of the FAB of xenon for the substances (III)-(Va, b) and (VII) in a glycerol matrix. Ionization by electron impact was utilized to register the spectra of the compounds (VIa, b). The accelerating voltage was 3.0 kV; the ionizing voltage was 70 eV. The emission current of the cathode was 1.0 mA; the temperature of the ionization chamber was 150°C. The UV spectra were recorded on an SP 8-100 spectrophotometer (Pye-Unicam). The melting temperatures were determined on a Boetius heating stage. The lyophilization of the aqueous solutions was performed on the Hetosicc unit. The purity of the substances synthesized was monitored by the method of TLC on Silufol UV-254 plates; the development was effected in UV light at $\lambda = 254$ nm.

6-(3-Methylureido)-1,2,4-triazine-5-carboxylic Acid (IIIa). The solution of 100 mg (0.56 mmole) of reumicin (Ia) in 10 ml of D_2O is rendered alkaline with a 1 N solution of NaOD to the pH 12. After 5 h, the solution is neutralized with a 1 N solution of DCl to the pH 6; the conversion of the reumicin comprises 45% according to the PMR data. The solution is concentrated by lyophilization. Compound (IIIa) is separated from reumicin by the method of preparative TLC on 20 by 20 cm glass plates (the sorbent in Silpearl; the 3:1 system of ethyl acetate-acetone), collecting and eluting the starting zones with methanol. The eluent is distilled on a rotary evaporator. The light yellow amorphous substance is obtained in the yield of 50 mg (45%). The R_f is 0.60 (methanol-butanol-water, 2:1:1). The PMR spectrum ($DMSO-D_6$) is as follows: 12.15 (1H, broad, NH), 9.26 (1H, s, 3-H), 8.74 (1H, broad, $NHCH_3$), and 2.81 ppm (3H, d, $J_{CH_3,NH} = 4.5$ Hz, $NHCH_3$).

4,4a-Dihydro-5-methyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one-4a-carboxylic Acid (IVa). A. To 518 mg (2.90 mmole) of reumicin (Ia) are added 29 ml of a 1 N solution of NaOH. After the complete decolorization, after 2 h, the solution is applied to a column with the Dowex 50 × 2 ion exchange resin in the H^+-form (volume 40 ml). The acid (IVa) is eluted with 200 ml of water; the completeness of the elution is monitored from the UV spectra. The eluate is lyophilized. The yield of the white amorphous substance is 455 mg (80%). The R_f values are 0.05 (ethyl acetate-acetone, 3:1) and 0.65 (methanol-butanol-water, 2:1:1).

B. To the suspension of 435 mg (2.43 mmole) of reumicin (Ia) in 50 ml of water are added 50 ml of a saturated solution of barium hydroxide. After the complete solution of the reumicin and the subsequent decolorization of the solution (5 h), the pH is brought to 4 (20% H_2SO_4) prior to the addition of 200 ml of water. The solution is separated from the residue of $BaSO_4$ by centrifugation (15 min at 9000 rpm) prior to filtartion and the lyophilization of the filtrate. The yield of the acid (IVa) obtained is 473 mg (99%).

4,4a-Dihydro-5-methyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one (Va). To 3 ml of distilled and degassed DMF is added the suspension of 49 mg (.20 mmole) of the acid (IVa) in 0.5 ml of water. The reaction mixture is degassed in vacuo (the release of gas is observed); it is heated for 30 min at 60°C. The solvent is distilled off into a trap cooled with liquid nitrogen. The residue is extracted with chloroform (5 portions of 2 ml); the extract is chromatographed on a 20 by 20 cm glass plate (Silpearl, the 5:3 mixture of acetone-chloroform). The elution of the zone with the R_f 0.35-0.45 with methanol, and the subsequent distillation of the solvent, gives 7 mg of compound (VIa). The zone with the R_f 0.10-0.15 gives 1.5 mg of compound (Va), which is combined with the residue of compound (Va) which was insoluble in chloroform; it is dissolved in water. After lyophilization, 20 mg (53%) of the triazinone (Va) is obtained. The PMR spectrum ($DMF-D_7$) is as follows: 7.50 (1H, d, $J_{3,4a} = 2.2$ Hz, 3-H), 4.53 (1H, d, $J_{4a,3} = 2.2$ Hz, 4a-H), and 3.00 ppm (3H, s, $N_{(5)}CH_3$).

5-Methyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one (VIa). A. To the solution of 332 mg (1.69 mmole) of the acid (IVa) in 30 ml of water are added 10 ml of a 1.5% aqueous solution of $KMnO_4$ in portions with stirring for 1 h. The pH of the solution is maintained at 4-6 by the addition of 1 N HCl. The reaction mixture is filtered. To the filtrate is added 0.1 ml of 30% H_2O_2; the solution is lyophilized. The substance (VIa) is extracted with chloroform (10 portions of 20 ml). The solvent is evaporated. The residue is dissolved in water and lyophilized. The yield is 144 mg (58%). The PMR spectrum ($CDCl_3$) is as follows: 9.03 (1H, s, 3-H), and 3.49 ppm (3H, s, $N_{(5)}CH_3$). The PMR spectrum ($DMSO-D_6$) is as follows: 8.85 (1H, s, 3-H) and 3.24 ppm (3H, s, $N_{(5)}CH_3$).

B. To the solution of 7.2 mg (0.05 mmole) of compound (Va) in D_2O is added a 1.5% solution (D_2O) of $KMnO_4$ in portions with stirring. The conversion of compound (Va) to (VIa) is monitored from the PMR spectra. After the complete conversion of compound (Va) to (VIa) is achieved, the reaction mixture is filtered. The filtrate is lyophilized, and the substance (VIa) is extracted with 1 ml of chloroform. The solvent is distilled off; the residue is dissolved in water and dried lyophilically. The yield of (VIa) obtained is 3 mg.

4,4a-Dihydro-5,7-dimethyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one-4a-carboxylic Acid (IVb). A. This is obtained analogously to (IVa) by the method A from 101 mg (0.53 mmole) of fervenulim (Ib) and 5.3 ml of a 1 N aqueous solution of NaOH for 20 min. The volume of the Dowex 50 × 2 resin is 8 ml. The elution is carried out with 140 ml of water. The yield of (IVb) is 105 mg (96%).

B. To the suspension of 116 mg (0.60 mmole) of fervenulin (Ib) in 5 ml of water are added 10 ml of a saturated solution of $Ba(OH)_2$. After the decolorization of the solution, which takes 1 h, the pH is adjusted to 4 with 20% H_2SO_4; 50 ml of water are added. The solution is separated from the residue by centrifugation at 4000 rpm for 7 min. The centrifugate is filtered, and the filtrate is lyophilized. The yield is 123 mg (97%).

4,4a-Dihydro-5,7-dimethyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one (Vb). This is obtained by analogy with (Va) from 56 mg (0.27 mmole) of the acid (IVb) in 4 ml of DMF for 50 min. After the distillation of the DMF, the residue is dissolved in 5 ml of chloroform; the solution is applied to a column (d 8 mm, h 20 mm) with silica gel type Silpearl. At first, compound (VIb) is eluted with 30 ml of chloroform (monitoring with TLC, 3:1 ethyl acetate-acetone, R_f 0.52). Then, the substance (Vb) is eluted with 10 ml of acetone (monitoring under the same conditions, R_f 0.28). The solvents are distilled off; the residues are dissolved in water and lyophilized. Compound (VIb) is obtained with a yield of 5 mg; compound (Vb) is obtained with a yield of 29 mg (66%). The PMR spectrum (DMF-D_7) is as follows: 7.53 (1H, d, $J_{3,4a}$ = 1.9 Hz, 3-H), 4.54 (1H, d, $J_{4a,3}$ = 1.9 Hz, 4a-H), 3.02 (3H, s, $N_{(5)}CH_3$), and 2.97 ppm (3H, s, $N_{(7)}CH_3$). The PMR spectrum ($CDCl_3$) is as follows: 7.83 (1H, broad, 4-H), 7.40 (1H, dd, $J_{3,4a}$ = $J_{3,4}$ = 2.3 Hz, 3-H), 4.44 (1H, d, $J_{4a,3}$ = 2.3 Hz, 4a-H), 3.14 (3H, s, $N_{(5)}CH_3$), and 3.06 ppm (3H, s, $N_{(7)}CH_3$).

5,7-Dimethyl-5H-imidazo[4,5-e]-1,2,4-triazin-6[7H)-one (VIb). A. This is obtained analogously to (VIa) by the method A from 322 mg (1.53 mmole) of the acid (IVb) in 35 ml of water and 10 ml of a 1.5% aqueous solution of $KMnO_4$. The yield is 212 mg (84%). The PMR spectrum ($CDCl_3$) is as follows: 9.01 (1H, s, 3-H), 3.59 (3H, s, $N_{(5)}CH_3$), 3.50 ppm (3H, s, $N_{(7)}(CH_3)$, DMSO-D_6 spectra: 8.98 (1H, s, 3-H), 3.39 (3H, s, N_5CH_3), 3.31 ppm (3H, s, $N_{(7)}CH_3$).

F. It is obtained analogously to compound (VIa) by the method B from 6 mg (0.03 mmole) of compound (Vb) with the yield of 3 mg of the triazinone (VIb).

4,4a-Dihydro-5,7-dimethyl-4a-methoxycarbonyl-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one (VII). To the suspension of 45 mg (0.21 mmole) of the acid (IVb) in 5 ml of methanol are added 15 ml of an ethereal solution of diazomethane, in portions with stirring, until a stable yellow coloration is present. The solution is concentrated by the fractional distillation of the solvents; it is applied to a 20 × 20 cm glass plate with a loose layer of the sorbent (Silpearl). Chromatography is performed in the 5:1 system of chloroform-ethyl acetate. After collecting the zone with the R_f 0.20-0.25 and eluting it with methanol, with the subsequent distillation of the solvent, the yield of 20 mg (42%) of the methyl ester (VIIb) is obtained. By extracting from the zone with the R_f 0.30-0.35, 9 mg of the compound (VIb) are obtained analogously. The PMR spectrum of compound (VIIb) (CD_3OD) is as follows: 7.67 (1H, s, 3-H), 3.82 (3H, s, $COOCH_3$), 3.13 (3H, s, $N_{(5)}CH_3$, and 3.06 ppm (3H, s, $N_{(7)}CH_3$). The PMR spectrum ($CDCl_3$) is as follows: 8.11 (1H, broad, 4-H), 7.58 (1H, d, $J_{3,4}$ = 2.3 Hz, 3-H), 3.74 (3H, s, $COOCH_3$), 3.08 (3H, s, $N_{(5)}CH_3$), and 3.05 ppm (3H, s, $N_{(7)}CH_3$).

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