SYNTHESIS OF ANALOGS OF 5(4)-AMINOIMIDAZOLE-4(5)-CARBOXAMIDE AND PURINES.

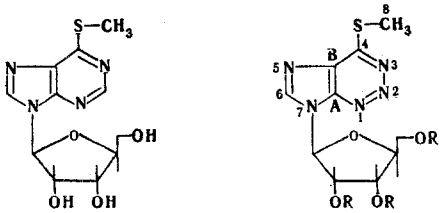
7.* 7-(β-D-RIBOFURANOSYL)-4-METHYLTHIOIMIDAZO[4,5-d]-1,2,3-TRIAZINE

V. A. Bakulev, V. S. Mokrushin,
V. I. Ofitserov, Z. V. Pushkareva,
and A. N. Grishakov

UDC 547.785.5.872.3'455.522.07

The synthesis of 7-(β-D-ribofuranosyl)-4-methylthioimidazo[4,5-d]-1,2,3-triazine, 7-methyl-4-methylthioimidazo[4,5-d]-1,2,3-triazine, and 5-methyl-4-methylthioimidazo[4,5-d]-1,2,3-triazine is described. The structures of the synthesized compounds were confirmed by ^{13}C NMR spectroscopy.

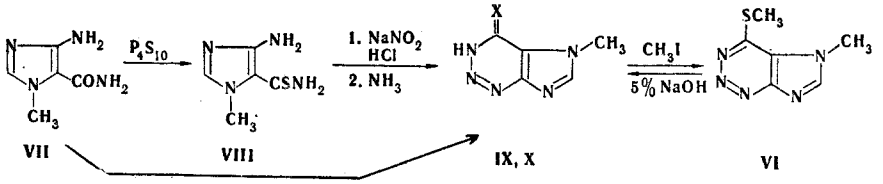
It is known that 9-ribofuranosyl-6-methylthiopurine (I) has high biological activity [2]. In order to obtain the 2-aza analog of I we carried out the direct ribosylation of 4-methylthioimidazo[4,5-d]-1,2,3-triazine (II) and obtained one of the possible isomers, viz., triacetylribofuranosyl-4-methylthioimidazo[4,5-d]-1,2,3-triazine III, the deacetylation of which gave riboside IV:



I III, IV

III R=$COCH_3$; IV R=H

We initially assumed [3] that the ribofuranosyl residue in III is incorporated in the 7 position of the imidazotriazine ring. In contrast to the results of glycosylation, methylation of II with methyl iodide gave two N-methyl derivatives that we were unable to separate by thin-layer chromatography (TLC). One might have expected that methylation takes place at the ring N_5 and N_7 atoms to give V and VI, respectively. The UV spectra of V and VI differ. At the same time, the UV spectrum of V is similar to the spectrum of riboside III. 5-Methyl-4-methylthioimidazo[4,5-d]-1,2,3-triazine (VI), which was obtained by alternative synthesis from VIII, is identical to the compound synthesized by methylation of triazine II. In the hydrolysis of VI we isolated a reaction product that is identical to 5-methylimidazo[4,5-d]-1,2,3-triazin-4-one (X), which was obtained by diazotization of 1-methyl-4-aminoimidazole-5-



VII VIII IX, X VI

IX X=S; X X=O

*See [1] for communication 6.

S. M. Kirova Ural Polytechnic Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 836-838, June, 1979. Original article submitted July 21, 1978.

0009-3122/79/1506-0685$07.50

TABLE 1. ^{13}C NMR Spectra of II, IIa, and III in d_6-DMSO

Compound	δ, ppm					SSCC,† C_m-C_nH						
	$C_{(4)}$	$C_{(6)}$	$C_{(A)}$	$C_{(B)}$	$C_{(8)}$	$C_{(4)}-C_{(8)}H$	$C_{(6)}-H$	$C_{(6)}-C_{(1')}H$	$C_B-C_{(6)}H$	$C_A-C_{(6)}H$	$C_A-C_{(1')}H$	$C_{(8)}-H$
II	154,3	146,8	148,2	125,4	11,6	4	213	—	9	9	—	145
IIa	153,1	150,3	151,0	126,8	11,5	—	—	—	—	—	—	—
III*	157,1	147,2	144,8	129,1	11,6	4,1	219	2,6	12,3	6,4	4,9	—

*[$COCH_3(CH_3)$]: 20.4, 20.3, and 20.1; [$COCH_3(CO)$]: 170.0, 169.3, and 169.2; C'_1 87.0, C'_2 70.0, C'_3 72.5, C'_4 80.2, and C'_5 62.6 ppm.
†These are the spin-spin coupling constants (SSCC) in the ^{13}C high-resolution NMR spectrum.

carboxamide (VII). These results provide a rigorous confirmation that the ribofuranosyl residue in IV is not in the 5 position of the imidazotriazine ring. To confirm [3] the structure of IV we recorded the ^{13}C NMR spectra of II, its anion (IIa), which was obtained by treatment of II in d_6-DMSO with a molar amount of LiOH, and III. The chemical shifts of the carbon atoms of these compounds are presented in Table 1. The C_A and C_B signals were assigned with the literature data for purines [4]. It is apparent from Table 1 that the C_6 and C_A signals in the spectrum of III undergo 3.1 and 6.2 Hz strong-field shifts, respectively, as compared with the signals of the corresponding carbon atoms of IIa, whereas the signal of the C_B atom is shifted 2.3 Hz to weak field. This character of the shift of the C_A, C_6, and C_B atoms in the spectrum of III as compared with anion IIa constitutes evidence for incorporation of the ribofuranosyl residue in the 7 position. In addition, the C_6 and C_A signals are split into a doublet of doublets, and the smaller constant (Table 1) characterizes the spin–spin coupling of the C_6 and C_A atoms with the 1-H' atom of the ribofuranosyl residue. This is possible only if III is 7-(β-D-2',3',5'-tri-O-acetylribofuranosyl)-4-methylthioimidazo[4,5-d]-1,2,3-triazine.

Thus the alternative synthesis of VI and the ^{13}C NMR spectra of II, IIa, and III unambiguously confirm structures III and IV.

EXPERIMENTAL

The UV spectra of solutions in 0.1 N hydrochloric acid or in methanol were obtained with a Perkin–Elmer 402 spectrophotometer. The PMR spectra were recorded with a Perkin–Elmer 12B spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard. The ^{13}C NMR spectra of d_6-DMSO solutions were recorded with a Brucker HX-90 spectrometer (22, 62 MHz) with d_6-DMSO and TMS as the internal standards. The specific rotation was measured with an Al-EPL automatic polarimeter.

Thin-layer chromatography (TLC) on Silufol UV-254 in the following systems was used to confirm the individuality of the substances: 1) n-butanol–acetic acid–water (4:1:1); 2) n-propanol–0.2 N ammonium hydroxide (3:1); 3) chloroform–n-propanol (7:3).

7-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-4-methylthioimidazo[4,5-d]-1,2,3-triazine (III). A 1-g (3 mmole) sample of triacetylribofuranosyl bromide was dissolved in 10 ml of nitromethane, and the resulting solution was added with stirring to a solution of 0.35 g (2.1 mmole) of II and 0.53 g (2.3 mmole) of mercurous cyanide in 30 ml of nitromethane. The mixture was then refluxed for 5 h, after which it was evaporated in vacuo to give a syrupy mass. The latter was dissolved in 50 ml of ethyl acetate, and the solution was washed with aqueous sodium bicarbonate solution, potassium iodide, and water. The ethyl acetate solution was filtered through silica gel, and the filtrate was evaporated to dryness. Compound III was separated from the decomposition products by TLC on LSL-254 silica gel in system 3 (R_f 0.35). The yield of product with mp 137-139°C (from methanol) and $[\alpha]_D^{25}$ −25.2° (c 0.96, $CHCl_3$) was 0.4 g (40.5%). UV spectrum (in methanol), λ_{max} (log ε): 208 (4.21); 233 (4.04); 279 (3.97); 297 nm (3.94). PMR spectrum (in CD_3OD), δ: 8.68 (s, 6H), 6.40 (d, 1'-H, $J_{1'-H,2'-H}$ = 5 Hz), 4.16-6.14 (m, 2'-, 3'-, 4'-, and 5'-H), 2.82 (3H, s, SCH_3), 2.12, 2.06, and 2.04 ppm (3H, s, CH_3COO). Found: C 45.2; H 4.6 N 16.5; S 7.3%. $C_{16}H_{19}N_5SO_7$. Calculated: C 45.2; H 4.5; N 16.5; S 7.5%. The following R_f values were obtained: 0.6 (1), 0.3 (2), and 0.35 (3).

7-(β-D-Ribofuranosyl)-4-methylthioimidazo[4,5-d]-1,2,3-triazine (IV). A 0.18-g (5.65 mmole) sample of III was dissolved in methanol, the solution was saturated with ammonia at room temperature, and the methanol was removed by vacuum distillation. Compound IV was separated from the decomposition products by TLC on LSL-254 silica gel in system 3, and the fraction with R_f 0.5 was collected. The yield of product with mp 165-167°C (from methanol) and $[\alpha]_D^{25}$ −43.5° [c 0.83, dimethylformamide (DMF)] was 0.06 g (62.5%). UV spectrum (0.1 N HCl), λ_{max} (log ε): 208 (4.04), 233 (4.03), 282 (3.96), 305 nm (3.93); (in methanol): 208 (4.01), 233 (4.11), 280 (4.01), 301 nm (3.99). PMR spectrum (in CD_3OD), δ: 8.68 (s, 6H), 6.26 (d, 1H, $J_{1'-H,2'-H}$ = 5 Hz), 3.68-4.88 (m, 2'-, 3'-, 4'-, and 5'-H), and 2.85 ppm (3H, s, SCH_3). Found: C 39.9; H 4.5; N 23.1; S 10.4%. $C_{10}H_{13}N_5O_4S$. Calculated: C 40.1; H 4.4; N 23.4; S 10.7%.

1-Methyl-4-aminoimidazole-5-thiocarboxamide (VIII). A 2.3-g (16.5 mmole) sample of 1-methyl-4-aminoimidazole-5-carboxamide was suspended in 30 ml of absolute dioxane, the suspension was heated to 70°C, and 3.7 g (8.3 mmole) of P_4S_{10} was added. The temperature was gradually raised, and the mixture was refluxed for 4 h. The dioxane was removed by distillation, and the residue was extracted with 3 N HCl. The extract was evaporated in vacuo to a small volume, and the concentrate was cooled and filtered. The solid material on the filter was washed with a small amount of cold water, alcohol, and ether. It was then converted to the base by treatment with 5% aqueous potassium carbonate. The yield of product with mp 226-227°C (from water) was 1 g (41%). Found: C 34.7; H 5.4; N 32.3; S 18.2%. $C_5H_8N_4S\cdot H_2O$. Calculated: C 34.7; H 5.4; N 32.2; S 18.4%. The following R_f values were obtained: 0.31 (1), 0.42 (2), and 0.29 (3).

5-Methyl-4-methylthioimidazo[4,5-d]-1,2,3-triazine (VI). A) A 0.9-g (5.1 mmole) sample of VIII was suspended in 10 ml of water, 0.44 g (6.4 mmole) of $NaNO_2$ was added, and the resulting suspension was added to a solution of 3 ml of concentrated HCl in 10 ml of water at a temperature below 0°C. The mixture was maintained at this temperature for 15 min, after which it was filtered, and the filtrate was made alkaline with sodium acetate. The resulting precipitate was removed by filtration and dissolved in 5% ammonium hydroxide. The solution was allowed to stand for 1 h, after which it was acidified to pH 3. The resulting precipitate was dried and dissolved in a solution of sodium methoxide obtained from 0.12 g (5.1 mmole) of sodium and 20 ml of methanol. Methyl iodide [1.42 g (10 mmole)] was added, and the mixture was stirred for 18 h. The methanol was evaporated in vacuo, 8 ml of water was added, and the mixture was filtered to give 0.1 g (11%) of a product with mp 214-216°C (from water). UV spectrum, λ_{max} (log ε): 210 (4.2), 238 (4.04), 298 nm (4.0). The following R_f values were obtained: 0.6 (1), 0.4 (2), and 0.1 (3). Found: C 40.1; H 3.6; N 38.7; S 17.6%. $C_6H_7N_5S$. Calculated: C 39.8; H 3.9; N 38.7; S 17.7%.

B) A 0.38-g sample of KOH was dissolved in a mixture of 40 ml of acetone and 6 ml of water, 1 g of I was added, and the mixture was stirred until the latter dissolved completely. Methyl iodide (0.5 ml) was added, and the mixture was stirred at room temperature for 2 h and refluxed for 1 h. It was then concentrated to a small volume and filtered. The precipitate was separated by TLC on LS 5/40 nm silica gel in a chloroform—n-propanol system (7:1). The band with R_f 0.2 was extracted with alcohol, and the extract was evaporated to dryness to give a product with mp 214-217°C (from water) in 10% yield.

7-Methyl-4-methylthioimidazo[4,5-d]-1,2,3-triazine (V). This compound was obtained as described for VI (method B). The zone containing the substance with R_f 0.4 was extracted with alcohol, and the extract was evaporated to dryness to give a product with mp 216°C (from water) in 12% yield. UV spectrum, λ_{max} (log ε): 210 (4.14); 235 (3.98); 284 (3.88); 305 nm (3.88). Found: C 40.2; H 3.7; N 38.9; S 17.7%. $C_6H_7N_5S$. Calculated: C 39.8; H 3.9; N 38.7; S 17.7%. The following R_f values were obtained: 0.52 (1) and 0.82 (2).

5-Methylimidazo[4,5-d]-1,2,3-triazin-4-one (IX). A solution of 0.1 g of V in 10 ml of 5% NaOH was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration to give 0.03 g (37%) of a product with mp 200-207°C. Found: C 31.2; H 3.1; N 45.0%. $C_5H_5N_5O\cdot H_2O$. Calculated: C 31.0; H 3.2; N 46.2%. UV spectrum (in 0.1 N HCl), λ_{max} (log ε): 277 (4.56); 252 nm (3.46). Compound IX was identical to the compound obtained by the method in [5].

LITERATURE CITED

1. V. I. Ofitserov, V. S. Mokrushin, Z. V. Pushkareva, and N. V. Nikiforova, Khim. Geterotsikl. Soedin., No. 8, 1119 (1976).

2. G. P. Bodey, H. S. Brodovsky, A. A. Isassi, L. Samuels, and E. J. Freireich, Cancer Chemother. Rep., 52, 315 (1968).
3. V. I. Ofitserov, V. S. Mokrushin, I. A. Korbukh, M. N. Preobrazhenskaya, and Z. V. Pushkareva, Zh. Obshch. Khim., 11, 909 (1975).
4. R. J. Pygmize, D. M. Grant, L. B. Townsend, and R. K. Robins, J. Am. Chem. Soc., 95, 2791 (1973).
5. R. P. Panzica and L. B. Townsend, J. Heterocycl. Chem., 9, 623 (1972).

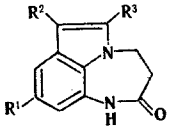
4,5-DIHYDRO-6H-PYRROLO[1,2,3-d,e]QUINOXALIN-5-ONES

A. V. Bogat-skii, R. Yu. Ivanova,
S. A. Andronati, and Z. I. Zhilina

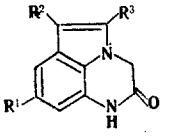
UDC 547.75'863.1.07

The synthesis of 1-R^1-2-R^2-8-R^3-4,5-dihydro-6H-pyrrolo[1,2,3-d,e]quinoxalin-5-one derivatives (where R^1 = CH_3, C_2H_5; R^2 = CH_3, $COOC_2H_5$; R^3 = H, CH_3, C_2H_5O, Cl, Br) is described. The physicochemical properties of these derivatives were also studied.

The present communication is devoted to the synthesis of 4,5-dihydropyrrolo[1,2,3-d,e]-quinoxalin-5(6H)-ones (II). The cyclohomologs of the latter, viz., 4,5,6,7-tetrahydro[1,2,3-e,f]-1,5-benzodiazepin-6-ones (I), have been described as substances that have tranquilizing and anticonvulsive action [1, 2]. The literature contains data on the synthesis of individual representatives of the II series by Fischer condensation of ketones with 1-amino-3-keto-1,2,3,4-tetrahydroquinoxaline [3, 4].



I



II a-g

II a R^1=H, R^2=R^3=CH_3; b R^1=H, R^2=CH_3, R^3=$COOC_2H_5$; c R^1=H, R^2=C_2H_5, R^3=$COOC_2H_5$; d R^1=CH_3, R^2=C_2H_5, R^3=$COOC_2H_5$; e R^1=Cl, R^2=CH_3, R^3=$COOC_2H_5$; f R^1=C_2H_5O, R^2=C_2H_5, R^3=$COOC_2H_5$; g R^1=Br, R^2=CH_3, R^3=$COOC_2H_5$

We have developed a new method for the synthesis of pyrrolo[1,2,3-d,e]quinoxalin-5-one derivatives (IIa-g) from o-nitrophenylhydrazones (III), which were converted by the Fischer reaction to 7-nitroindoles (IV) with subsequent reduction of the latter to 7-aminoindoles (V). In view of their instability, V were not isolated in pure form, but hydrogenation products V were dissolved in acetic acid and treated with chloroacetyl chloride in the pres-

TABLE 1. 7-Nitro- (IVb-g) and 7-Chloroacetamidoindoles (VIa-g)

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IVb	135—136			11,0	$C_{12}H_{12}N_2O_4$			11,3	62
IVc	93—95			10,5	$C_{13}H_{14}N_2O_4$			10,7	55
IVd	123—125			10,0	$C_{14}H_{16}N_2O_4$			10,1	52
IVe	143—145			10,0	$C_{12}H_{11}ClN_2O_4$			9,9	65
IVf	155—156			9,0	$C_{15}H_{18}N_2O_5$			9,1	45
IVg	131—132			8,2	$C_{12}H_{11}BrN_2O_4$			8,5	61
VIa	142—143	60,8	5,8	12,0	$C_{12}H_{13}ClN_2O$	60,9	5,5	11,8	72
VIb	110—112	56,7	4,8	9,3	$C_{14}H_{15}ClN_2O_3$	57,0	5,1	9,5	68
VIc	145—147	58,1	5,0	8,8	$C_{15}H_{17}ClN_2O_3$	58,3	5,1	9,1	61
VId	180—181	59,3	5,6	8,6	$C_{16}H_{19}ClN_2O_3$	59,6	5,9	8,7	55
VIe	80—81	51,2	4,0	8,4	$C_{14}H_{14}Cl_2N_2O_3$	51,1	4,2	8,5	75
VIf	88—90	58,1	6,1	8,1	$C_{17}H_{21}ClN_2O_4$	57,9	5,9	7,9	68
VIg	162—163	45,1	3,5	7,4	$C_{14}H_{14}ClBrN_2O$	44,9	3,7	7,5	70

Institute of Physical Chemistry, Academy of Sciences of the Ukrainian SSR, Odessa 270080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 839-841, June, 1979. Original article submitted May 3, 1978.

 0009-3122/79/1506-0688$07.50