LITERATURE CITED

1. D. R. Bender and D. L. Koffen, J. Org. Chem., 33, 2504 (1968).
2. B. J. Warawa and J. R. Campbell, J. Org. Chem., 39, 3511 (1974).
3. O. I. Gorbyleva, T. Ya. Filipenko, E. E. Mikhlina, K. F. Turchin, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 9, 1232 (1982).
4. K. F. Turchin, A. D. Yanina, T. Ya. Filipenko, E. E. Mikhlina, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 9, 1248 (1985).
5. V. A. Vorob'eva, V. A. Bondarenko, E. E. Mikhlina, K. F. Turchin, L. F. Linberg, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 10, 1370 (1988).
6. K. F. Turchin, E. E. Mikhlina, V. A. Vorob'eva, A. D. Yanina, Yu. N. Sheinker, and L. N. Yakhontov, Dokl. Akad. Nauk SSSR, 192, 823 (1970).
7. A. T. Nielsen, J. Org. Chem., 31, 1053 (1966).
8. J. P. Bégué and M. Fétzon, Bull. Soc. Chim. Fr., No. 4, 1251 (1969).
9. E. E. Mikhlina and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 2, 147 (1984).
10. L. A. Kheifits, I. S. Aul'chenko, and G. M. Shchegoleva, Zh. Org. Khim., 2, 2059 (1966).
11. L. I. Mastafanova, I. P. Isakovich, T. Ya. Shvarts, I. F. Faermark, O. S. Anisomova, K. F. Turchin, Yu. N. Sheinker, M. D. Mashkovskii, and L. N. Yakhontov, Khim.-farm. Zh., No. 1, 85 (1988).

PURINES, PYRIMIDINES, AND CONDENSED SYSTEMS BASED ON THEM.

6.* REACTIVITY OF 7- AND 9-AMINOXANTHINES TOWARD OXIDIZING AGENTS AND SOME ELECTROPHILES. SYNTHESIS OF THE ANTIBIOTICS FERVENULIN AND RHEUMYCIN

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The action of various oxidizing agents on 7- and 9-aminotheophyllines and also on 1-methyl-9-aminoxanthine was studied. 7-Aminotheophyllines are oxidized by almost all the oxidizing agents to 6,8-dimethylpyrimido[4,5-e]-as-triazine-5, 7(6H,8H)-dione (40-90%). 1-Methyl-9-aminoxanthine and 9-aminotheophylline are oxidized with greater difficulty. The best results are obtained with hydrogen peroxide, which transforms these amines with yields of ~40% into the antibiotics rheumycin and fervenulin, respectively. Under certain conditions the action of bromine and nitric acid leads to the bromination and nitration of the N-aminoxanthines at position 8. A series of the physicochemical characteristics of the N-aminoxanthines were investigated. The factors which affect their behavior toward oxidizing agents and electrophiles are discussed.

Earlier we showed that 7-aminotheophylline (I) and other 7-aminoxanthines [2, 3] are oxidized by lead tetraacetate, forming good yields of pyrimido[4,5-e]-as-triazine-5,7-dione derivatives such as isofervenulin (III). In the present work we attempted to introduce the recently synthesized [4] 1-methyl-9-aminoxanthine (IVa) and 9-aminotheophylline (IVb) into an analogous reaction. It was assumed that the transformation products in these cases would be the antibiotic rheumycin (VIa) and fervenulin (VIb) (see scheme on following page).

It was found that the amines (IVa,b) are not oxidized by lead tetraacetate. At the same time the action of potassium chlorate, periodic acid, or potassium permanganate leads

*For Communication 5, see [1].

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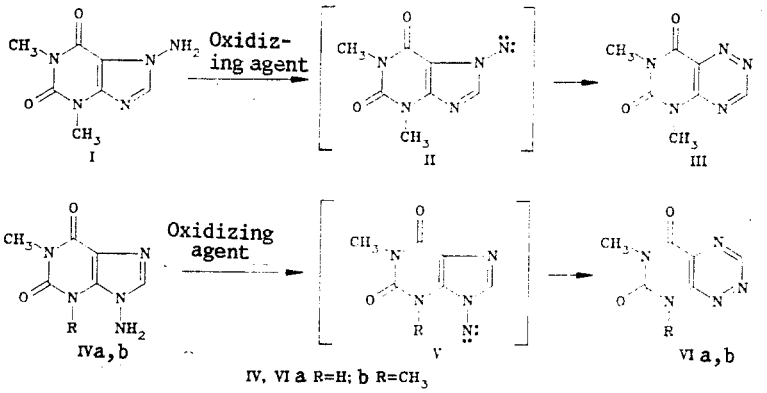

to the formation of rheumycin and fervenulin with yields of 10-25% (Table 1). The highest yield of the antibiotics (~40%) was obtained with 30% hydrogen peroxide, which has the highest oxidation potential among the investigated oxidizing agents. Bromine water, which has a low oxidizing potential, does not oxidize the amines (IVa, b) but brominates them with the formation of 8-bromo-9-aminoxanthines (VIIa, b) with yields of 88 and 98%, respectively. Bromination also takes place during the action of bromine in glacial acetic acid on compounds (IVa, b). Nitric acid in concentrated sulfuric or glacial acetic acid does not oxidize and does not nitrate compounds (IVa, b); under these conditions both amines are regenerated, and only the amine (IVb) is partly deaminated with the formation of theophylline.

In light of the obtained data it seemed of interest to study the action of the same oxidizing agents on 7-aminotheophylline (I). Apart from lead tetraacetate, the amine (I) is also oxidized by bromine water, nitric acid in concentrated sulfuric acid, potassium chlorate, periodic acid, potassium permanganate, and 30% hydrogen peroxide. The yield of isofervenulin (III) was 40-90% (Table 1). In glacial acetic acid compound (I) is brominated by bromine and is nitrated by nitric acid, and although the yields of the 8-bromo and 8-nitro derivatives (IX, X) only amount to 20 and 33%, respectively, these reactions have some preparative value, since it is not possible to obtain (X) by the direct amination of 8-nitrotheophylline with hydroxylamine-O-sulfonic acid (HASA), while 8-bromotheophylline is aminated by HASA, giving the amine (IX) with a yield only slightly higher (25%) [2].

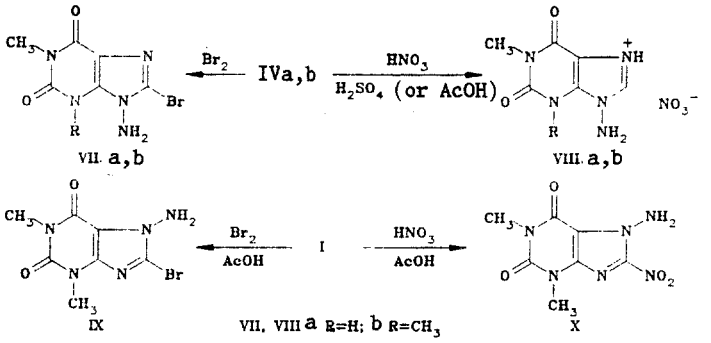

TABLE 1. Results from Oxidation of N-Aminoxanthines (I, IVa, IVb)

Oxidizing agent	Oxidation potential E^0, B [5]	Yield, %		
		III from I	VIa from IVa	VIb from IVb
Br_2—H_2O	1,065	40	—	—
HNO_3—H_2SO_4	1,246	40	—	—
$KClO_3$—H_2SO_4	1,451	75	13	25
H_5IO_6	1,600	62	10	10
$KMnO_4$—H_2SO_4	1,692	79	13	15
$Pb(OAc)_4$	1,694	74 [2]*	—	—
H_2O_2	1,776	50	39	42

*In our experiment the yield amounted to 90%.

TABLE 2. PMR Spectra of 7- and 9-Aminoxanthines (I, IVa, IVb)

Compound	Solvent	pD	Chemical shift, δ, ppm*		
			$N_{(1)}-CH_3$	$N_{(3)}-CH_3$	$H_{(8)}$
I	DMSO-D_6		3,23	3,40	7,89
	D_2O	~8,8	3,22	3,39	7,82
	D_2O	~3,0	3,21	3,39	7,81
	D_2O	~0,3	3,23	3,41	8,01
	D_2O	~0,1	3,24	3,43	8,15
	Conc. DCl		3,17	3,44	8,93
IV a	DMSO-D_6		3,08	—	7,55
	D_2O		3,33	—	7,74
	D_2O	~12	3,35	—	7,64
	D_2O	~6	3,18	—	7,56
	D_2O	~1	3,20	—	8,41
IV b	DMSO-D_6		3,22	3,76	7,56
	D_2O	~4,7	3,25	3,77	7,62
	D_2O	~0,1	3,28	3,81	8,79

*The signal of $N-NH_2$ protons for the neutral molecules of (I, IVa, IVb) in DMSO-D_6 lies at 6.27, 5.95, and 6.34 ppm, respectively.

Thus, the experiments showed that 7-aminotheophylline compared with 9-aminoxanthines is more readily oxidized and nitrated but is brominated with greater difficulty. Let us consider the possible reasons for this. It is thought that the oxidative transformations of the N-amino derivatives of NH-heterocycles, accompanied by ring enlargement, take place through the formation of N-nitrenes [6]. Can the difficulty in the oxidation of 9-aminoxanthines be due to the lower reactivity of the nitrene (V) compared with the nitrene (II)? This seems unlikely. Nitrenes are highly reactive electron-deficient particles, and the stage of their generation and not their subsequent transformation is controlling. Analysis of the physicochemical characteristics of the amines (I) and (IV) leads to sounder conclusions.

The electrochemical oxidation potentials of the amines (I) ($E_{1/2}^{ox}$ = 1.40 V) and (IVb) ($E_{1/2}^{ox}$ = 1.47 V), which we measured recently [7], confirm that 9-aminoxanthines are in fact oxidized with greater difficulty than 7-aminoxanthines. However, the difference in the oxidation potentials is nevertheless small, and there are probably other factors responsible for the difficulty in the oxidation of the amines (IVa, b).

One such factor may be the substantially higher basicity of the 9-aminoxanthines compared with the basicity of the 7-aminoxanthines. The pK_a value of the amine (I) measured in acetonitrile is 7.6, while that of the amine (IVb) is 9.7 [7].* Under the influence of oxidizing agents, as stronger bases the 9-aminoxanthines probably form cations of type (VIII) resistant to further oxidation (if the reaction is conducted in an acidic medium) or complexes at the $N_{(7)}$ atom (e.g., in the case of lead tetraacetate), the stability of which may promote chelation with the participation of the $C_{(6)}=O$ carbonyl group. The protonation of the amines (I) and (IV) in the imidazole ring and not at the amino group is confirmed by the PMR spectra. From Table 2 it is seen that the signal of the $H_{(8)}$ proton for the neutral molecule of (I) in DMSO-D_6 lies at 7.89 ppm. This value changes little in D_2O solution at pD 8.8-3.0, from which it can be concluded that the amine is unprotonated under these conditions. With further increase in the acidity of the medium the signal of the $H_{(8)}$ proton is gradually shifted downfield, and in concentrated DCl it lies at 8.93 ppm. A shift of such a magnitude, i.e., of about 1 ppm, in the transition from the neutral molecules to their protic salts is typical of a proton at the μ-carbon atom of imidazoles [8]. From this it can be supposed that in concentrated DCl the amine (I) exists preferentially in the imidazolium form. The same is observed for the amines (IV). For instance, the signal of the $H_{(8)}$ proton in the neutral molecule of (IVa) and in its nitrate (VIIIa) in DMSO-D_6 appears at 7.55 and 8.92 ppm, respectively. (The measurement was not made in concentrated DCl.)

*In the present work we also measured the basicity of the amine (IVb) in water, which proved to be 0.97, by the PMR method.

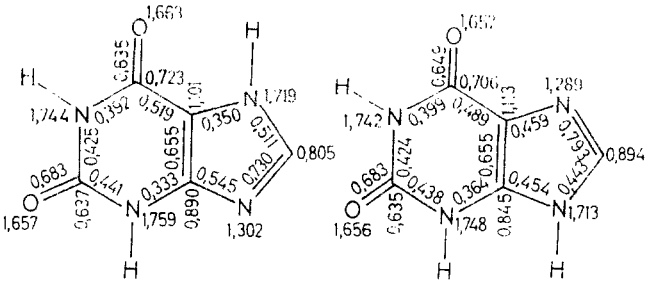

Fig. 1. The π-electron density and the orders of the π bonds in the molecules of 7H- and 9H-xanthines (the HMO method).

The difference in the basicity of compounds (I) and (IV) also explains to some degree their behavior toward electrophiles. Clearly, in the presence of concentrated nitric acid the amines (IVa, b) are transformed fully into the cations (VIIIa, b) inert both with respect to oxidation and with respect to electrophilic substitution. In view of its low solubility we isolated the salt (VIIIa) from the reaction mixture in the form of the nitrate. During nitration in acetic acid the less-basic amine (I) is evidently present partly in the form of the neutral molecule, which undergoes nitration, although with difficulty. The amines (IVa, b) also probably exist in the unprotonated form to a small degree in acetic acid. This is why they are brominated so readily in acetic acid.

The great ease of the bromination of compounds (IV) compared with (I) is explained well by the fact that the π-electron density at the $C_{(8)}$ atom in the 9H-xanthine system (0.894) is significantly higher than in 7H-xanthine (0.805) (Fig. 1). The calculated data are confirmed by the ^1H and ^{13}C NMR spectra (Tables 2 and 3). They show that the signals of the $H_{(8)}$ proton or the $^{13}C_{(8)}$ nucleus in the amines (IVa, b) lie downfield in comparison with the same signals of the amine (I). (For a correlation of the electron density with the chemical shifts of the ^1H and ^{13}C nuclei, see [9].)

During examination of the reactivity of the amine (I) the question arises as to why it is oxidized to isofervenulin (III) by the action of nitric acid in sulfuric acid or of bromine in water, while it is nitrated and brominated by the action of the same reagents in acetic acid. It can be supposed that this is due to the different ratios of the electrophilicity and oxidizing power of the respective reagents. Thus, the nitronium cation, which is formed in sulfuric acid, has a significantly higher oxidation potential than acetyl nitrate, and it is this which leads to the transformation of the amine (I) into isofervenulin. The same applies to bromine water, which is more active as an oxidizing agent than bromine dissolved in acetic acid. It should be noted that the nitroamine (X), unlike the amine (I) and its 8-bromine-substituted derivative (IX) [2], is not oxidized by lead tetraacetate, bromine water, or hydrogen peroxide.

The amines (I) and (IV) differ from each other not only in reactivity but also in their mass-spectrometric fragmentation (Table 4). Compounds (IVa, b) are characterized by typical fragmentation of hydrazines with the removal of the NH group, and this leads to the formation of the pseudomolecular ion of 1-methylxanthine (m/z 166) and 1,3-dimethylxanthine (m/z 180), respectively. Their subsequent fragmentation is typical of methylated xanthines and uraciles (e.g., see [10]). In contrast to this the mass spectrum of the amine (I) does not contain a peak with m/z 180, due to the removal of the NH group from the M^+ ion. At the same time there are peaks for ions with m/z 152 and 140, which are absent in its isomer (IVb). They may be due to the synchronous removal of particles (NH and CO) and (CO and HCN), respectively, from the M^+ ion.

EXPERIMENTAL

The IR spectra were recorded in Vaseline oil on a UR-20 instrument. The PMR spectra of compounds (VIIIa) and (X) were obtained on a Tesla BS 487 instrument at 80 MHz. The other spectra were obtained on a Bruker WH-90 spectrometer at 90 MHz for ^1H and 22.6 MHz for ^{13}C with TMS (^1H) and dioxane (^{13}C, δ_{do} 67.40 ppm) as internal standards. The mass spectra were recorded on a MAT-311A spectrometer with direct injection into the ion source (accelerating potential 3 kV, ionization potential 70 eV, cathode emission current 1 mA). The quantum-chemical calculation of the 7H- and 9H-xanthines was conducted by the simple HMO method with

TABLE 3. ^{13}C NMR Spectra of N-Aminoxanthines (I, IVa, b)

Compound	Solvent	Chemical shifts, δ, ppm (J, Hz)						
		$N_{(1)}-CH_3$, q	$N_{(3)}-CH_3$, q	$C_{(5)}$, d	$C_{(8)}$, d	$C_{(4)}$	$C_{(2)}$	$C_{(6)}$, q
I	DMSO-D_6	28,20 (^1J=141,1)	29,91 (^1J=141,6)	107,61 (^3J=4,8)	142,76 (^1J=214,2)	147,76 m	152,12q/q ($^3J=^3J$=3,1)	155,12 (^3J=2,3)
IVa	D_2O (pD ~ 12)	28,87 (^1J=140,8)	—	113,34 (^3J=11,3)	139,76 (^1J=214,2)	151,15 d (^3J=4,3)	160,30 q (^3J=2,7)	161,70 (^3J=2,7)
IVb	DMSO-D_6	28,96 (^1J=140,8)	31,40 (^1J=142,4)	115,31 (^3J=11,8)	140,30 (^1J=216,3)	139,43 m	152,16 m	157,89 (^3J=3,7)

TABLE 4. Mass-Spectroscopic Fragmentation of N-Aminoxanthines (I, IVa, b)*

Compound	m/z (I/I_{max})						
	$[M+1]^+$	$M^{+\cdot}$**	$[M-NH]^+$	$[M-CO]^+$	$[M-NH-CO]^+$	$[M-CO-HCN]^+$	$[M-CH_3NCO]^+$
I	196 (9)	195 (100) [25,3]	—	—	152 (2)	140 (9)	138 (6), 123 (2), 122 (3), 111 (14), 110 (29)
IVa	182 (8)	181 (100) [22,0]	166 (9)	153 (7)	—	151 (5)	124 (73), 110 (10), 109 (6)
IVb	196 (9)	195 (100) [23,2]	180 (5)	—	—	—	138 (55), 123 (3), 122 (4), 110 (16)

*Ions with m/z < 100 are not given.
**The W_M values are given in brackets.

Streitwieser's parameters [11]. The reactions and the purity of the obtained compounds were monitored by TLC on aluminum oxide of III Brockman activity, on silica gel 40/100, or on Silufol UV-254 plates with development in UV light. The data from elemental analysis for C, H, N, and Br agreed with the calculated data.

Oxidation of 7-Aminotheophylline (I). A. To a suspension of 1.0 g (5 mmole) of the amine (I) in 25 ml of water over 3-5 min we added 80 ml of bromine water [0.8 ml (14 mmole) of bromine in 80 ml of water]. The initial substance dissolved, and a yellow solution was formed. It was stirred at 20°C for 1 h and left overnight in the refrigerator. The orange precipitate was filtered off and washed with a small amount of cold water. The yield of isofervenulin (III) was 0.37 g (40%), and the product formed pale-yellow needles; mp 209-211°C (from butanol), which agrees with published data [2]. The isofervenulin obtained in this and subsequent experiments did not give a melting-point depression with an authentic sample.

B. To a solution of 0.39 g (2 mmole) of the amine (I) in 5 ml of concentrated sulfuric acid we added dropwise 0.1 ml (2.5 mmole) of nitric acid (d = 1.52) at 0-5°C. The mixture was stirred at 0-5°C for 30 min and at 20°C for 1 h, poured onto 15 g of ice, and extracted with chloroform (4 × 20 ml). After evaporation of the solvent the residue was recrystallized from butanol. The yield of (III) was 0.15 g (40%).

C. A mixture of 0.2 g (1 mmole) of the amine (I), 0.24 g (2 mmole) of potassium chlorate, and 8 ml of 5% sulfuric acid was heated at 80°C for 2 h. After cooling it was treated with concentrated ammonium hydroxide to pH 4-5 and extracted with chloroform (3 × 15 ml). The chloroform solution was concentrated to 10 ml and passed through a column (2 × 30 cm) of aluminum oxide and eluted with chloroform. The first yellow fraction with R_f 0.33 was collected. The yield of (III) was 0.15 g (75%).

D. To a suspension of 0.5 g (2.5 mmoles) of the amine (I) in 20 ml of methanol we added 1.15 g (5 mmoles) of periodic acid. The orange solution was stirred at 20°C for 1 h, and a precipitate gradually formed. The methanol was evaporated, the residue was rubbed with 10 ml of water, and the precipitate was filtered off and washed on the filter at first with ammonia and then with water. It weighed 0.2 g. The filtrate was extracted with chloroform (3 × 20 ml). After evaporation of the solvent a further 0.1 g of the substance was obtained. The total yield of (III) was 0.3 g (62%).

E. A mixture of 0.2 g (1 mmole) of the amine (I) and 0.24 g (1.5 mmoles) of potassium permanganate in 10 ml of 5% sulfuric acid was heated at 80°C for 2 h. On cooling ammonia was added to pH 4-5, and the mixture was extracted with chloroform (2 × 15 ml). The chloroform solution was concentrated to 10 ml and purified by column chromatography (2 × 30 cm) with aluminum oxide and with chloroform as eluant. The first yellow fraction with R_f 0.33 was collected. The yield of isofervenulin (III) was 0.16 g (79%).

F. A solution of 0.2 g (1 mmole) of the amine (I) in 10 ml of 30% hydrogen peroxide was stirred at 80°C for 2 h. The mixture was poured onto aluminum oxide (20 g), dried in air, transferred to a column (2 × 30 cm) with aluminum oxide (80 g), and isolated as described above. The yield of isofervenulin was 0.1 g (50%).

Oxidation of 1-Methyl-9-aminoxanthine (IVa). A. A mixture of 0.18 g (1 mmole) of the amine (IVa) and 0.24 g (2 mmoles) of potassium chlorate in 10 ml of 5% sulfuric acid was stirred at 80°C for 2 h. On cooling the mixture was treated with ammonia to pH 4-5 and poured onto silica gel (20 g). The silica gel was dried in air, placed in a column (2 × 30 cm) with silica gel (40 g), and eluted with ethyl acetate. The fraction with R_f 0.6 was collected. The rheumycin was recrystallized twice from methanol. The yield was 0.025 g (13%), and the product formed bright-yellow crystals; mp 244-245°C, which corresponds to [12]. The rheumycin obtained in this and subsequent experiments did not give a melting-point depression in a mixed melting test with an authentic sample.

B. A solution of 0.18 g (1 mmole) of the amine (IVa) and 0.34 g (1.5 mmoles) of periodic acid in 10 ml of water was stirred at 80°C for 2 h, and the solution acquired a yellowish-brown color. The product was isolated and purified as in method A. The yield of (VIa) was 0.02 g (10%).

C. A mixture of 0.18 g (1 mmole) of the amine (IVa) and 0.24 g (1.5 mmoles) of potassium permanganate in 10 ml of 5% sulfuric acid was heated at 80°C for 2 h. On cooling the mixture was treated with ammonia to pH 4-5. The product was isolated and purified as in method A. The yield of rheumycin was 0.025 g (13%).

D. A solution of 0.18 g (1 mmole) of the amine (IVa) in 15 ml of 30% hydrogen peroxide was stirred at 80°C for 2 h. The product was isolated and purified as in method A. The yield of rheumycin was 0.07 g (39%). Increase in the reaction time led to a decrease in the yield of rheumycin.

Oxidation of 9-Aminotheophylline (IVb). The oxidation was realized similarly to the oxidation of the amine (IVa). The product fervenulin (VIb) (Table 1) formed bright-yellow crystals; mp 175-176°C, which agrees with published data [12]. Mixed melting tests with an authentic sample of fervenulin did not give a melting-point depression.

7-Amino-8-bromotheophylline (IX). To a solution of 0.39 g (2 mmoles) of the amine (I) in 10 ml of glacial acetic acid we added dropwise 0.1 ml (2 mmoles) of bromine. A red-orange precipitate separated, and it dissolved at 60°C. The solution was stirred at 70°C for 2 h, and the acetic acid was distilled at reduced pressure. The residue was rubbed with water, and the cream-colored precipitate was filtered off. The yield of (IX) was 0.11 g (20%); mp 201-202°C (decomp., from water), which corresponds to published data [2]. A mixed melting test with an authentic sample did not give a melting-point depression.

7-Amino-8-nitrotheophylline (X, $C_7H_8N_6O_4 \cdot H_2O$). To a solution of 1.0 g (5 mmoles) of the amine (I) in 5 ml of glacial acetic acid we added dropwise 0.2 ml (5 mmoles) of nitric acid (d = 1.52) at 40°C. The mixture was stirred at 70°C for 2 h. The acetic acid was distilled at reduced pressure, and the residue was recrystallized from water. The yield of (X) was 0.48 g (40%), and the product formed yellow crystals; mp 275-277°C (decomp.). IR spectrum: 1650, 1690 (CO), 2400-3600 (NH), 3400, 3480 cm^{-1} (water). PMR spectrum (DMSO-D_6): 3.20 (3H, s, N—CH_3), 3.30 (3H, s, N—CH_3), 5.65 ppm (b, NH_2, disappears after deuteration).

1-Methyl-8-bromo-9-aminoxanthine (VIIa, $C_6H_6BrN_5O_2$). A. To a solution of 0.43 g (2.4 mmoles) of the amine (IVa) in 10 ml of hydrobromic acid (1:5) we added, in portions, the bromine water obtained by dissolving 0.26 ml (3.75 mmoles) of bromine in 40 ml of water. A precipitate separated. After 1 h it dissolved, and a new precipitate began to form. After 12 h, the precipitate was filtered off and washed with water, alcohol, and ether. It weighed 0.38 g. The filtrate was evaporated to dryness, and the residue was rubbed with alcohol and separated. The yield was 0.17 g. The total yield of (VIIa) was 0.55 g (88%), and the product formed fibrous needles; mp 256-257°C (decomp., from water). IR spectrum: 1602, 1635, 1720 (CO), 3335 cm^{-1} (NH). Mass spectrum, m/z (I_{rel}, %): M^+ 261 (75.7), 259 (78.4), $[M - NH]^+$ 246 (5.15), 244 (5.35), $[M - 1\text{-}HNCO]^+$ 217 (32.1), 215 (99.36), $[M - CH_3NCO]^+$ 204 (78.1), 202 (78.1), $[M - Br]^+$ 180 (25.3), 160 (33.5), 158 (97.3), 142 (22.0), 137 (13.9), 130 (14.3), 123 (18.6), 121 (16.1), 109 (10.5), 103 (17.5), 101 (4.4).

B. To a suspension of 0.2 g (1 mmole) of the amine (IVa) in 15 ml of glacial acetic acid we added dropwise 0.06 ml (1.1 mmoles) of bromine. The mixture was stirred at 80°C for 2 h. On cooling the precipitate was filtered off and washed with a small amount of ice water. The yield of (VIIa) was 0.17 g (65%). A mixed melting test with a sample from experiment A did not give a melting-point depression.

8-Bromo-9-aminotheophylline (VIIb, $C_7H_8BrN_5O_2$). The compound was obtained similarly to (VIIa) by methods A and B with yields of 98 and 74%, respectively. The product formed colorless needles; mp 225-227°C (decomp., from water). IR spectrum: 1622, 1658, 1698 (CO), 3230, 3320 cm^{-1} (NH).

The Action of a Nitrating Mixture on 9-Aminotheophylline (IVb). To a solution of 0.2 g (1 mmole) of the amine (IVb) in 3 ml of concentrated sulfuric acid we added dropwise 0.06 ml (1.5 mmoles) of nitric acid (d = 1.52), and we stirred the mixture at 80°C for 1 h. On cooling the mixture was poured onto 10 g of ice and treated with ammonia to pH 4-5. The precipitate was filtered off and recrystallized from water. The yield of theophylline was 0.07 g (38%), and the product formed a white powder; mp 272-274°C. A mixed melting test with an authentic sample of theophylline did not give a melting-point depression.

1-Methyl-9-aminoxanthinium Nitrate (VIIIa, $C_6H_7N_5O_2 \cdot HNO_3$). A 0.4-g sample (2.2 mmoles) of the amine (IVa) was dissolved in 5 ml of concentrated sulfuric acid at 5°C, and 0.12 ml (3 mmoles) of nitric acid (d = 1.52) was then added dropwise with stirring at a temperature not higher than 5°C. The mixture was stirred at 5°C for 30 min and at 20°C for 1 h. It was then poured onto 20 g of ice. The precipitate was filtered off and washed with water. The yield of the nitrate (VIIIa) was 0.25 g (56%), and the product formed colorless crystals; mp >320°C (from water). IR spectrum: 1675, 1715 (CO), 2400-3200, 3145 cm^{-1} (NH). PMR spectrum (DMSO-D_6): 3.15 (3H, s, N—CH_3), 6.25-6.75 (b, NH), 8.92 ppm (1H, s, $H_{(8)}$).

A similar product was formed after 2 h when the amine (IVa) was heated in the nitrating mixture at 40-50°C or treated with nitric acid (d = 1.37) at 50-60°C for 3-5 min.

When 0.24 g (1 mmole) of the nitrate (VIIIa) and 0.06 g (1.1 mmoles) of potassium hydroxide were heated in 4 ml of water for 2-3 min, a precipitate of the amine (IVa) was formed. The product formed colorless crystals; mp 305-306°C (from water). A mixed melting test with the authentic amine (IVa) did not give a melting-point depression.

LITERATURE CITED

1. V. V. Kuz'menko, A. V. Gulevskaya, and A. F. Pozharskii, Zh. Org. Khim., 24, 1524 (1988).
2. A. F. Pozharskii, I. M. Nanavyan, and V. V. Kuz'menko, Khim. Geterotsikl. Soedin., No. 11, 1564 (1983).
3. S. V. Shorshnev, S. E. Esipov, A. I. Chernyshev, A. F. Pozharskii, I. M. Nanavyan, and V. V. Kuz'menko, Khim. Geterotsikl. Soedin., No. 11, 1555 (1987).
4. V. V. Kuz'menko, T. A. Kuz'menko, G. G. Aleksandrov, A. F. Pozharskii, and A. V. Gulevskaya, Khim. Geterotsikl. Soedin., No. 6, 836 (1987).
5. V. A. Rabinovich and Z. Ya. Khavin, Concise Chemical Reference Book [in Russian], Khimiya, Leningrad (1978), p. 312.
6. B. V. Ioffe, M. A. Kuznetsov, and A. A. Potekhin, Chemistry of Organic Derivatives of Hydrazine [in Russian], Khimiya, Leningrad (1979), p. 104.
7. A. F. Pozharskii, V. V. Kuz'menko, A. A. Bumber, É. S. Petrov, M. I. Terekhova, N. L. Chikina, and I. M. Nanavyan, Khim. Geterotsikl. Soedin. (1989) (in press).
8. R. J. Pugmire and D. M. Grant, J. Am. Chem. Soc., 93, 1880 (1971).
9. A. F. Pozharskii, Theoretical Principles of the Chemistry of Heterocycles [in Russian], Khimiya, Moscow (1985), p. 58.
10. S. E. Esipov, M. A. Klyuev, L. A. Saburova, and V. M. Adanin, Khim. Prikl. Spektr., No. 1, 85 (1981).
11. A. Stretiwieser, Molecular Orbital Theory [Russian translation], Mir, Moscow (1965), p. 126.
12. S. E. Esipov, M. N. Kolosov, and L. A. Saburova, J. Antibiotics, 26, No. 9, 537 (1973).
13. W. Pfleiderer and K. H. Schundenhütte, Lieb. Ann., 615, 42 (1958).

TEMPLATE SYNTHESIS OF METAL COMPLEXES OF 7,16-DISUBSTITUTED DIBENZO[b,i][1,4,8,11]TETRAAZA[14]ANNULENES FROM MALONIC ALDEHYDE ACETALS

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Metal complexes of 7,16-dialkyl- and 7,16-diphenyldibenzo[b,i][1,4,8,11]tetraaza[14]annulenes have been prepared by template condensation of o-phenylenediamine with 2-alkyl- and 2-phenyl-1,1,3,3-tetraethoxypropanes, respectively, in the presence of divalent metals salts. The effects of substituents in the meso-position and of the metal ion on the nature of the electronic and vibrational spectra of these metal complexes are discussed.

The chemistry of nitrogenous macroheterocycles has attracted increased research interest recently [1, 2]. Members of this class of chemical compounds are finding practical applications in new areas [3]. The bis(dimethylacetal) of malonaldehyde has been used successfully in the synthesis of unsubstituted (in the meso-position) nickel complexes of dibenzo[b,i] ×

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