ELECTROPHILIC AND NUCLEOPHILIC SUBSTITUTION REACTIONS IN THE SERIES OF 3-METHYLXANTHINE AND ITS DERIVATIVES

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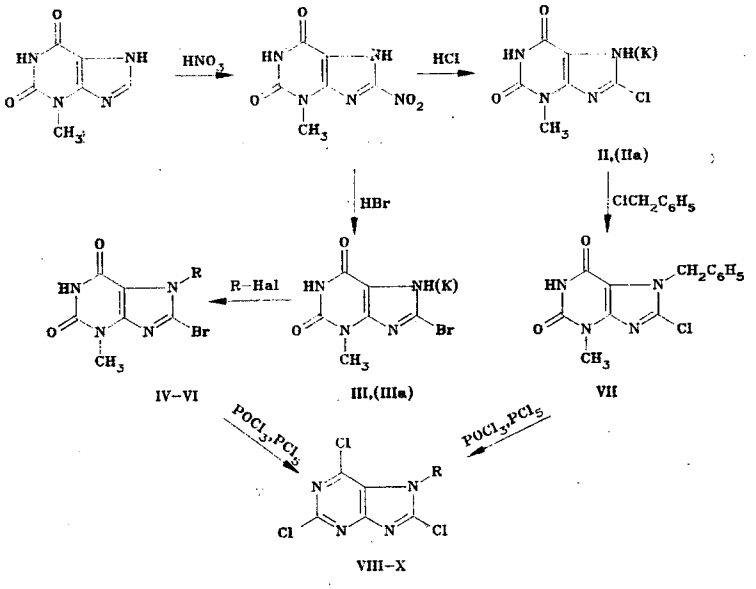
The reactions of nitration and bromination of 3-methylxanthine were studied. Heating 3-methyl-8-nitroxanthine with conc. HCl and HBr leads to a replacement of the nitro group by a halogen atom. The alkylation of 8-haloxanthines by alkyl halides were studied. It was shown that boiling 7-substituted 3-methyl-8-bromoxanthine derivatives with $POCl_3$ and PCl_5 leads to the formation of 2,6,8-trichloro-7-alkylpurines. The structure of the synthesized compounds was confirmed by counter-synthesis, the data of elementary analysis, and mass spectrometry.

It is known that theophylline, theobromine, and caffeine enter into electrophilic substitution reactions [1-3]. 3-Methylxanthine has been virtually unstudied from this standpoint, although it is their analog. In this work we attempted to carry out the bromination and nitration of 3-methylxanthine and to study the behavior of 8-bromo- and 8-nitroderivatives toward certain electrophilic and nucleophilic reagents. It was established experimentally that the heating of 3-methylxanthine with conc. HNO_3 in glacial acetic acid leads to 3-methyl-8-nitroxanthine (I). Analogously to [4], the bromination of 3-methylxanthine by potassium bromate and the hydrobromic acid reaction in glacial CH_3COOH also proceed at the 8-position. As a result, 8-bromo-3-methylxanthine (III) was obtained in a high yield.



IV, VIII R=CH_3; V, IX R=$CH_2C_6H_5$; VI, X R=$CH_2CH_2OC_6H_5$

It was found that the bormine III is formed in a good yield after brief boiling of the nitroxanthine I with hydrobromic acid, as was shown earlier for other 8-nitroxanthines [5]. The nitro group is also exchanged for a chlorine atom when compound I is heated with conc. HCl; in this case 3-methyl-8-chloroxanthine (II) identical with the sample described according to the method of [6], is formed.

To study the alkylation of compounds II and III, we obtained the potassium salts IIa and IIIa by the usual method [7]. In previous studies [7, 8] we established that 3-methyl-8-

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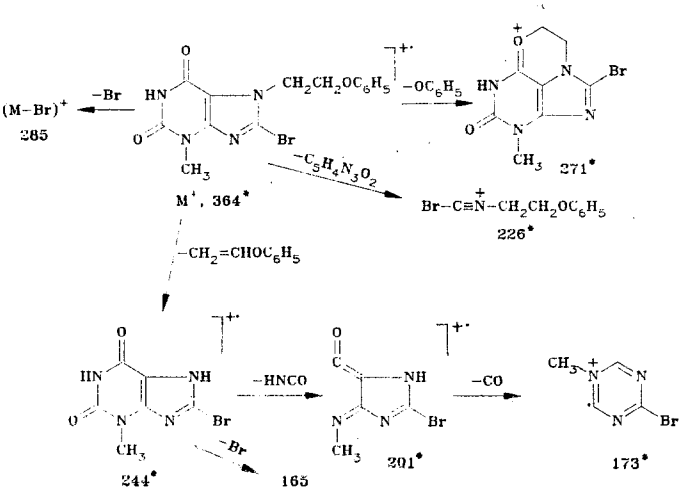
TABLE 1. Characteristics of the Synthesized Compounds I-III, V-X

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, % (method)
		C	H	Hal	N		C	H	Hal	N	
I	324	34,1	2,6	—	33,7	$C_6H_5N_5O_4$	34,1	2,4	—	33,2	83
II	>350 (dec.)	35,8	2,8	17,4	28,1	$C_6H_5ClN_4O_2$	35,9	2,5	17,7	27,9	54
III	>330 (dec.)	29,5	2,2	32,5	22,8	$C_6H_5BrN_4O_2$	29,4	2,0	32,6	22,9	83 (А), 64 (Б)
V	241—242	46,4	3,5	23,6	16,6	$C_{13}H_{11}BrN_4O_2$	46,6	3,3	23,8	16,7	75
VI	207	46,2	3,7	21,6	15,0	$C_{14}H_{13}BrN_4O_3$	46,0	3,6	21,9	15,3	77
VII	233—235	53,6	3,5	12,3	19,3	$C_{13}H_{11}ClN_4O_2$	53,7	3,8	12,2	19,3	82
VIII	156—157	30,2	1,5	44,5	23,5	$C_6H_3Cl_3N_4$	30,3	1,3	44,8	23,6	84
IX	138—139	45,8	2,3	33,8	17,6	$C_{12}H_7Cl_3N_4$	46,0	2,2	33,9	17,9	60
X	168	45,2	3,0	31,0	16,8	$C_{13}H_9Cl_3N_4O$	45,4	2,6	31,0	16,3	90

chloroxanthine is alkylated by haloalcohols and haloketones at the 7-position of the imidazole fragment of the molecule. Under analogous conditions the reaction of the salt IIIa with methyl iodide, benzyl chloride, and β-bromoethoxybenzene leads to the formation of the corresponding compounds IV-VI, substituted in the 7-position. The melting point of 8-bromotheobromine (IV) coincides with the data of [4]. For more convincing evidence of the structure of compounds IV-VI we made a mass spectrometric study of 3-methyl-7-(β-phenoxyethyl)-8-bromoxanthine (VI). The peaks M^+ with m/z 364 and 366, with a 1:1 intensity distribution, were recorded in the mass spectrum of compound VI, which is an indication of the presence of one bromine atom in the molecule. The decomposition of M^+ of compound VI can be represented by the scheme:*



The reaction of xanthines with $POCl_3$ and PCl_5 has been studied in rather great detail [9]. However, there are no data in the literature on the behavior of 8-bromoxanthines under analogous conditions. It was found that brief heating of compounds IV-VI in excess $POCl_3$ and PCl_5 unexpectedly leads to 7-substituted 2,6,8-trichloropurine derivatives VIII-X, i.e., there is not only a replacement of oxygen atoms but also a replacement of bromine atoms. Thus, in the reaction of the bromide IV with $POCl_3$ and PCl_5, a substance identical with 2,6,8-trichloro-7-methylpurine (VIII), synthesized previously by another method [10], was formed. We also carried out the counter-synthesis of compound IX by alkylation of the salt IIa with benzyl chloride in DMFA, followed by heating of the 3-methyl-7-benzyl-8-chloroxanthine (VII) formed with $POCl_3$ and PCl_5. A mixed melting point test of samples IX, produced from the chloro-derivative IIa and the bromide V, gave no depression of the melting point. In the mass spectra of compounds VIII and X the peaks of the molecular ions with m/z 236:238:240 and 342:344:346, respectively, were recorded. The nature of the distribution of the intensities of the peaks with M^+ 100:94.2:29.9 for compound VIII and 100:92.5:19.1 for compound X shows the presence of three chlorine atoms in the molecules of VIII and X.

Possibly at the first stage of transhalogenation, a complex is formed (according to the CTC type) between the electron-deficient phosphorus and the unshared pair of electrons of the

*The masses of the ions containing ^{79}Br are cited.

TABLE 2. Mass Spectra of the Synthesized Compounds*

Compound	m/z (intensity of the peaks in % of the maximum)
VI	51 (15); 65 (35); 67 (32); 77 (100); 78 (10); 79* (18); 91 (25); 93 (7); 94 (11); 107 (20); 111 (10); 120 (70); 121 (53); 122 (9); 173* (7); 201* (14); 244* (52); 271* (21); 285 (13); 364* (19)
VIII	52 (19); 53 (11); 58 (27); 61 (9); 67 (47); 68 (14); 73 (23); 76 (13); 77 (12); 87 (12); 88 (7); 105 (12); 123 (17); 131 (6); 134 (12); 140 (8); 142 (3); 151 (12); 166* (29); 201* (90); 202 (8); 204 (5); 205 (9); 236* (100); 237 (9); 239 (8)
X	51 (10); 61 (5); 65 (12); 66 (12); 67 (53); 77 (51); 79 (16); 85 (17); 93 (4); 94 (12); 95 (12); 107 (72); 108 (7); 111 (12); 121 (4); 123 (24); 131 (4); 151 (16); 152 (6); 166* (9); 179 (11); 201* (26); 213* (4); 236* (26); 239 (8); 307* (4); 342* (100); 343 (25); 345 (10)

*The peaks of the ions with intensity 3% (for VIII, X), 5% for VI are cited. The temperature of heating of the system of admission for VI was 165°C, for VIII 80°C, and for X 120°C. The peaks of the isotropic halide ions are excluded.

$N_{(9)}$ atom. This, in turn, induces a displacement of the pair of π-electrons from the $C_{(8)}=N_{(9)}$ bond to the nitrogen atom, as a result of which the electron density of the carbon atom in the 8-position is sharply lowered, and it becomes susceptible to nucleophilic attack, which is also realized at the last stage of the reaction, consisting of displacement of a bromine atom by a chlorine atom. However, additional investigations will be necessary to resolve this question.

EXPERIMENTAL

The mass spectra were recorded on a Varian MAT-311A instrument with direct introduction of the sample into the ion source, accelerating voltage 3 kV, emission current of the cathode 300 μA, ionizing voltage 70 eV.

3-Methyl-8-nitroxanthine (I). A mixture of 66.45 g (0.4 mole) 3-methylxanthine and 150 ml of glacial CH_3COOH was heated to 120°C, and 30 ml of 62% HNO_3 was added dropwise at this temperature over a period of 1 h. After the addition of all the acid, the mixture was mixed for another 30 min, cooled, the precipitate filtered off, washed with n-propanol, dried, and crystallized from water. The characteristics of compounds I-III, V-X are cited in Table 1.

3-Methyl-8-chloroxanthine (II). A suspension of 4.2 g (0.02 mole) of compound I in 40 ml of conc. HCl was boiled for 4 h. It was cooled, diluted with water, the precipitate filtered off, washed with water, and dried.

3-Methyl-8-bromoxanthine (III). A. In a mixture of 350 ml of glacial CH_3COOH and 150 ml conc. HBr was suspended 49.84 g (0.3 mole) of 3-methylxanthine. The suspension was mixed vigorously and heated to 50°C. Then 25.05 g (0.15 mole) of $KBrO_3$ was introduced in small portions. The mixture was kept at this temperature within the range 80-95°C. After addition of all the potassium bromate (10-12 h), the reaction mixture was mixed at 80-95°C for another 12 h, left at room temperature for 24 h, the precipitate filtered off, washed thoroughly with water, and dried.

B. A mixture of 4.2 g (0.02 mole) of compound I and 30 ml of conc. HBr was boiled for 4 h. It was cooled, diluted with water, the precipitate filtered off and dried.

Potassium salts IIa and IIIa were produced according to the method of [7].

Alkylation of Salts IIa and IIIa by Methyl Iodide, Benzyl Chloride, and β-Bromoethoxybenzene. A mixture of 0.1 mole of the salt IIa or IIIa, 0.12 mole of the corresponding alkyl halide, and 150 ml DMFA was boiled with vigorous mixing for 1 h 30 min to 2 h, cooled, the reaction mixture diluted with water, the precipitate filtered off, washed with water, with acetone, and dried. Compounds IV-VII were obtained. They were crystallized from aqueous DMFA. 8-Bromotheobromine was obtained with a yield of 65%, mp 296-298°C. According to the data of [4], mp 294-298°C.

Chlorination of Compounds IV-VII. A mixture of 0.1 mole of compounds IV-VII was boiled in 300-400 ml of $POCl_3$ for 5-6 h, cooled, 0.2 mole of PCl_5 was added, and the mixture boiled for another 5 h. The excess $POCl_3$ was distilled off and the residue poured out into ice. It

was neutralized with 25% NH_4OH without permitting the mixture to heat up. The precipitates were filtered off, washed with ice water, and dried in air. The products were crystallized from ethanol (VIII), n-propanol (IX), and acetone (X).

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BROMINATION OF 8R-4-PHENYL-2,3-DIHYDRO-1H-1,5-BENZODIAZEPINONES-2

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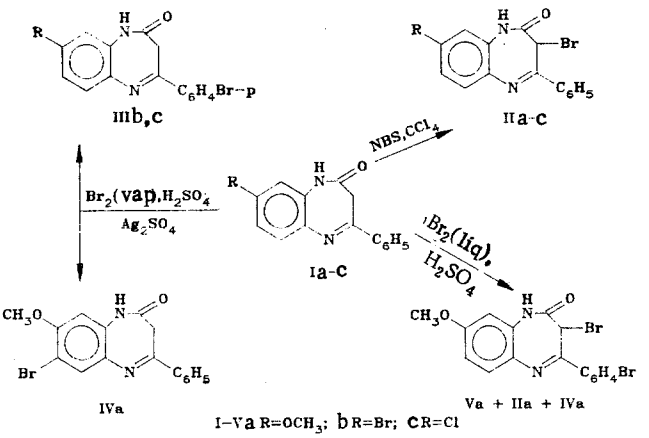
The influence of the nature of the substituents and the brominating agent on the direction of the bromination of 8R-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepinones-2 containing various substituents in the annelated benzene ring.

Protonation of the heterocycle deactivates the annelated benzene ring of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepinone-2 and promotes the incorporation of bromine into the phenyl radical [1]. This communication is devoted to a study of the bromination of 8R-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepinones-2 (Ia-c), containing substituents of different types in the benzene ring of the heterocycle:



I-V a R=OCH_3; b R=Br; c R=Cl

Bromination of compounds Ia-c by N-bromosuccinimide in CCl_4 solution with heating for 6 h leads to 3-bromo-4-phenyl-8R-2,3-dihydro-1H-1,5-benzodiazepinones-2 (IIa-c). The PMR spectra of compounds IIa-c contain a singlet of the methine proton at 6.02-6.04 ppm. The product of acid hydrolysis [2] of compounds IIa-c is α-bromoacetophenone, which confirms the indicated reaction pathway.

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