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HETEROCYCLIC DERIVATIVES OF PURINES.

4.* REACTIONS OF THIAZOLO[3,2-f]XANTHINES

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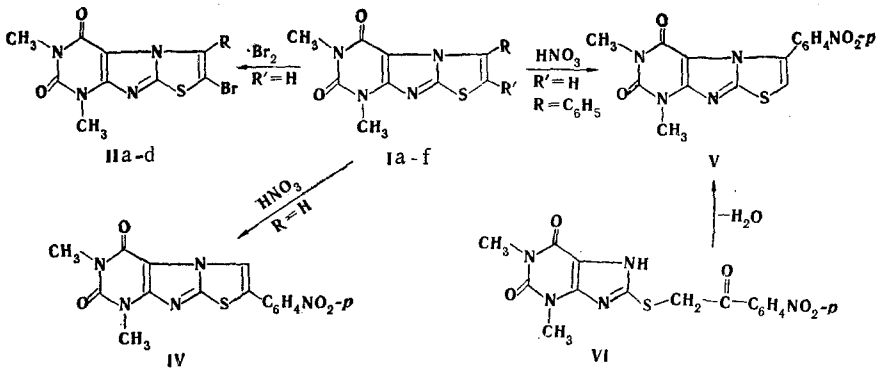
The chemical transformations of 2- and 3-substituted thiazolo[3,2-f]xanthines with electrophilic reagents were studied, and it was established that the 2 position of the thiazole ring is active in bromination, while the para position of the aryl substituent is active in nitration. The structures of the substances obtained were established from the IR, PMR, and mass-spectral data.

We have previously observed [2] that imidazo[1,2-f]xanthines readily undergo electrophilic substitution, as a result of which derivatives that have physiological activity are formed. The synthesis of these substances by other methods is either extremely complex or is completely impossible. In a continuation of our research on condensed heterocyclic derivatives of purine we verified the possibility of the direct replacement of the hydrogen atoms by electrophilic reagents in the case of 2- or 3-substituted thiazolo[3,2-f]xanthines, the chemical properties of which have not been investigated up until now. We attempted to determine the conditions for carrying out the bromination, nitration, acylation, formylation, and hydroxy-, amino-, and chloromethylation of 2- or 3-substituted thiazolo[3,2-f]xanthines (Ia-f).

In contrast to imidazo[1,2-f]xanthines [2], the bromination of Ia-f with molecular bromine or N-bromosuccinimide under various conditions takes place only in the 2 position of the thiazole ring to give 2-bromo derivatives (IIa-d). We were unable to realize the bromination of 2-substituted thiazolo[3,2-f]xanthines in the free 3 position.



Ia R=R′=H; Ib R=CH$_3$, R′=H; Ic R=C$_6$H$_5$, R′=H; Id R=C$_6$H$_4$Br-*p*, R′=H; Ie R=H, R′=CH$_3$; If R=H, R′=C$_6$H$_5$; IIa R=H; IIb R=CH$_3$; IIc R=C$_6$H$_5$; IId R=C$_6$H$_4$Br-*p*; V R′=H; IV R=H

The bromine atoms in IIa-d are inactive in nucleophilic substitution reactions and do not undergo exchange in the case of interaction of these compounds with ammonia and various amines.

*See [1] for Communication 3.

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TABLE 1. Data from the PMR Spectra of Thiazolo[3,2-f]xanthine Derivatives

Compound	Chemical shifts, ppm			
	N_8—CH_3	N_8—CH_3	R	R′
Ib	3,24 (s, 3H)	3,44 (s, 3H)	2,71 (d, 3H, J=1,25 Hz)	7,01 (d, 1H, J=1,25 Hz)
Ie	3,28 (s, 3H)	3,48 (s, 3H)	7,87 (s, 1H)	2,58 (s, 3H)
IIc	3,06 (s, 3H)	3,48 (s, 3H)	7,50 (m, 5H)	—
IId	3,18 (s, 3H)	3,45 (s, 3H)	AB system : ν_{A+B}=7,53, J_{AB}=10,5 Hz	—
IV	3,38 (s, 3H)	3,55 (s, 3H)	7,23 (s, 1H)	AB system ν_{A+B}=8,03, J_{AB}=9,3 Hz
V	3,12 (s, 3H)	3,42 (s, 3H)	AB system : ν_{A+B}=8,07, J_{AB}=9 Hz	7,58 (s, 1H)

TABLE 2. Mass Spectra of Thiazolo[3,2-f]xanthine Derivatives

Compound	m/z values (ratio of the intensity to the intensity of the maximum peak, %)
IIa	57 (18,0), 61 (13,0), 62 (5,2), 63 (74,1), 67 (39,0), 70 (18,3), 78 (60,0), 79 (6,7), 80 (8,7), 81 (6,7), 83 (17,4), 99 (27,5), 109 (27,5), 123 (11,5), 125 (10,3), 150 (24,6), 151 (19,0), 178 (8,7), 204 (8,9), 228 (19,7), 229 (47,9), 230 (31,8), 231 (48,5), 232 (13,3), 257 (30,6), 258 (9,4), 259 (31,8), 285 (8,1), 314 (94,4), 315 (11,5), 316 (100,0), 317 (11,2); W_M=7,5%
IIb	42 (13,6), 43 (6,4), 45 (12,4), 55 (5,0), 57 (7,5), 67 (29,9), 70 (17,8), 71 (11,5), 72 (7,5), 80 (6,1), 82 (5,9), 94 (7,0), 99 (19,4), 123 (9,8), 137 (4,4), 164 (14,0), 165 (10,4), 192 (4,9), 216 (8,9), 217 (5,3), 218 (9,4), 219 (5,7), 242 (19,4), 243 (36,7), 244 (27,3), 245 (41,5), 271 (23,8), 272 (7,6), 273 (24,0), 274 (3,0), 299 (3,9), 301 (3,8), 328 (100,0), 329 (12,7), 330 (98,7), 331 (12,9); W_M=11,3%
IIc	51 (6,7), 57 (5,5), 63 (6,0), 67 (24,0), 75 (6,5), 78 (8,8), 80 (3,5), 82 (3,4), 89 (2,8), 93 (4,1), 99 (27,6), 100 (5,6), 101 (9,2), 113 (5,8), 114 (8,0), 115 (5,3), 121 (4,0), 127 (13,6), 133 (14,0), 141 (8,0), 155 (17,1), 158 (7,3), 159 (17,8), 184 (5,0), 185 (12,0), 196 (6,0), 197 (7,8), 226 (9,9), 254 (6,7), 276 (13,2), 278 (14,1), 304 (5,0), 305 (11,7), 306 (7,6), 307 (11,6), 316 (23,8), 317 (4,6), 318 (24,0), 319 (4,5), 332 (42,3), 333 (16,8), 334 (46,5), 335 (17,5), 390 (100,0), 391 (20,3), 392 (92,4), 393 (18,9); W_M=8,9%
IId	56 (17,0), 58 (12,5), 63 (14,8), 67 (63,4), 70 (15,8), 72 (12,8), 74 (13,7), 75 (16,3), 77 (11,2), 80 (8,6), 82 (7,9), 88 (8,9), 89 (10,6), 93 (10,9), 99 (71,4), 100 (20,4), 101 (11,5), 112 (13,9), 114 (23,2), 123 (5,4), 125 (5,4), 126 (12,8), 132 (19,4), 155 (6,3), 157 (6,2), 158 (11,8), 179 (7,8), 181 (7,8), 184 (15,5), 185 (17,6), 194 (33,6), 195 (35,0), 211 (10,3), 213 (9,3), 225 (9,6), 226 (10,1), 258 (7,0), 260 (12,4), 262 (6,9), 271 (12,6), 272 (26,6), 273 (7,0), 300 (11,8), 327 (15,9), 332 (11,4), 334 (12,8), 354 (11,3), 356 (20,9), 357 (56,9), 358 (15,4), 394 (13,5), 396 (26,8), 398 (13,9), 410 (13,2), 411 (8,6), 412 (34,4), 413 (15,8), 414 (18,9), 415 (8,9), 468 (49,6), 469 (10,0), 470 (100,0), 471 (19,3), 472 (55,2), 473 (8,8); W_M=3,9%
IV	57 (12,3), 63 (11,9), 67 (14,4), 69 (8,3), 70 (9,6), 74 (8,3), 75 (16,6), 76 (8,6), 77 (8,2), 89 (29,8), 99 (41,0), 101 (13,9), 114 (12,7), 127 (10,7), 133 (14,7), 147 (5,0), 159 (10,9), 173 (10,2), 179 (13,5), 185 (11,9), 199 (10,3), 200 (12,7), 225 (10,8), 226 (18,2), 245 (19,5), 271 (36,2), 272 (87,8), 273 (23,9), 299 (5,4), 300 (87,9), 311 (9,5), 327 (22,4), 328 (9,1), 357 (100,0), 358 (22,7); W_M=7,6%
V	45 (4,3), 51 (4,6), 57 (5,0), 73 (5,7), 75 (6,3), 99 (13,4), 100 (3,1), 101 (6,1), 114 (6,9), 127 (7,2), 155 (5,3), 197 (10,6), 198 (5,8), 226 (8,9), 232 (4,8), 243 (8,3), 244 (6,4), 245 (6,1), 246 (4,0), 271 (8,5), 272 (5,7), 299 (26,4), 300 (16,9), 301 (4,5), 310 (6,8), 311 (6,9), 327 (8,6), 328 (3,6), 357 (100,0), 358 (22,9); W_M=13,4%

In addition to bromination, we were unable to accomplish any of the electrophilic substitution reactions enumerated above, except for the nitration of 2- or 3-phenylthiazolo[3,2-f]xanthines (Ic, f), which takes place in the para position of the aryl substituent rather than in the thiazole ring.

The structures of the synthesized 2-bromo (IIa-d) and nitro (IV and V) derivatives were proved by alternative synthesis and the IR, PMR, and mass spectra. Thus nitro derivative V proved to be identical to the product of cyclization of 8-(p-nitrophenacylthio)-theophylline VI in phosphoric acid [3].

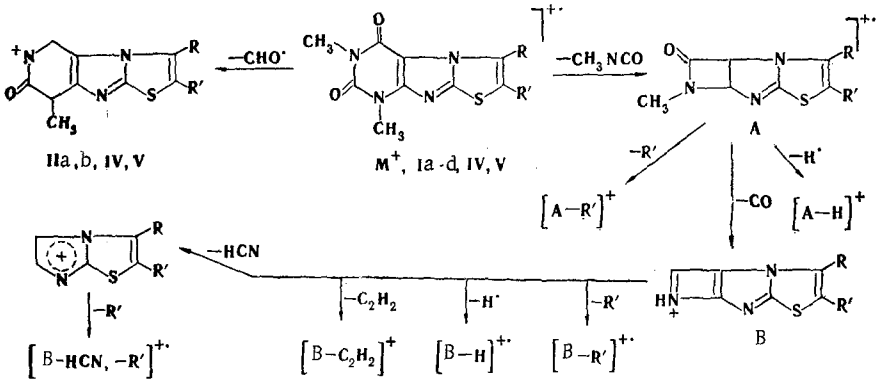
The IR spectra of the synthesized compounds contain individual bands of stretching and deformation vibrations of CH_3, NO_2, C=C, and other bands; however, this information is clearly not sufficient for the formation of a judgment regarding the site of substitution of the starting 2- or 3-substituted thiazolo[3,2-f]xanthines. The data from the PMR spectra make it possible to monitor this process more rigorously (Table 1).

TABLE 3. 6,8-Dimethylthiazolo[3,2-f]xanthines

Compound	mp,* °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Br	N		C	H	Br	N	
IIa	242—243	34,9	2,4	25,7	17,9	$C_9H_7BrN_4O_2$	34,3	2,2	25,4	17,8	50 (A)
IIb	200	36,6	2,4	24,4	17,2	$C_{10}H_9BrN_4O_2$	36,5	2,8	24,3	17,0	95 (A), 66 (B)
IIc	256—258	45,9	2,9	20,9	13,9	$C_{15}H_{11}BrN_4O_2$	46,0	2,8	20,5	14,3	98 (A), 70 (B)
IId	260	38,1	2,4	33,7	11,6	$C_{15}H_{10}Br_2N_4O_2$	38,3	2,2	34,0	11,9	90 (A)
IV	324—325	50,3	3,0	—	19,8	$C_{15}H_{11}N_5O_4$	50,4	3,1	—	19,6	82 (A)
V	354	50,6	3,7	—	19,4	$C_{15}H_{11}N_5O_4$	50,4	3,1	—	19,6	80 (A), 90 (B)

*The compounds were recrystallized: IIa from DMSO, IIb from aqueous dioxane, IIc from dioxane, IId from butanol—DMF (1:1), IV from acetic acid, and V from DMF—dioxane (2:1).

Thus the absence of a signal from a proton attached to the C_2 atom and the presence of a multiplet of aromatic protons centered at 7.50 ppm constitute evidence that the bromine atom in bromo derivative IIc is located in the 2 position. 2-Bromo-3-(p-bromophenyl) structure IId is confirmed by the absence of a signal of a proton attached to the C_2 atom and the presence of signals of an AB two-spin system centered at 7.53 ppm formed by the protons of the p-bromophenyl substituent attached to the C_3 atom. The position of the nitro group in IV and V is determined by the presence of signals of protons of a thiazole ring and the presence of an AB two-spin nuclear system formed by the protons of the p-nitroaryl substituent (Table 1).



The mass-spectrometric data also make it possible to rigorously monitor the trend of electrophilic substitution in the thiazolo[3,2-f]xanthine series. The overall trend of the fragmentation of the $M^{+\cdot}$ ions of Ib, IIa-c, and III-V in the first step is due to fragmentation of the dioxopyrimidine part of the molecule [2, 4, 5]; the subsequent fragmentation of the indicated compounds is presented in the scheme.

The presence of a bromine atom in the 2 position of the thiazole ring of 2-bromo derivatives IIa-d is confirmed by the presence in the mass spectra of these compounds of ion peaks with m/z 123 and 125,* which correspond to the $[SCBr]^+$ composition.

The structure of dibromo derivative IId is also confirmed by the presence in the spectrum of peaks of 179 and 181 ($\overset{+}{C}\equiv C-C_6H_4Br$-p) and 258, 260, and 262 ($[Br-C\equiv CC_6H_4Br$-p$]^+$) ions with a distribution of the intensities of the peaks of 1:2:1, respectively.

The peaks of 80 and 82 ions (HBr) constitute evidence for the presence of bromine atoms in the perbromide III molecule. Attempts to obtain M^+ peaks of the π complex of III even by means of field desorption (a solution in DMSO) were unsuccessful. In all cases we recorded ion peaks identical to those of the starting Ie.

The $[M - NO]^+$, $[M - NO_2]^+$, and $[M - NO_2, - H]^+$ ion peaks constitute evidence for the presence of a nitro group in IV and V. In addition, the position of the p-nitroaryl sub-

*The numbers that characterize the ions are the mass-to-charge ratios.

stituent in IV is confirmed by the presence in the mass spectrum of 179 ($[S{=}C{-}C_6H_4{-}NO_2\text{-}p]^+$) and 133 ($[S{=}C{=}C_6H_4]^+$) ions. Peaks of the indicated ions are not observed in the mass spectra of V.

EXPERIMENTAL

The IR spectra of KBR pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $CF_3COOH + D_2O$ and in $(CH_3)_2SO$ were recorded with a Bruker WH-90 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT-311A spectrometer under standard recording conditions [4] with direct introduction of the samples into the ion source.

6,8-Dimethylthiazolo[3,2-f]xanthines Ia-f. These compounds were obtained by the methods in [3, 6].

2-Bromo-6,8-dimethylthiazolo[3,2-f]xanthines (IIa-d). A) A solution of 11 mmole of bromine in 10 ml of $CHCl_3$ or CCl_4 was added dropwise to a solution of 10 mmole of Ia-d in the same solvent, and the mixture was stirred for 2 h. The solvent was evaporated, the residue was treated with water, and 2-bromo derivatives IIa-d were removed by filtration.

B) A 1.78-g (10 mmole) sample of N-bromosuccinimide was added to a solution of 5 mmole of Ib, c in 30 ml of CCl_4, and the mixture was refluxed for 3 h. It was then filtered, and the solvent was evaporated. The residue was treated with hot water, and the 2-bromo derivatives were removed by filtration. Compounds IIa-d were white crystalline substances (see Table 3).

2,6,8-Trimethylthiazolo[3,2-f]xanthine Perbromide (III). A 3.2-g (20 mmole) sample of bromine was added to a solution of 1.25 g (5 mmole) of Ie in 40 ml of CCl_4, and the resulting bright-orange crystals were removed by filtration, washed with $CHCl_3$ or CCl_4, and dried in a vacuum desiccator to give a product with mp 156-158°C (dec.) in 99% yield. Found: C 24.0; H 2.2; Br 49.0; N 10.9; S 6.3%. $C_{10}H_{10}Br_3N_4O_2S$. Calculated: C 24.5; H 2.1; Br 48.9; N 11.4; S 6.5%.

3-(p-Nitrophenyl)-6,8-dimethylthiazolo[3,2-f]xanthine (V). A) A solution of 1.01 g (10 mmole) of KNO_3 in 10 ml of H_2SO_4 was added dropwise to a solution of 3.12 g (10 mmole) of Ic in 30 ml of H_2SO_4 (sp. gr. 1.83), and the mixture was stirred for 3 h. It was then poured over 150 g of ice, and the resulting yellow precipitate was removed by filtration and washed repeatedly with water (Table 3).

B) Compound V was also obtained by the method in [3] by refluxing VI in phosphoric acid for 2.5 h.

2-(p-Nitrophenyl)-6,8-dimethylthiazolo[3,2-f]xanthine (IV). This compound was obtained by the reaction of equivalent amounts of If and KNO_3 in H_2SO_4 by the method used to prepare V (Table 3).

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