

RESEARCH IN THE IMIDAZOLE SERIES
 LXXXV.* SYNTHESIS OF THIAZOLO[2,3-f]XANTHINE
 DERIVATIVES FROM 8-BROMOTHEOPHYLLINE

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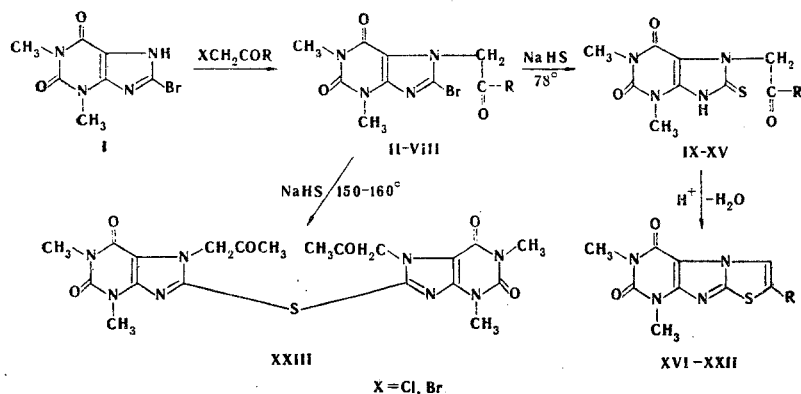
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2-Alkyl(aryl, hetaryl)-6,8-dimethylthiazolo[2,3-f]xanthines were synthesized from 8-bromotheophylline and α -halo ketones with subsequent replacement of the bromine atom by sulfur and cyclization of the resulting 7-acylmethyl-8-thiotheophyllines under the influence of dehydrating agents.

We have previously described [2] the synthesis of 2,6,8-trimethylthiazolo[2,3-f]xanthine by means of the reaction of 8-thiotheophylline with α -bromopropionaldehyde diethylacetal. However, because of the inaccessibility of other α -halo aldehydes, the indicated method for the introduction of substituents, in the 2 position of the thiazolopurine three-ring system has not found extensive application.

In a continuation of our research in [3] we have made a detailed study of a new simple method for the synthesis of 2-alkyl(aryl, hetaryl)-substituted thiazolo[2,3-f]xanthines from the accessible 8-bromotheophylline (I) [4]. In the reaction of I with α -halo ketones, as has been described in individual cases [5-9], 7-acylmethyl-8-bromotheophyllines (II-VIII) are formed readily. When the latter are refluxed in an alcohol solution of NaHS they are converted to 7-acylmethyl-8-thiotheophyllines (IX-XV). Under more severe conditions (150-160° C), the corresponding sulfides, for example, XXIII, are formed. Compounds IX-XV split out a water molecule and cyclize to 2-alkyl(aryl,hetaryl)-6,8-dimethylthiazolo[2,3-f]xanthines (XVI-XXII) under the influence of dehydrating agents (concentrated H₂SO₄, POCl₃) or when they are heated in aqueous solutions of mineral acids.

Bands of stretching vibrations of C = O groups at 1634-1735 cm⁻¹ are observed in the IR spectra of II-XV.



*See [1] for communication LXXXIV.

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TABLE 1. 7-Acylmethyl-8-bromotheophyllines (II-VIII), 7-Acylmethyl-8-thiotheophyllines (IX-XV), and 2-alkyl(aryl, hetaryl)-6,8-dimethylthiazolo[2,3-f]xanthines (XVI-XXII)

Com- pound	R	mp, °C	Empirical formula	Found, %				Calculated, %				IR spectrum, $\nu_{C=O}$ cm ⁻¹		Yield, %		
				C	H	Br	N	S	C	H	Br	N	S		in mineral oil	in CHCl ₃
II	CH ₃	203-204 ^a	C ₁₀ H ₁₁ BrN ₄ O ₃	—	—	—	—	—	—	—	—	—	—	—	—	75
III	C(CH ₃) ₃	147-148 ^b	C ₁₃ H ₁₇ BrN ₄ O ₃	43.9	4.6	22.2	15.5	—	—	—	—	—	—	—	—	99
IV	C ₆ H ₅	283-284 ^b	C ₁₅ H ₁₃ BrN ₄ O ₃	—	—	—	—	—	—	—	—	—	—	—	—	85
V	<i>p</i> -BrC ₆ H ₄	241-242 ^c	C ₁₅ H ₁₂ Br ₂ N ₄ O ₃	—	—	—	—	—	—	—	—	—	—	—	—	95
VI	<i>p</i> -CH ₃ C ₆ H ₄	193-194	C ₁₆ H ₁₅ BrN ₄ O ₃	49.4	4.1	20.7	14.5	—	—	—	—	—	—	—	—	92
VII	<i>p</i> -CH ₃ OC ₆ H ₄	191-192	C ₁₈ H ₁₅ BrN ₄ O ₅	47.4	3.1	19.5	13.5	—	—	—	—	—	—	—	—	91
VIII	C ₄ H ₉ S ^d	261-262	C ₁₄ H ₁₁ BrN ₄ O ₃ S	40.7	4.5	20.4	14.3	8.1	—	—	—	—	—	—	—	95
IX	CH ₃	275-277	C ₁₀ H ₁₂ N ₄ O ₃ S	45.1	4.5	—	21.1	12.0	—	—	—	—	—	—	—	74
X	C(CH ₃) ₃	253-254	C ₁₃ H ₁₆ N ₄ O ₃ S	50.6	5.9	—	17.9	10.1	—	—	—	—	—	—	—	86
XI	C ₆ H ₅	248-250	C ₁₅ H ₁₄ N ₄ O ₃ S	54.9	4.6	—	17.1	10.0	—	—	—	—	—	—	—	85
XII	<i>p</i> -BrC ₆ H ₄	273-275	C ₁₆ H ₁₃ BrN ₄ O ₃ S	44.5	3.6	19.3	13.3	7.5	—	—	—	—	—	—	—	92
XIII	<i>p</i> -CH ₃ C ₆ H ₄	253-254	C ₁₆ H ₁₆ N ₄ O ₃ S	53.9	4.8	—	16.4	9.3	—	—	—	—	—	—	—	92
XIV	<i>p</i> -CH ₃ OC ₆ H ₄	255-256	C ₁₈ H ₁₆ N ₄ O ₅ S	53.1	4.4	—	15.3	9.1	—	—	—	—	—	—	—	84
XV	C ₄ H ₉ S ^d	257-258	C ₁₄ H ₁₂ N ₄ O ₃ S ₂	46.4	3.6	—	16.1	19.1	—	—	—	—	—	—	—	74
XVI	CH ₃	218	C ₉ H ₉ N ₄ O ₂ S	47.7	3.7	—	26.2	13.0	—	—	—	—	—	—	—	74
XVII	C(CH ₃) ₃	207-209	C ₁₂ H ₁₁ N ₄ O ₂ S	53.1	5.4	—	19.0	11.4	—	—	—	—	—	—	—	97
XVIII	C ₆ H ₅	260-262	C ₁₅ H ₁₂ N ₄ O ₂ S	57.4	4.0	—	17.8	10.4	—	—	—	—	—	—	—	84
XIX	<i>p</i> -BrC ₆ H ₄	285-287	C ₁₅ H ₁₁ BrN ₄ O ₂ S	46.1	3.1	20.5	13.8	8.3	—	—	—	—	—	—	—	94
XX	<i>p</i> -CH ₃ C ₆ H ₄	247-249	C ₁₆ H ₁₄ N ₄ O ₂ S	58.6	4.8	—	17.4	10.0	—	—	—	—	—	—	—	98
XXI	<i>p</i> -CH ₃ OC ₆ H ₄	269-270	C ₁₈ H ₁₄ N ₄ O ₄ S	56.1	4.1	—	16.6	9.5	—	—	—	—	—	—	—	90
XXII	C ₄ H ₉ S ^d	245-246	C ₁₃ H ₁₁ N ₄ O ₂ S ₂	48.9	2.7	—	17.3	20.3	—	—	—	—	—	—	—	97

^aAccording to [5,6], this compound has mp 203°; mp 208° [7], and mp 204-206° [8].

^bAccording to [6], this compound has mp 284°.

^cAccording to [9], this compound has mp 241-242°.

^dThe C₄H₉S grouping denotes 2-thienyl.

The 7-acylmethyl-8-thiotheophylline structure was assigned to IX-XV on the basis of the presence of intense absorption bands at 1475-1485 cm^{-1} (C = S) [10] and 3166-3320 cm^{-1} (NH) and the absence of the absorption band of an SH group at 2500-2600 cm^{-1} .

EXPERIMENTAL METHOD

The IR spectra of the compounds were recorded with a UR-10 spectrometer.

7-Acylmethyl-8-bromotheophyllines (II-VIII, Table 1). A 12.95-g (50 mmole) sample of I and 50-55 mmole of an α -halo ketone were added to a solution of 50 mmole of sodium ethoxide in 100 ml of absolute ethanol, after which the mixture was refluxed for 5 h. It was then cooled, and the resulting precipitate was removed by filtration.

7-Acylmethyl-8-thiotheophyllines (IX-XV, Table 1). A 6.2-g (110 mmole) sample of NaHS was added to a solution of 40 mmole of II-VIII in 125 ml of absolute ethanol, after which the mixture was refluxed for 25 h. It was then filtered, the filtrate was acidified with acetic acid, and the precipitate was removed by filtration.

2-Alkyl(aryl, hetaryl)-6,8-dimethylthiazolo[2,3-f]xanthines (XVI-XXII, Table 1). A) A solution of 10 mmole of thiotheophyllines IX, XI, and XIII in 40 ml of POCl_3 was refluxed for 1.5-3 h, after which the POCl_3 was removed by vacuum distillation, and the residue was decomposed with water. The acidic solution was neutralized with ammonium hydroxide, and the precipitated XVI, XVIII, or XX was removed by filtration.

B) A 10-mmole sample of X or XII-XV in 30 ml of 85% H_3PO_4 was refluxed for 0.5-3 h, after which the mixture was cooled and poured into water. The aqueous mixture was neutralized with ammonium hydroxide, and the precipitated XVII or XIX-XXII was removed by filtration. Thiazolopurine XXII was also obtained by refluxing XV in concentrated HBr (for 2 h).

C) A solution of 5 mmole of XV in 20 ml of concentrated H_2SO_4 was allowed to stand at 20-25° for 20-24 h, after which it was poured into water, and the aqueous mixture was worked up as in experiment B to give XXII.

Compounds II-XXII were obtained as colorless or slightly cream-colored crystalline substances and were purified for analysis by crystallization from methanol (II-V), ethanol (IX, XI, XVI), butanol (X, XIV), dioxane (XIX, XXI, XXII), methanol- CHCl_3 (3:1) (VI, VII), glacial acetic acid (XX), ether (XVII), or dimethylformamide (VIII, XII, XIII, XV, and XVIII).

Bis(7-acetyl-8-theophyllinyl) Sulfide (XXIII). A mixture of 3.15 g (10 mmole) of bromo derivative II and 20 ml of 5% (17 mmole) alcohol solution of NaHS was heated in an autoclave at 150-160° for 4 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with water to give 2.2 g (80%) of a product with mp 242-243° (from aqueous ethanol). Found: C 47.3; H 4.5; N 22.1; S 6.4%. $\text{C}_{20}\text{H}_{22}\text{N}_8\text{O}_6\text{S}$. Calculated: C 47.8; H 4.4; N 22.3; S 6.4%.

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