RESEARCH IN THE IMIDAZOLE SERIES

LXXXV.* SYNTHESIS OF THIAZOLO[2, 3-f]XANTHINE

DERIVATIVES FROM 8-BROMOTHEOPHYLLINE

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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 the reaction of 8-thiotheophylline with α -bromopropional dehyde 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 $\rm H_2SO_4$, $\rm POCl_3$) or when they are heated in aqueous solutions of mineral acids.

Bands of stretching vibrations of C = 0 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)-6,8dimethylthiazolo[2,3-f]xanthines (XVI-XXII)

Chi	Com-			Empirical		Fou	Found, %				Ca1	Calculated, %	%		IR spectrum, "C=O" cm	o cm ⁻¹	V:014 %
CCH ₃ 203–204 ^a Cultibrilo, 3, 43, 4.6 22.2 15.5 - 43.7 4.8 22.4 15.7 - 1665, 1707, 1736 1665, 1710, 1736 1665, 1710, 1736 1665, 1710, 1736 1665, 1710, 1736 1665, 1710, 1736 1665, 1710, 1734 1747-148 Cultibrilo, 3, 4.6 22.2 15.5 - 43.7 4.8 22.4 15.7 - 1665, 1698 1710, 1736 1665, 1710, 1736 1665, 1710, 1736 1665, 1710, 1736 1665, 1710, 1736 1665, 1710, 1736 1665, 1710, 1734 1736,	punod	æ		formula	ပ	11	Br		s	၁	н	Br	z	s	in mineral oil	in CHC13	· into
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	=	CH	203—204ª	C ₁₀ H ₁₁ BrN ₄ O ₃		+		- 1	' 	1	1		I	1	1707.	1713.	75
Cells 288—284 Cultibrity 281—284 Cultibrity 281—284 Cultibrity 281—284 Cultibrity 281—284 Cultibrity 281—284 Cultibrity 281—285 Cultibrity 282—285	III	C(CH ₃) ₃	147148,	_	43,9	4.6	22.2	15,5	1	43,7	4,8	22,4	15,7	1	1710,	1710,	66
PBC6H4 241—242° CishlaBrN40³ — 160 3.9	N	C,H,	283—284 D	C15H13BrN4O3	1		1	1	1	1				i			82
P-CH ₃ CeH ₄ 193-194 C ₁₀ H ₁₈ BrN ₄ O ₃ 49.4 4.1 20.7 14.5 - 49.1 3.9 20.4 14.3 - 1665, 1688 1666, 1708 1666, 1708 CH ₃ SG C ₁₀ H ₁₈ BrN ₄ O ₃ 47.4 4.1 19.5 13.5 - 16.5 1666, 1708 1666, 1708 C ₁ CH ₃ SG C ₁₀ H ₁₈ BrN ₄ O ₃ S 46.7 4.1 12.0 44.8 4.5 - 16.0 16.6 1666, 1708 1666, 1708 C ₁ CH ₃ SG C ₁₀ H ₁₈ N ₁ O ₃ S 45.7 - 21.0 12.0 1650, 1685, 1716, 1735 1666, 1708 1666, 188, 1706 1666, 1708 1666, 1708 1666, 1708 1718 1666, 1708 1718 1718	>	p-BrC ₆ H ₄	$241 - 242^{\circ}$	C15H12B12N4O3	1	1	1	-	1	-1	1	1	1				38
P.CH ₃ C ₆ H ₄ 191—192 Cuch ₁ sBnNO ₄ 47.4 4,1 19.5 13.5 — 156,1700 1666,1700 1676,1715,175 1685,1715,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1668,1715 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175 1765,175	I	p-CH ₃ C ₆ H ₄	193-194	C ₁₆ H ₁₅ BrN ₄ O ₃	49,4	4,1	20.7	14,5	1	49.1	3,9	20,4	14,3	*	1698		95
C,H,S,U 261—262 C,JH,BNA,O,S 40,7 3,1 20.4 14,3 8,1 40,7 2,9 20,9 14,6 8,4 1658,1896 C,JH,BNA,O,S 6,1 4,5 — 21,1 12,0 4,4 8, 4,5 — 21,0 12,0 12,0 1650,1865,1716,1725 1685,1715,1725 C,JH,ANA,O,S 54,9 4,6 — 17,1 10,0 54,5 4,3 — 17,0 12,0 1650,1865,1715,1725 1685,1715,1729 C,JH,ANA,O,S 54,9 4,6 — 17,1 10,0 54,5 4,3 — 17,0 9,7 1685,1705 1685,1715 1729 C,JH,ANA,O,S 54,9 4,6 — 17,1 10,0 54,5 4,7 — 16,3 9,7 16,3 13,7 7,8 1685,1705 1685,1715 1685,1715 1685,1715 1729 185,1715 1729 185,1715 1729 185,1715 1729 185,1715 18	IIA	p-CH ₃ QC ₆ H ₄	191 - 192	C16H15BrN4O4	47.4	4,1	19,5	13,5	1	47,2	3,7	19,6	13,8	1	1700	1666, 1708	91
CH ₃ 255—277 CultipNo ₃ S 45,1 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 45,0 -1,1 12,0 -14,8 -14,0 -17,0 -	VIII	C4H3Sa	261 - 262	C13H11BrN4O3S	40,7	3,1	20,4	14,3		40,7	2,9	20,9	14,6	8,4	1696		95
C(CH ₃) ₃ 253—254 C ₁₃ H ₁₈ N ₄ O ₃ S 5 ₄ G 5 ₅ G 5 ₇ G 5	IX	CH3	275 - 277	CloH12N4O3S	45,1	5,5	1	21,1	12,0	44.8	4,5	1	21.0	12,0	1685, 1716, 1	1715,	74
C ₆ H ₅ 248—250 C ₁₈ H ₁₄ N ₁ O ₃ S 54.9 4.6 — 17.1 10.0 54.5 4.3 — 17.0 9.7 1685, 1705 1685, 1715 P-BrC _H ₄ 273—275 C ₁₈ H ₁₈ Br ₁ A ₂ S 44.5 3.6 19.3 13.3 7.5 44.0 3.2 19.5 13.7 7.8 1685, 1715 1685, 1715 P-CH ₂ G ₄ H ₄ 255—256 C ₁₆ H ₁₈ N ₁ O ₃ S 53.1 4.4 — 15.3 9.1 53.3 4.7 — 1684, 1713 1684, 1713 1684, 1715 1684, 1716	×	C(CH ₃) ₃	253-254		50,6	5,9	1	17,9	1.0	50.3	ထို	ı	189	10,3	1675, 1715, 1	1716,	%
P.Br.C.H., 273—275 CL6H ₁₈ BrN ₄ O ₂ S 44.5 3.6 19.3 13.3 7.5 44.0 3.2 19.5 13.7 7.8 1685, 1705 1655, 1715 P.C.H.s.G.H., 253—254 C.G.H.g.N.A.O.S. 55.9 4.8 — 16.4 9.3 55.8 4.7 — 16.3 9.3 1636, 1674, 1706 1714 1685, 1715 P.C.H.s.G.H., 255—256 C.G.H.g.N.O.S. 45.4 3.6 — 16.1 19.1 46.4 3.6 — 16.6 19.1 1684, 1715 1684, 1715 C.H.s. C.G.H.g.N.O.S. 47.7 3.7 — 22.2 13.0 48.0 4.0 — 22.4 12.8 1674, 1715 1684, 1715 C.H.s. C.G.H.g.N.O.S. 53.1 5.4 — 16.1 19.1 46.4 3.6 — 16.6 19.2 11.7 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 1684, 1715 <t< td=""><td>IX</td><td>C,H,</td><td>248250</td><td></td><td>9</td><td>4.6</td><td>1</td><td>17.1</td><td>10.01</td><td>54.5</td><td>4.3</td><td>1</td><td>17,0</td><td>2.6</td><td>1706</td><td></td><td>& G</td></t<>	IX	C,H,	248250		9	4.6	1	17.1	10.01	54.5	4.3	1	17,0	2.6	1706		& G
P-CH ₃ CeH ₄ 255–254 C ₁₆ H ₁₀ N ₄ O ₃ S 55.9 4.8 - 16.4 9.3 55.8 4.7 - 16.3 9.3 1635,1674,1700,1714 1664,1713 1625,255 C ₁₆ H ₁₀ N ₄ O ₃ S 55.9 4.8 - 16.4 16.4 16.3 9.3 16.5 16.5 16.5 16.5 16.5 16.5 16.5 16.5	XII	p-BrC ₆ H ₄	273—275		44.5	3.6	19,3	13,3	7.5	44.0	3.5	19,5	13,7	7,8	1705		3 5
P-CH ₃ OC ₆ H ₄ 255–256 C ₁₆ H ₁₀ N ₄ O ₄ S 53,1 4,4 — 15,3 4,5 — 15,5 8,9 1651, 1675, 1684, 1723 1685, 1715 C _{H3} S d 257–256 C ₁₈ H ₂ N ₄ O ₂ S 46,4 3.6 — 16,1 19,1 46,4 3.6 — 16,1 19,1 46,4 3.6 — 16,1 19,1 46,4 3.6 — 16,1 19,1 46,4 3.6 — 16,1 19,1 46,4 3.6 — 16,1 19,1 46,4 3.6 — 16,1 10,1 10,3 17,1 16 17,1 16 17,1 10,3 17,1 16 17,1 10,3 17,1 16 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3 17,1 10,3	IIIX	p-CH ₃ C ₆ H ₄	253254		55.9	4,8		16.4	9,3	25,8	4.7	1	16.3	93	1674, 1700,		95
C.H.; S. d. 257—258 C.3H.; N.O.; S. d.	VIX	p-CH3OCeH4	255-256		53,1	4,4	1	15,3	6.	53,3	4,5	1	5,5	6,0	1675, 1684,		\$
CH ₃ 2077–209 CuH ₁ eN ₁ O ₂ S 47.7 3.7 — 22.2 13.0 48.0 4.0 — 22.4 12.8 1674,1716 CC(CH ₃) 2077–209 CuH ₁ eN ₁ O ₂ S 57.4 4.0 — 17.8 10.4 57.7 2.9 — 17.9 10.3 CuH ₁ eN ₂ O ₂ S 57.4 4.0 — 17.8 10.4 57.7 2.9 — 17.9 10.3 CuH ₁ eN ₂ O ₂ S 57.4 4.0 — 17.8 10.4 57.7 2.9 11.0 1675,1715 CuH ₁ eN ₂ O ₂ S 57.4 4.0 — 17.8 10.4 57.7 2.9 17.9 10.3 CuH ₁ eN ₂ O ₂ S 58.6 4.8 — 17.4 10.0 58.9 4.3 — 17.2 9.8 1661,1703 CuH ₂ S 58.1 4.1 — 16.6 9.5 56.1 4.1 — 16.4 9.4 1665,1704 1665,1710	ΛX	C'H3S d	257—258	_	46,4	3,6		16,1		46,4	3.6	1	9'91	1.61	1671, 1		35
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	XVI	CH ₃	218	_	47.7	3,7	1	22,2	13.0	18.0	4,0	1	22,4	12,8			74
CeH ₅ 260—262 C ₁₅ H ₁₂ N ₁ O ₂ S 57.4 4.0 — 17.8 10.4 57.7 3.9 — 17.9 10.3 10.3 10.5 17.8 10.4 57.7 3.9 — 17.9 10.3 10.3 10.5 17.8 10.4 57.7 3.9 10.3 10.3 10.5 17.8 10.4 10.0 58.9 4.3 17.2 9.8 1661,1706 17.0 17.2 17.2 17.2 17.2 17.2 17.2 17.2 17.2	XVII	C(CH ₃) ₃	207209	C13H16N4O2S		5,4		0.61	1.4	53.4	5		192	0,1			26
p-BrC ₆ H ₄ 285–287 C ₁₆ H ₁ BrN ₄ O ₂ S 46,1 3.1 20.5 13.8 8.3 46,0 2.8 20.4 14.3 8.2 1665,1706 p-CH ₃ C ₆ H ₄ 247–249 C ₁₆ H ₄ N ₄ O ₂ S 58,6 4.8 — 17,4 10,0 58,9 4.3 — 17,2 9.8 1661,1703 CCH ₃ C ₆ H ₄ 269–270 C ₁₆ H ₄ N ₄ O ₃ S 56,1 4.1 — 16,6 9.5 56,1 4.1 — 16,6 9.5 56,1 4.1 1665,1710 1665,1710 C.H ₃ Sd C ₁₆ H ₄ N ₄ N ₄ O ₃ S 56,1 4.1 — 17,3 20,3 149,0 3.2 — 17,6 1704 1665,1710	IIIAX	C ₆ H ₅	260-262	C15H12N4O2S	57.4	4.0	1	17.8	10,4	57.7	9	!	17.9	10,3			æ
p-CH ₃ C ₆ H ₄ 247—249 C ₁₆ H ₄ N ₄ N ₄ O ₃ 58.6 4.8 — 17.4 10.0 58.9 4.3 — 17.2 9.8 1661, 1703 C-CH ₃ C ₆ H ₄ 286—270 C ₁₆ H ₄ N ₄ N ₄ O ₃ 5.6 4.1 — 17.5 16.6 9.3 1.6 9.1 1.6 17.0 1.0	XIX	p-BrC ₆ H,	285-287	ClgH11BrN4O2S	46,1	3.1	20,5	13.8	83	46.0	2.8	20,4	14,3	8,2	-		94
P-CH ₃ OC ₆ H ₄ 269—270 C ₁₆ H _{4,N} N ₀ S ₅ 56.1 4.1 — 16.6 9.5 56.1 4.1 — 16.4 9.4 1665, 1704 1665, 1710 C ₂ H ₃ Sd C ₃	XX	p-CH ₃ C ₆ H ₄	247249	C16H14N4O5S	986	4,8	1	17.4	10.0	58.0	4,3		17,2	86			86
C.H.5d 245-246 C.H.N.O.S. 48.9 2.7 - 17.3 20.3 49.0 3.2 - 17.6 20.1 1665, 1705	IXX	P-CHOC.H.	- 1	C. H. N.O.S	26.1	4.1		16.6	5.5	26.	4.1	-	16.4	4.6		1665, 1710	8
	XXII	C,H,Sd	í	Ch.HinN,O.S.	48.9	2.7	1	17.3	20,3	49.0	3.2	1	9.2	20.1			26

^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 C_4H_9S 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 $1475-1485 \text{ cm}^{-1}$ (C = S) [10] and $3166-3320 \text{ cm}^{-1}$ (NH) and the absence of the absorption band of an SH group at $2500-2600 \text{ cm}^{-1}$.

EXPERIMENTAL METHOD

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

 $\frac{7-\text{Acylmethyl-8-bromotheophyllines}}{1000}$ M 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 $\rm H_2SO_4$ 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-CHCl₃ (3:1) (VI, VII), glacial acetic acid (XX), ether (XVII), or dimethylformamide (VIII, XII, XIII, XV, and XVIII).

Bis(7-acetonyl-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 $150-160^{\circ}$ 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 $242-243^{\circ}$ (from aqueous ethanol). Found: C 47.3; H 4.5; N 22.1; S 6.4%. $C_{20}H_{22}N_{8}O_{6}S$. Calculated: C 47.8; H 4.4; N 22.3; S 6.4%.

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