RESEARCH IN THE IMIDAZOLE SERIES

LXXIX.* REACTION OF 8-THIOTHEOPHYLLINE WITH α-HALO KETONES

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It was established that the reaction of 8-theophylline with α-halo ketones gives 8-acylalkylthiotheophyllines or their cyclization products – thiazolo[2,3-f]xanthine derivatives – depending on the conditions used to carry out the reaction and the structure of the halo ketones. Derivatives of two new heterocyclic systems – cyclopentathiazolo[2,3-f]purine and benzothiazolo[2,3-f]purine – were synthesized from 2-bromocyclopentadienone and cyclohexanone. The structure and the conditions for the cyclization of 8-acylalkylthiotheophyllines to three-(four)-ring compounds were studied. The structure of the thiazolo[2,3-f]xanthines was proved by reductive desulfuration to 1,3,7-trialkylxanthines.

Little study has been devoted to the reaction of 8-thioxanthines with α-halo ketones [2, 3], whereas it seems of great interest, inasmuch as it opens up possibilities for the synthesis of 8-acylalkylthioxanthines and thiazolo[2,3-f]xanthine derivatives. We have found that the reaction of 8-thiotheophylline (I) with α-halo ketones of the aliphatic, alicyclic, aliphatic-aromatic, and heterocyclic series proceeds unambiguously and, depending on the conditions used (temperature and pH of the medium) and the structure of the halo ketone, gives 8-acylalkylthiotheophyllines or their cyclization products – thiazolo[2,3-f]xanthine derivatives. Thus 8-acylalkylthiotheophyllines (II-XIII, Table 1) are obtained in high yields by reaction of I with halo ketones in alcohol or dimethylformamide (DMF) in the cold and even on heating to 60-100° in the presence of an alkaline reagent. Refluxing of thioxanthine I with halo ketones in organic solvents (alcohols, CH_3COOH, DMF) in the absence of an alkaline reagent gives different compounds. 8-Acylalkylthiotheophyllines (VIII-XIII) are formed in the case of aliphatic-aromatic and heterocyclic halo ketones, while the process does not stop in the first step with aliphatic and alicyclic halo ketones but proceeds further with closing of the thiazole ring to give the corresponding three- and four-ring compounds (XIV-XVII, XXIII, and XXIV).

This difference in the course of the reaction of I with α-halo ketones with different structures is explained by the different tendencies of the acylalkylthiotheophyllines (II-XIII) to undergo cyclization with closing of a thiazole ring. Compounds II-VII are readily cyclized to three- and four-ring XIV-XVII and XXIV on refluxing in lower alcohols in the presence of HCl, on heating in $POCl_3$ and organic or mineral acids (HCOOH, CH_3COOH, HCl, HBr, and H_3PO_4), and also on treatment with cold concentrated H_2SO_4. In contrast to II-VII, IX-XIII are very stable and cyclize to XVIII-XXII only on prolonged refluxing in $POCl_3$ or 85-90% H_3PO_4.

The closing of the thiazole ring is catalyzed by acids. Thus V does not change when it is refluxed in ethanol, while under the same conditions, but in the presence of HCl, it is cyclized almost quantitatively to XVI. Thus, three(four)-ring compounds (XIV-XVII, XXIII, and XXIV) are formed in the reaction of thiotheophylline I with halo ketones of the aliphatic or alicyclic series in ethanol, while in the presence of alkali, which neutralizes the evolved HCl or HBr, the process stops in the first step to give acylalkylthiotheophyllines (II-VII).

*See [1] for communication LXXVIII.

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TABLE 1. 8-Acylalkylthiotheophyllines (II-XIII) and Thiazolo[3,2-f]xanthine Derivatives (XIV-XXIV)

Compound	R	R′	mp, °C	IR spectrum, cm^{-1}	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	N	S	C	H	N	S	
II	H	CH_3	198—200[a]	1660, 1690, 1710, 3090, 3140	$C_{10}H_{12}N_4O_3S$	44,7	4,5	20,9	12,2	44,8	4,5	20,9	11,9	97
III	H	C_2H_5	199—200	1665, 1705, 3090, 3140	$C_{11}H_{14}N_4O_3S$	47,0	5,2	20,1	11,5	46,8	5,0	19,8	11,3	92
IV	H	$C(CH_3)_3$	250—251	1650, 1695, 1725, 3090, 3140	$C_{13}H_{18}N_4O_3S$	50,7	5,8	18,0	10,4	50,3	5,8	18,0	10,3	84—98
V	CH_3	CH_3	190—191	1650, 1715, 3080, 3120	$C_{11}H_{14}N_4O_3S$	47,1	5,0	20,0	11,2	46,8	5,0	19,8	11,3	88
VI	C_3H_7	CH_3	194—195	1650, 1705, 3090, 3130	$C_{13}H_{18}N_4O_3S$	50,2	5,9	18,4	10,4	50,3	5,8	18,1	10,3	94
VII	C_6H_9O[b]		171—173	1665, 1705, 3110, 3170	$C_{13}H_{16}N_4O_3S$	50,5	5,4	18,2	10,6	50,6	5,2	18,2	10,4	65
VIII	H	C_4H_3S[c]	246—248		$C_{13}H_{12}N_4O_3S_2$	46,5	3,9	16,6	19,1	46,4	3,6	16,6	19,1	92
IX	H	C_6H_5	242—243	1660, 1700, 3080, 3140	$C_{15}H_{14}N_4O_3S$	54,5	4,2	17,1	9,9	54,5	4,3	17,0	9,7	79—87
X	H	p-BrC_6H_4	241—242	1660, 1705, 3090, 3140	$C_{15}H_{13}BrN_4O_3S$[d]	43,8	2,9	13,8	7,7	44,0	3,2	13,7	7,9	73
XI	H	p-$O_2NC_6H_4$	223—224	1670, 1700, 3090, 3140	$C_{15}H_{13}N_5O_5S$	48,0	3,6	18,6	9,0	48,0	3,5	18,7	8,8	92
XII	CH_3	C_6H_5	242—243	1665, 1705, 3080, 3150	$C_{16}H_{16}N_4O_3S$	55,4	4,7	16,2	9,3	55,8	4,7	16,3	9,3	91
XIII	C_6H_5	C_6H_5	229—230	1660, 1710, 3090, 3140	$C_{21}H_{18}N_4O_3S$	61,5	4,6	13,4	8,3	62,0	4,7	13,8	7,9	91
XIV	H	CH_3	262—263[e]	1685, 1715	$C_{10}H_{10}N_4O_2S$	—	—	—	—	—	—	—	—	—
XV	H	C_2H_5	223—224	1670, 1710	$C_{11}H_{12}N_4O_2S$	50,1	4,6	21,4	12,0	50,0	4,6	21,2	12,1	78—98
XVI	CH_3	CH_3	232—233	1675, 1715	$C_{11}H_{12}N_4O_2S$	50,2	4,3	21,5	12,1	50,0	4,6	21,2	12,1	82
XVII	CH_3	C_2H_5	161—162	1670, 1710	$C_{12}H_{14}N_4O_2S$	51,7	5,2	19,9	11,8	51,8	5,1	20,1	11,5	88
XVIII	H	C_6H_5	288—289	1660, 1705	$C_{18}H_{12}N_4O_2S$	57,3	3,6	17,6	10,6	57,7	3,9	17,9	10,3	93
XIX	H	p-BrC_6H_4	298—300	1655, 1695	$C_{15}H_{11}BrN_4O_2S$[f]	45,7	2,7	14,1	8,4	46,0	2,8	14,3	8,2	95
XX	H	p-$O_2NC_6H_4$[a]	343—345	1660, 1700	$C_{15}H_{11}N_5O_4S$	50,3	3,4	19,1	8,9	50,4	3,1	19,6	8,9	90
XXI	CH_3	C_6H_5	227—229		$C_{16}H_{14}N_4O_2S$	58,8	4,3	17,6	10,2	58,9	4,3	17,2	9,8	90
XXII	C_6H_5	C_6H_5	234—236	1680, 1720	$C_{21}H_{16}N_4O_2S$	65,0	4,0	13,9	8,0	64,9	4,1	14,4	8,2	92
XXIII	$-(CH_2)_3-$		264—266		$C_{12}H_{12}N_4O_2S$	52,2	4,5	20,1	11,9	52,1	4,4	20,3	11,6	89
XXIV	$-(CH_2)_4-$		226—227	1670, 1700	$C_{13}H_{14}N_4O_2S$	53,4	5,2	19,5	11,3	53,8	4,9	19,3	11,0	72

[a]According to [2], this compound has mp 204-205°. [b]This formula stands for SCHRCOR = 2-cyclohexanonyl. [c]This formula stands for 2-thienyl. [d]Found %: Br 19.7. Calculated %: Br 19.5. [e]According to [2], this compound has mp 263°. [f]Found %: Br 20.6. Calculated %: Br 20.4.

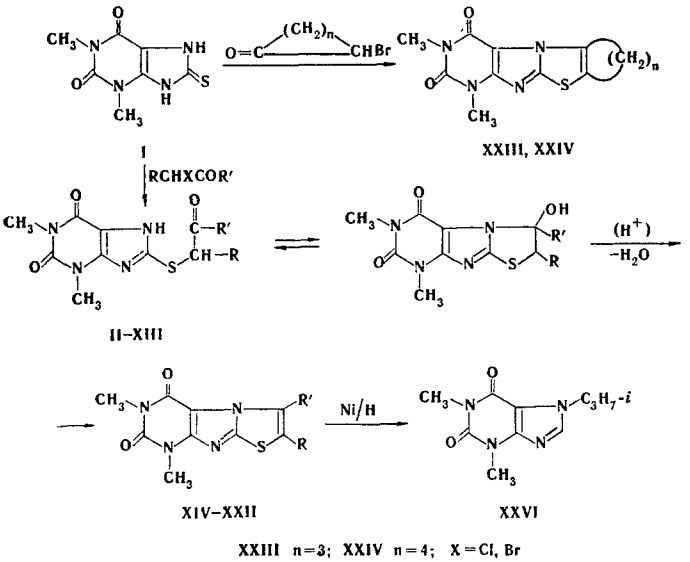
It was established by means of physicochemical methods that ring-chain tautomerism is characteristic for II-XIII. These compounds display the properties of ketones and give derivatives at the carbonyl group, for example, 2,4-dinitrophenylhydrazones (XXV). At the same time, judging from the IR and PMR spectra [4, 5], these ketones are in equilibrium with the corresponding 3-hydroxythiazolino[2,3-f]xanthines in solution.

As a consequence of tautomerism in the 8-thiopurine series, closing of the thiazole ring during cyclization of II-XIII might have proceeded with the participation of the NH group in both the 7 and 9 positions of the purine ring to give thiazolo[2,3-f]xanthines XIV-XXIV and the isomeric thiazolo[2,3-e]xanthine derivatives. In all cases we isolated only one of the isomers (as monitored by chromatography). The affiliation of XIV-XXIV with the series of thiazolo[2,3-f]xanthine derivatives was proved in the case of the reductive desulfuration of XIV under the influence of Raney nickel to 7-isopropyltheophylline (XXVI).

EXPERIMENTAL

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

Chromatography on a fixed layer of silica gel for XV, XVI, XVIII, and XX was realized in a CCl_4–CH_3COOH (4:1) system, and the chromatograms were developed with iodine vapors. The R_f values were: XV 0.91, XVI 0.94, XVIII 0.83, and XX 0.90.



8-Acylalkylthiotheophyllines (II-XIII, see Table 1). A) A 0.05-0.055-mole sample of the α-halo ketone (chloro ketones were used for the synthesis of II, VII, and XIII, while bromo ketones were used in all of the rest of the cases) was added to a solution of 0.05 mole of I and 0.05 mole of sodium ethoxide in 100-150 ml of ethanol, and the mixture was stirred at 60-65° for 1-1.5 h, refluxed for 10 min, and cooled. The precipitate was then removed by filtration and washed with water.

B) A solution of 0.05 mole of I and 0.055 mole of the α-halo ketone in 150 ml of ethanol or DMF was stirred at 18-20° for 5-6 h, after which it was poured into water, and the precipitate was removed by filtration to give IV and IX in 84 and 79% yields, respectively. Compound IX was isolated in 79-87% yield when I was refluxed with phenacyl bromide in ethanol, hexanol, DMF, and glacial CH_3COOH for 5-8 h. The substances were purified for analysis by crystallization from aqueous ethanol (II, VII, and IX), ethanol (IV, V, and VI), butanol (III, X, and XII), dioxane (VIII), or glacial CH_3COOH (XI, XIII).

Derivatives of Thiazolo[2,3-f]-, Cyclopentathiazolo[2,3-f]-, and Tetrahydrobenzothiazolo[2,3-f]xanthines (XIV-XXIV, see Table 1). A) A solution of 0.01 mole of I and 0.011-0.012 mole of α-halo ketone (a chloro ketone was used for the synthesis of XIV, while a bromo ketone was used for the synthesis of the other compounds) in 30-60 ml of ethanol was refluxed for 4-5 h (in the preparation of XIV, XV, and XVII) or 7 h (in the preparation of XXIII and XXIV), after which it was cooled, and the precipitate was removed by filtration. Evaporation of the mother liquor to a small volume gave additional amounts of the compounds.

B) A solution of 0.01 mole of III in 15 ml of glacial CH_3COOH, 85% HCOOH, concentrated HCl, or HBr was refluxed for 4-5 h, after which the solvent was removed by vacuum distillation. The residue was

made alkaline with NH_3, and the precipitate was removed by filtration and washed with water. The yield of XV was 87-98%.

C) A solution of 0.01 mole of V or IX in 15 ml of 85% H_3PO_4 was heated, respectively, at 95-98° for 1 h or at the reflux temperature of the mixture for 2.5 h, after which it was worked up as described in method A. The yields of XVI and XVIII were 93 and 98%.

D) A solution of 2.8 g (0.01 mole) of III in 15 ml of 96% H_2SO_4 was allowed to stand at 18-20° for 24 h, after which it was worked up as described above. The yield of XV was 91%.

E) A mixture of 0.01 mole of IX-XIII in 30-35 ml of $POCl_3$ was refluxed for 6-10 h, after which the $POCl_3$ was removed by vacuum distillation, the residue was decomposed with water, and the precipitated XVIII-XXII were removed by filtration. The compounds were purified by crystallization from ethanol–$CHCl_3$ (XIV), ethanol (XVI), aqueous ethanol (XVII), acetone (XXII), glacial CH_3COOH (XV), butanol (XXI, XXIV), DMF (XIX, XX, XXIII), or butanol-DMF (1:1) (XVIII).

8-Acetonylmercaptotheophylline 2,4-Dinitrophenylhydrazone (XXV). This compound was obtained from II and 2,4-dinitrophenylhydrazine in ethanol (after refluxing for 1 h). The yield of product with mp 252-253° (from DMF) was 80%. Found %: C 42.8; H 3.7; N 25.0; S 6.8. $C_{16}H_{16}N_8O_6S$. Calculated %: C 42.8; H 3.6; N 25.0; S 7.1.

7-Isopropyltheophylline (XXVI). A) A mixture of 2.37 g (0.01 mole) of the hydrated potassium salt of theophylline and 2.55 g (0.015 mole) of isopropyl iodide in 30 ml of ethanol was refluxed for 8 h, after which the solvent was removed by distillation, and the residue was washed with water. The yield of XXVI, with mp 174-176° (from petroleum ether) (mp 140° [6]), was 1.44 g (65%). IR spectrum: 1660, 1700 cm^{-1} (CO). Found %: C 53.9; H 6.2; N 25.3. $C_{10}H_{14}N_4O_2$. Calculated %: C 54.0; H 6.3; N 25.2.

B) A mixture of 1 g of XIV, 15 g of an alcohol paste of Raney nickel, and 50 ml of ethanol was refluxed for 2 h, after which it was filtered. The filtrate was evaporated, and the residue was crystallized from petroleum ether. The yield of XXVI, with mp 174-176°, was 0.7 g (79%). No melting-point depression was observed for a mixture of this product with a sample of XXVI obtained by method A.

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