The Synthesis of Some 8-Alkylthio-2-thiotheophyllines and 8-Alkylthio-6-thiotheophyllines[1]

ALBERT J. DIETZ, JR., AND RAYMOND M. BURGISON

Department of Pharmacology, University of Maryland, School of Medicine, Baltimore, Maryland 21201

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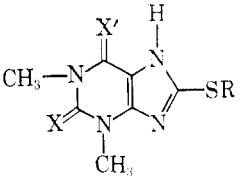
Previous investigations in this laboratory[2] have shown that certain 8-alkylthioxanthines possess slight anticancer activity and, unexpectedly, some central nervous system depressant activity in rats and rabbits in nontoxic doses. In this communication, the synthesis of a series of related compounds is reported, wherein the 2-oxygen or 6-oxygen of the theophylline nucleus has been replaced by sulfur. The pharmacologic properties of these compounds, shown in Table I, will be published elsewhere when the data are complete.

TABLE I

DERIVATIVES OF 8-MERCAPTO-2-THIOTHEOPHYLLINE AND 8-MERCAPTO-6-THIOTHEOPHYLLINE



No.	R	X	X′	M.p., °C.	Method	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
1	H	O	S	335–338 dec.	—	$C_7H_8N_4OS_2$	36.84	36.50	3.51	3.56	24.56	25.00
2	CH_3	O	S	253	A	$C_8H_{10}N_4OS_2$	39.67	39.56	4.13	4.13	23.14	23.20
3	C_2H_5	O	S	223	A	$C_9H_{12}N_4OS_2$	42.19	42.21	4.69	4.58	21.87	21.85
4	*n*-C_3H_7	O	S	231	B	$C_{10}H_{14}N_4OS_2$	44.44	44.67	5.18	5.12	20.74	20.96
5	*n*-C_4H_9	O	S	204	B	$C_{11}H_{16}N_4OS_2$	46.48	46.48	5.63	5.72	19.72	19.65
6	*n*-C_5H_{11}	O	S	176–177	B	$C_{12}H_{18}N_4OS_2$	48.32	48.44	6.04	6.07	18.79	19.08
7	*n*-C_6H_{13}	O	S	165–166	B	$C_{13}H_{20}N_4OS_2$	50.00	50.49	6.41	6.52	17.95	18.45
8	*n*-C_7H_{15}	O	S	166–167	B	$C_{14}H_{22}N_4OS_2$	51.33	51.75	6.75	6.72	17.18	17.38
9	*n*-C_8H_{17}	O	S	161	B	$C_{15}H_{24}N_4OS_2$	52.94	53.35	7.06	7.11	16.47	16.23
10	*n*-C_9H_{19}	O	S	152	B	$C_{16}H_{26}N_4OS_2$	54.24	54.75	7.34	7.46	15.82	16.04
11	*n*-$C_{10}H_{21}$	O	S	151	B	$C_{17}H_{28}N_4OS_2$	55.43	55.37	7.61	7.69	15.22	15.25
12	$(CH_3)_2CH$	O	S	255–256 dec.	B	$C_{10}H_{14}N_4OS_2$	44.44	44.94	5.18	5.18	20.74	20.98
13	H	S	O	335 dec.	—	$C_7H_8N_4OS_2$	36.84	36.98	3.51	3.77	24.56	24.41
14	CH_3	S	O	335	A	$C_8H_{10}N_4OS_2$	39.67	39.41	4.13	4.10	23.14	23.40
15	C_2H_5	S	O	290	A	$C_9H_{12}N_4OS_2$	42.19	41.86	4.69	4.65	21.87	22.18
16	*n*-C_3H_7	S	O	214–215	B	$C_{10}H_{14}N_4OS_2$	44.44	44.10	5.18	5.16	20.74	21.08
17	*n*-C_4H_9	S	O	214–215	B	$C_{11}H_{16}N_4OS_2$	46.48	46.55	5.63	5.47	19.72	19.96
18	*n*-C_5H_{11}	S	O	198	B	$C_{12}H_{18}N_4OS_2$	48.32	48.79	6.04	6.06	18.79	18.83
19	*n*-C_6H_{13}	S	O	181–182	B	$C_{13}H_{20}N_4OS_2$	50.00	49.92	6.41	6.42	17.95	17.94
20	*n*-C_7H_{15}	S	O	175	B	$C_{14}H_{22}N_4OS_2$	51.33	51.47	6.75	6.59	17.18	17.08
21	*n*-C_8H_{17}	S	O	163–164	B	$C_{15}H_{24}N_4OS_2$	52.94	53.38	7.06	6.97	16.47	16.50
22	*n*-C_9H_{19}	S	O	160	B	$C_{16}H_{26}N_4OS_2$	54.24	54.01	7.34	7.04	15.82	16.32
23	*n*-$C_{10}H_{21}$	S	O	153–154	B	$C_{17}H_{28}N_4OS_2$	55.43	55.40	7.61	7.67	15.22	15.51

Experimental Section

The compounds described in Table I were prepared by reacting either 8-mercapto-2-thiotheophylline or 8-mercapto-6-thiotheophylline with the appropriate alkyl sulfate (method A) or alkyl halide (method B). Some of the required starting materials were obtained from commercial sources and others by published procedures, *viz.*, 5,6-diamino-1,3-dimethyl-2-thiouracil[3] and 5,6-diamino-1,3-dimethyluracil.[4]

8-Mercapto-2-thiotheophylline (13).—To 500 ml. of 50% alcohol was added 26 g. (0.47 mole) of KOH and 80 g. (0.43 mole) of 5,6-diamino-1,3-dimethyl-2-thiouracil. Carbon disulfide (35.7 g., 0.47 mole) was then added and the mixture was refluxed for 3 hr. and filtered. The filtrate was cooled and acidified to pH 5 with glacial acetic acid giving 90 g. of 8-mercapto-2-thiotheophylline (**13**).[5,6]

8-Mercapto-6-thiotheophylline (1).—To 700 ml. of 50% alcohol was added 38 g. (0.68 mole) of KOH and 102 g. (0.60 mole) of 5,6-diamino-1,3-dimethyluracil. Carbon disulfide (52 g., 0.68 mole) was then added, and the mixture was refluxed for 3 hr. and filtered. The filtrate was cooled and acidified to pH 5 with glacial acetic acid to give 8-mercaptotheophylline, m.p. 320°. To 1 l. of dry pyridine was added 80 g. (0.38 mole) of 8-mercaptotheophylline and 155.4 g. (0.7 mole) of phosphorus pentasulfide. The mixture was refluxed for 8 hr. The solution was cooled and 2 l. of water was slowly added. The solution was concentrated to about 1 l. The yellow precipitate was filtered and reprecipitated from dilute NH_4OH by the addition of dilute acetic acid. The product weighed 70 g.

Method A.—8-Mercapto-2-thiotheophylline (22.8 g., 0.1 mole) was dissolved in 300 ml. of water containing 4.0 g. (0.1 mole) of NaOH. To the clear solution was slowly added 12.62 g. (0.1 mole) of dimethyl sulfate. The mixture was stirred at 60° for 3 hr. The precipitate was filtered, washed with water, and recrystallized from methanol to give 8-methylthio-2-thiotheophylline (**14**), 22.5 g.

Method B.—8-Mercapto-2-thiotheophylline 22.8 g. (0.1 mole) and butyl bromide[7] (18.9 g., 0.125 mole) were refluxed together in 700 ml. of alcohol for 24 hr., and filtered. The filtrate was evaporated to dryness, and the residue was dissolved in dilute NH_4OH. The ammonia solution was evaporated to dryness, and the residue was extracted with acetone and cooled to give 8-butylthio-2-thiotheophylline (**17**). The product was recrystallized from methanol.

(1) This work was supported by a National Cancer Institute grant (CA-05084-C5).

(2) R. H. Goldsmith, Doctorate Dissertation, University of Maryland, School of Medicine, Department of Pharmacology, August 1964.

(3) K. R. H. Wooldridge and R. Slack, *J. Chem. Soc.*, 1865 (1962).

(4) F. F. Blicke and H. C. Godt, *J. Am. Chem. Soc.*, **76**, 2799 (1954).

(5) Melting points were taken on a Mel-Temp melting point apparatus.

(6) Analysis was done by Drs. Weiler and Strauss, Oxford, England.

(7) The alkyl bromide was used to prepare all but the propyl derivatives. Propyl iodide was used because of its higher boiling point.