The Synthesis and Pharmacologic Evaluation of a Series of 8-Alkylthio-Thiated Theophyllines[1]

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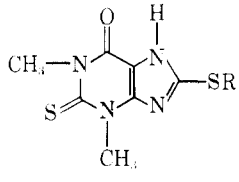
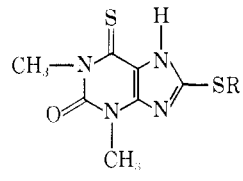
Received February 5, 1966

A series of 8-alkylthio-thiated theophyllines were prepared and screened for their pharmacologic activity. The 8-alkylthio-6-thiotheophylline series manifested two types of activity, both CNS depression and CNS stimulation. The most active CNS depressant, 8-ethylthio-6-thiotheophylline, compared well with thiopental and pentobarbital with respect to induction time and sleeping time at equivalent doses in rats. 8-(2-N,N-Diethylaminoethyl)-thio-6-thiotheophylline was by far the most potent CNS stimulant causing tonic and clonic convulsions and death within 2 min.

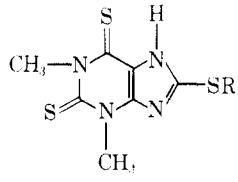
During the synthesis of a series of methylated xanthines as potential antimetabolites of purines, it was found[2] that certain 8-alkylthioxanthines possess slight anticancer activity and, unexpectedly, some central nervous system depressant activity in rats and rabbits. It was decided to further investigate these findings since it is generally held that the xanthines as a group stimulate the cerebral cortex, medulla, and the spinal cord. A series of 8-alkylthiotheophyllines was prepared in which the 2-oxygen (I), 6-oxygen (II), and the 2- and 6-oxygens (III) were replaced by sulfur on the general premise that increased lipid solubility increases CNS depressant activity. This report is primarily



I



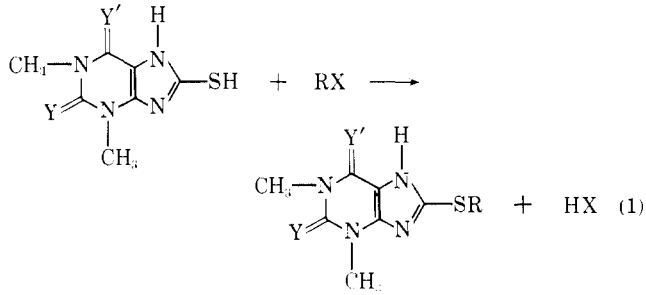
II



III

concerned with the synthesis and pharmacologic properties of these thiated theophyllines (see Tables I–V).

Chemistry.—The preparation of the 8-alkylthio-thiated theophyllines reported here was effected by the general reaction 1 in which the 8-mercapto-thiated theophylline was treated under various conditions with an alkyl sulfate or halide. The conditions for the alkylation were varied according to the reactivity of the halide, length of the alkyl group, steric factors, and the boiling point of the alkylating reagent. When yields were low because of steric hindrance, the reaction was carried out at a higher temperature by refluxing in propyl alcohol. For very reactive halides the reaction was carried out in water at 60° for 3 hr using the sodium or ammonium salts of the mercaptan and the alkyl halide.



(1)

Experimental Section

In general the 8-mercapto-thiated theophylline was refluxed with the alkyl halide in alcohol for a period of 24 hr. The alcohol solution was evaporated to dryness and the residue was dissolved in dilute NH_4OH and evaporated to dryness to convert any unreacted mercaptotheophylline to an ammonium salt which remained behind when the residue was extracted with acetone. Concentrating the acetone extract gave the crude product. The best yields were obtained when the sodium mercaptide was formed by dissolving the mercaptan in an ethanol solution of sodium ethoxide, then adding the alkyl halide and refluxing the mixture for 24 hr.

8-Mercapto-2-thiotheophylline (51) and 8-mercapto-6-thiotheophylline (1) were prepared by a method analogous to that previously reported.[3]

2,6-Dithio-8-mercaptotheophylline (71).—8-Mercapto-2-thiotheophylline (114 g, 0.5 mole) and 222 g (1.0 mole) of P_2S_5 were added to 1 l. of dry pyridine, and 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.

Procedure A.—8-Mercapto-6-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 22.5 g of 8-methylthio-6-thiotheophylline (**2**).

Procedure B.—8-Mercapto-6-thiotheophylline (22.8 g, 0.1 mole) and *n*-butyl bromide (18.9 g, 0.125 mole) were refluxed in 700 ml of alcohol for 24 hr and filtered. The filtrate was evaporated to dryness and the residue dissolved in dilute NH_4OH. The ammonia solution was evaporated to dryness and the residue was extracted with acetone and cooled to give 8-*n*-butylthio-6-thiotheophylline (**4**). The product was recrystallized from methanol.

Procedure C.—To 400 ml of absolute methanol, 2.3 g (0.1 g-atom) of sodium was added. When the sodium had reacted 22.8 g (0.1 mole) of 8-mercapto-6-thiotheophylline was added and when dissolved, 17.1 g (0.125 mole) of 1-methylpropyl bromide

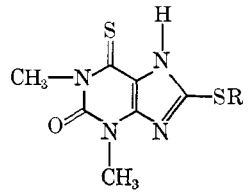
(1) Some of the compounds reported in this paper were prepared as potential anticancer agents under Public Health Service Grant No. CA-05084-C5, from the National Cancer Institute.

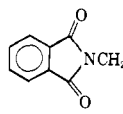
(2) R. H. Goldsmith, Doctorate Dissertation, University of Maryland School of Medicine, Department of Pharmacology, August 1964.

(3) A. J. Dietz, Jr., and R. M. Burgison, *J. Med. Chem.*, **9**, 160 (1966).

Table I

Derivatives of 8-Mercapto-6-Thiotheophylline

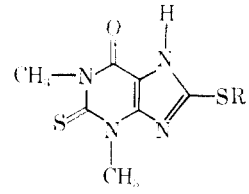


No.	R	Procedure	Mp, °C[a]	% yield	Recrystn solvent[b]	Formula	% calcd C	% calcd H	% calcd N	% found C[c]	% found H	% found N
1	H[d]	..	335–338 dec	80	A	$C_7H_8N_4OS_2$						
2	CH_3[d]	A	253	91	B	$C_8H_{10}N_4OS_2$						
3	C_2H_5[d]	A	223	72	B	$C_9H_{12}N_4OS_2$						
4	n-C_3H_7[d]	B	231	57	B	$C_{10}H_{14}N_4OS_2$						
5	n-C_4H_9[d]	B	204	62	B	$C_{11}H_{16}N_4OS_2$						
6	n-C_5H_{11}[d]	B	176–177	45	B	$C_{12}H_{18}N_4OS_2$						
7	n-C_6H_{13}[d]	B	165–166	43	B	$C_{13}H_{20}N_4OS_2$						
8	n-C_7H_{15}[d]	B	166–167	73	B	$C_{14}H_{22}N_4OS_2$						
9	n-C_8H_{17}[d]	B	161	49	A	$C_{15}H_{24}N_4OS_2$						
10	n-C_9H_{19}[d]	B	152	37	A	$C_{16}H_{26}N_4OS_2$						
11	n-$C_{10}H_{21}$[d]	B	151	45	A	$C_{17}H_{28}N_4OS_2$						
12	n-$C_{11}H_{23}$	B	153	54	A	$C_{18}H_{30}N_4OS_2$	56.54	7.85	14.66	56.38	7.78	14.78
13	n-$C_{12}H_{25}$	B	151	62	A	$C_{19}H_{32}N_4OS_2$	57.58	8.08	14.14	57.98	8.33	13.80
14	$(CH_3)_2CH$[d]	B	255–256 dec	53	B	$C_{10}H_{14}N_4OS_2$						
15	CH_2=$CHCH_2$	B	243 dec	70	A	$C_{10}H_{12}N_4OS_2$	44.78	4.48	20.90	45.14	4.69	21.38
16	$CH_3CH_2CH(CH_3)$	C	230	85	A	$C_{11}H_{16}N_4OS_2$	46.48	5.63	19.72	46.42	5.52	19.70
17	$CH_3CH(CH_3)CH_2$	C	245	85	A	$C_{11}H_{16}N_4OS_2$	46.48	5.63	19.72	46.32	5.61	19.70
18	C_6H_{11}	C	240–241	35	A	$C_{13}H_{18}N_4OS_2$	50.32	5.81	18.06	50.14	5.72	18.12
19	C_5H_4N-2-CH_2[e]	E	243 dec	68	C	$C_{13}H_{13}N_5OS_2$	48.90	4.08	21.94	49.28	4.10	21.89
20	C_5H_4N-3-CH_2	E	281–282 dec	72	C	$C_{13}H_{13}N_5OS_2$	48.90	4.08	21.94	48.58	4.16	21.94
21	C_5H_4N-4-CH_2	E	234 dec	74	C	$C_{13}H_{13}N_5OS_2$	48.90	4.08	21.94	49.07	4.13	22.10
22	$C_5H_{10}N(CH_2)_2$[f]	E	234 dec	80	C	$C_{14}H_{21}N_5OS_2$	49.56	6.19	20.65	49.97	6.24	20.25
23	C_4H_7O-2-CH_2[g]	D	213–214	60	A	$C_{12}H_{16}N_4O_2S_2$	46.15	5.13	17.95	46.56	5.15	17.91
24	p-$FC_6H_4CO(CH_2)_3$	F	215–216	45	C	$C_{17}H_{17}FN_4O_2S_2$	52.04	4.34	14.29	52.32	4.44	14.32
25	$C_4H_8NO(CH_2)_2$[h]	E	295 dec	70	C	$C_{13}H_{19}N_5O_2S_2$	45.75	5.57	20.53	45.35	5.08	20.64
26	$C_4H_8N(CH_2)_2$[i]	G	238 dec	75	A	$C_{13}H_{19}N_5OS_2$	48.00	5.85	21.54	48.39	5.75	21.58
27	$CH_2OHCH_2CH_2$	D	161	50	A	$C_{10}H_{14}N_4O_2S_2$	41.96	4.89	19.58	42.41	4.77	20.00
28	$CH_3CHOHCH_2$	D	145	43	A	$C_{10}H_{14}N_4O_2S_2$	41.96	4.89	19.58	42.33	5.28	19.55
29	$H_2NCH_2CH_2$	G	193–195	73	C	$C_9H_{13}N_5OS_2$	39.85	4.80	25.83	39.52	4.88	25.65
30	N-Ethyl-3-piperidyl	E	181–182	75	A	$C_{14}H_{21}N_5OS_2$	49.56	6.19	20.65	49.26	5.90	20.70
31	2-C_4H_3S[j]	D	>350	42	A	$C_{11}H_{10}N_4OS_3$	42.58	3.23	18.06	42.90	3.57	18.03
32	$(CH_3)_2NCH_2CH_2$	E	229	65	C	$C_{11}H_{17}N_5OS_2$	44.15	5.68	23.41	44.52	5.66	23.45
33	$C_3H_7CH(CH_3)$	D	157	56	B	$C_{12}H_{18}N_4OS_2$	48.32	6.04	18.79	48.54	5.11	18.95
34	$C_4H_9CH(CH_3)$	D	138	59	B	$C_{13}H_{20}N_4OS_2$	50.00	6.41	17.95	50.46	6.42	17.95
35	$C_6H_5CH_2$	F	244–246 dec	36	A	$C_{14}H_{14}N_4OS_2$	52.83	4.40	17.61	52.76	4.42	17.28
36	$C_5H_7CH(C_2H_5)$	D	165 dec	48	B	$C_{13}H_{20}N_4OS_2$	50.00	6.41	17.95	49.99	6.21	18.00
37	$C_6H_{13}CH(CH_3)$	D	169	46	B	$C_{15}H_{24}N_4OS_2$	52.94	7.06	16.47	52.46	7.06	16.47
38	$(CH_3)_2CHCH_2CH_2$	D	219	51	B	$C_{12}H_{18}N_4OS_2$	48.32	6.04	18.79	48.66	6.14	18.88
39	$(CH_3)_3CCH_2CH_2$	D	219–220	50	B	$C_{13}H_{20}N_4OS_2$	50.00	6.41	17.95	50.24	6.73	17.75
40	$C_4H_9CH(C_2H_5)CH_2$	D	178	56	B	$C_{15}H_{24}N_4OS_2$	52.94	7.06	16.47	52.51	6.65	16.50
41	$(C_2H_5)_2CHCH_2$	D	191	59	B	$C_{13}H_{20}N_4OS_2$	50.00	6.41	17.95	49.95	6.42	17.92
42	$(C_2H_5)_2NCH_2CH_2$	G	176–177	78	C	$C_{13}H_{21}N_5OS_2$	47.71	6.42	21.42	47.58	6.51	21.25
43		F	287–288	62	C	$C_{17}H_{15}N_5O_3S_2$	50.84	3.74	17.46	50.43	3.78	17.10
44	$C_6H_5CH_2CH_2$	F	205	45	C	$C_{15}H_{16}N_4OS_2$	54.22	4.82	16.87	54.21	5.04	16.85
45	$C_6H_5(CH_2)_3$	F	149–151	36	C	$C_{16}H_{18}N_4OS_2$	55.49	5.20	16.18	55.95	5.43	16.18
46	p-$O_2NC_6H_4CH_2$	F	290 dec	68	C	$C_{14}H_{13}N_5O_3S_2$	46.28	3.58	19.28	46.58	3.85	19.61
47	3,4-$(CH_3)_2C_6H_3CH_2$	F	266 dec	48	C	$C_{16}H_{18}N_4OS_2$	55.49	5.20	16.18	55.89	5.65	15.90
48	CH_3COCH_2	B	185–187	58	A	$C_{10}H_{12}N_4O_2S_2$	42.25	4.23	19.72	42.62	4.22	19.42
49	Cyclopentyl	B	260	82	A	$C_{12}H_{16}N_4OS_2$	48.65	5.41	18.92	48.66	5.47	18.90
50	p-Methylcyclohexyl	D	192	53	A	$C_{14}H_{20}N_4OS_2$	51.85	6.17	17.28	51.82	6.03	17.12

[a] Melting point taken on a Mel-Temp melting point apparatus and not corrected. [b] A = ethanol, B = methanol, C = dimethylformamide, D = dissolved in dilute NaOH and precipitated with dilute HCl. [c] Analysis done by Drs. G. Weiler and J. B. Strauss, Microanalytical Laboratory, Oxford, England. [d] See ref 3. [e] C_5H_4N = pyridyl. [f] $C_5H_{10}N$ = piperidino. [g] C_4H_7O = tetrahydrofuryl. [h] C_4H_8NO = morpholino. [i] C_4H_8N = pyrrolidinyl. [j] C_4H_3S = 2-thienyl.

TABLE II

DERIVATIVES OF 8-MERCAPTO-2-THIOTHEOPHYLLINE

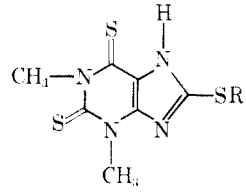


No.	R	Procedure	Mp, °C[a]	% yield	Recrystn solvent[b]	Formula	% calcd C	% calcd H	% calcd N	% found C[c]	% found H	% found N
51	H[d]	..	335 dec	89	A	$C_7H_8N_4OS_2$						
52	CH_3[d]	A	335	93	B	$C_8H_{10}N_4OS_2$						
53	C_2H_5[d]	A	290	90	B	$C_9H_{12}N_4OS_2$						
54	n-C_3H_7[d]	B	214–215	45	B	$C_{10}H_{14}N_4OS_2$						
55	n-C_4H_9[d]	B	214–215	48	B	$C_{11}H_{16}N_4OS_2$						
56	n-C_5H_{11}[d]	B	198	35	B	$C_{12}H_{18}N_4OS_2$						
57	n-C_6H_{13}[d]	B	181–182	48	B	$C_{13}H_{20}N_4OS_2$						
58	n-C_7H_{15}[d]	B	175	46	B	$C_{14}H_{22}N_4OS_2$						
59	n-C_8H_{17}[d]	B	163–164	52	A	$C_{15}H_{24}N_4OS_2$						
60	n-C_9H_{19}[d]	B	160	51	A	$C_{16}H_{26}N_4OS_2$						
61	n-$C_{10}H_{21}$[d]	B	153–154	55	A	$C_{17}H_{28}N_4OS_2$						
62	n-$C_{14}H_{29}$	B	138	38	A	$C_{18}H_{30}N_4OS_2$	56.54	7.85	14.66	56.23	7.75	14.82
63	n-$C_{12}H_{25}$	B	143	34	A	$C_{19}H_{32}N_4OS_2$	57.58	8.08	14.14	57.53	8.06	13.82
64	C_6H_{11}	C	239	33	B	$C_{13}H_{18}N_4OS_2$	50.32	5.81	18.06	50.08	5.83	17.95
65	C_5H_4N-2-CH_2[e]	E	257 dec	78	C	$C_{13}H_{13}N_5OS_2$	48.90	4.07	21.94	49.07	4.01	21.85
66	C_5H_4N-3-CH_2	E	276	73	C	$C_{13}H_{13}N_5OS_2$	48.90	4.07	21.94	48.45	4.39	22.04
67	C_5H_4N-4-CH_2	E	267 dec	75	C	$C_{13}H_{13}N_5OS_2$	48.90	4.07	21.94	48.61	4.21	22.04
68	$C_5H_{10}N(CH_2)_2$[f]	E	232–234 dec	72	C	$C_{14}H_{21}N_5OS_2$	49.56	6.19	20.65	49.29	6.39	20.63
69	C_4H_7O-2-CH_2[g]	E	228–229 dec	68	C	$C_{13}H_{19}N_5O_2S_2$	45.75	5.75	20.53	45.83	5.61	20.05
70	$H_2NCH_2CH_2$	G	218–219	82	C	$C_9H_{13}N_5OS_2$	39.85	4.80	25.83	40.00	4.69	25.39

[a–g] See corresponding footnotes in Table I.

TABLE III

DERIVATIVES OF 2,6-DITHIO-8-MERCAPTOTHEOPHYLLINE



No.	R	Procedure	Mp, °C[a]	% yield	Recrystn solvent[b]	Formula	% calcd C	% calcd H	% calcd N	% found C[c]	% found H	% found N
71	H	..	310–311 dec	74	D	$C_7H_8N_2S_3$	34.43	3.28	22.95	34.90	3.28	22.95
72	CH_3	A	271–272 dec	98	C	$C_8H_{10}N_4S_3$	37.21	3.86	21.71	37.35	4.03	21.75
73	C_2H_5	A	284–287 dec	98	C	$C_9H_{12}N_4S_3$	39.71	4.41	20.59	39.29	4.67	20.95
74	n-C_3H_7	D	214	45	A	$C_{10}H_{14}N_4S_3$	41.96	4.89	19.58	42.40	4.62	20.05
75	n-C_4H_9	D	137	34	A	$C_{11}H_{16}N_4S_3$	44.00	5.33	18.67	44.35	5.71	19.06
76	n-C_5H_{11}	D	196	37	A	$C_{12}H_{18}N_4S_3$	45.86	5.73	17.83	46.10	5.65	18.25
77	n-C_6H_{13}	D	123–125	47	A	$C_{13}H_{20}N_4S_3$	47.56	6.10	17.07	47.95	6.17	17.35
78	n-C_7H_{15}	D	171	43	A	$C_{14}H_{22}N_4S_3$	49.12	6.43	16.37	49.45	6.63	16.72
79	n-C_8H_{17}	D	142	53	A	$C_{15}H_{24}N_4S_3$	50.56	6.74	15.73	51.01	6.85	15.82
80	n-C_9H_{19}	D	145	65	A	$C_{16}H_{26}N_4S_3$	51.89	7.03	15.14	52.44	7.13	14.95
81	n-$C_{10}H_{21}$	D	130	58	A	$C_{17}H_{28}N_4S_3$	53.13	7.29	14.58	53.60	7.31	14.35
82	C_6H_{11}	D	224	26	A	$C_{13}H_{18}N_4S_3$	47.85	5.52	17.18	48.30	5.72	17.66

[a–c] See corresponding footnotes in Table I.

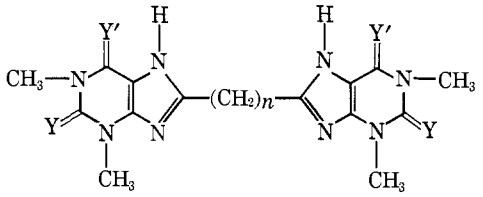
was added, and the mixture refluxed for 24 hr. The solution was filtered and evaporated to dryness. The residue was dissolved in dilute NH_4OH, evaporated to dryness, extracted with acetone, and concentrated. The precipitate was filtered and recrystallized from ethanol to give 8-(1-methylpropyl)thio-6-thiotheophylline (**16**).

Procedure D.—To 700 ml of absolute alcohol, 1.15 g (0.05 g-atom) of sodium was added. When the sodium had reacted 12.2 g (0.05 mole) of 2,6-dithio-8-mercaptotheophylline was added and, when dissolved, 10.6 g (0.0625 mole) of n-propyl iodide was added. The solution was refluxed for 24 hr. The solution was filtered and evaporated to dryness. The residue was dissolved in dilute NH_4OH, evaporated to dryness, extracted with acetone, and concentrated to give 2,6-dithio-8-propylthiotheophylline (**74**).

Procedure E.—8-Mercapto-6-thiotheophylline (11.4 g, 0.05 mole) was dissolved in 200 ml of concentrated NH_4OH. To this 8.6 g (0.053 mole) of 2-picolyl chloride hydrochloride was added and the mixture was stirred at 60° for 3 hr. The solution was cooled to 5° and the precipitate was filtered and washed with

Table IV

Derivatives of 8,8′-Methylenebis(thiotheophylline)

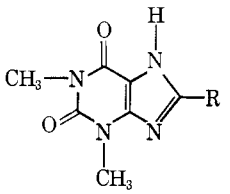


No.	Y	Y′	n	Procedure	Mp, °C[a]	% yield	Recrystn solvent[b]	Formula	% calcd C	% calcd H	% calcd N	% found C[c]	% found H	% found N
83	S	O	1	H	>350	55	D	$C_{15}H_{16}N_8O_2S_2$	44.58	3.95	27.72	44.89	4.41	27.80
84	S	O	2	H	>350	53	D	$C_{16}H_{18}N_8O_2S_2$	45.93	4.31	26.79	45.61	4.61	26.95
85	S	O	3	H	>350	53	D	$C_{17}H_{20}N_8O_2S_2$	47.22	4.63	25.92	47.24	4.80	26.40
86	S	O	4	H	>350	48	D	$C_{18}H_{22}N_8O_2S_2$	48.43	4.93	25.11	48.11	4.92	25.10
87	S	O	5	H	>350	45	D	$C_{19}H_{24}N_8O_2S_2$	49.56	5.22	24.35	49.13	5.10	24.60
88	O	S	1	H	>350	51	D	$C_{15}H_{16}N_8O_2S_2$	44.58	3.95	27.72	44.12	4.41	27.30
89	O	S	2	H	>350	48	D	$C_{16}H_{18}N_8O_2S_2$	45.93	4.31	26.79	46.32	4.72	26.48
90	O	S	4	H	325–328 dec	49	D	$C_{18}H_{22}N_8O_2S_2$	48.43	4.93	25.11	48.85	4.98	25.01
91	O	S	5	H	268–270 dec	60	D	$C_{19}H_{24}N_8O_2S_2$	49.56	5.22	24.35	49.10	5.44	24.60
92	O	S	6	H	325 dec	39	D	$C_{20}H_{26}N_8O_2S_2$	50.63	5.48	23.62	51.02	5.69	23.59
93	O	S	8	H	250 dec	42	D	$C_{22}H_{30}N_8O_2S_2$	52.41	5.98	22.31	52.87	6.21	22.11

[a–c] See corresponding footnotes in Table I.

Table V

Miscellaneous Derivatives of Theophylline



No.	R	Procedure	Mp, °C[a]	% yield	Recrystn solvent[b]	Formula	% calcd C	% calcd H	% calcd N	% found C[c]	% found H	% found N
94	*c*-$C_6H_{11}S$–	D	186–187	45	A	$C_{13}H_{18}N_4O_2S$	53.06	6.12	19.05	53.25	6.10	19.08
95	$HSCH_2$	H	266–267	62	A	$C_8H_{10}N_4O_2S$	42.48	4.42	24.78	42.50	4.55	24.85
96	CH_3SCH_2	A	228–229	62	A	$C_9H_{12}N_4O_2S$	45.00	5.00	23.33	44.57	5.14	22.90
97	$(CH_3)_3CSCH_2$	H	203	65	B	$C_{12}H_{18}N_4O_2S$	51.06	6.38	19.86	51.16	6.51	19.83
98	CH_3CHSH	H	243 dec	50	A	$C_9H_{12}N_4O_2S$	45.00	5.00	23.33	45.02	5.31	23.22
99	$HSCH_2CH_2$	H	306 dec	62	A	$C_9H_{12}N_4O_2S$	45.00	5.00	23.33	45.09	5.24	23.18
100	$C_6H_5CH_2SCH_2$	H	210–212	71	A	$C_{15}H_{16}N_4O_2S$	56.96	5.06	17.72	56.51	5.11	17.76
101	$C_6H_5SCH_2$	H	235	54	C	$C_{14}H_{14}N_4O_2S$	55.63	4.64	18.54	55.36	4.68	18.40
102	$CH_3SCH_2CH_2$	A	231–232	60	C	$C_{10}H_{14}N_4O_2S$	47.24	5.51	22.05	46.90	5.44	22.31

[a–c] See corresponding footnotes in Table I.

water. The product, 8-(2-pyridylmethyl)thio-6-thiotheophylline (**19**), was recrystallized from dimethylformamide and water.

Procedure F.—To 700 ml of 1-propanol, 1.15 g (0.05 g-atom) of sodium was added. When the sodium had reacted, 11.4 g (0.05 mole) of 8-mercapto-6-thiotheophylline was added and when dissolved 12.06 g (0.0625 mole) of γ-chloro-*p*-fluorobutyrophenone was added and the mixture refluxed for 24 hr. The solution was filtered and evaporated to dryness. The residue was dissolved in dilute NH_4OH, evaporated to dryness, extracted several times with acetone, and concentrated to give 8-(3-*p*-fluorobenzoylpropyl)thio-6-thiotheophylline (**24**). The product was recrystallized from dimethylformamide and water.

Procedure G.—8-Mercapto-6-thiotheophylline (11.4 g, 0.05 mole) was dissolved in 150 ml of water contining 4 g (0.01 mole) of NaOH. N-(2-Chloroethyl)pyrrolidine hydrochloride (7.1 g, 0.053 mole) was added and the mixture was stirred at 60° for 3 hr. The solution was cooled to 5°, and the precipitate was filtered and washed with water. The crude product 8-(2-N-pyrrolidinoethyl)thio-6-thiotheophylline (**26**) was recrystallized from dimethylformamide.

Procedure H.—A mixture of 18.6 g (0.1 mole) of 5,6-diamino-1,3-dimethyl-2-thiouracil,[4] 5.2 g (0.05 mole) of malonic acid, and 35 ml of ethylene glycol was heated at 190° for 1.5 hr. Water (300 ml) containing 8 g (0.2 mole) of NaOH was added and the solution was boiled for 15 min. Charcoal was added and the solution was boiled for an additional 2 min, filtered, and cooled. Carbon dioxide was bubbled through the filtrate until pH 8 was reached. The precipitate was filtered, dissolved in dilute NaOH, and heated to boiling, charcoal was added, and the solution filtered. The filtrate was cooled and the product, 8,8-methylenebis(2-thiotheophylline) (**83**) (Table IV), was precipitated by the addition of dilute HCl.

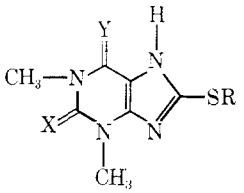
Pharmacology General Screen.—Groups of ten male albino rats weighing between 150 and 250 g were used for each compound. The compounds were injected intraperitoneally as their sodium salt in a dose of 100 mg/kg. The animals were observed and rated subjectively for: changes in response to pain (inflicted by the pressure of a bulldog clamp on the tail), ataxia, sedation, hypnosis, stimulation, respiration, heart rate, and vasodilatation (changes in skin color of the ears, tail, and foot pads). Results are recorded in Table VI.

Diuretic Screen.—Two groups of two rats each were used for testing the effect of selected compounds on the volume of urine excreted over a 24-hr period. One group was injected intraperitoneally with 50 mg/kg of the sodium salt of the compound to be tested. The other group received an equivalent dose of

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

TABLE VI

GENERAL PHARMACOLOGIC EVALUATION OF SOME THIATED THEOPHYLLINES



No.	X	Y	R	Activity[a] Anal	Ataxia	Sed	Hypn	Stim	Resp	Heart rate	Vasodil
1	O	S	H	0	0	0	0	0	+1	+1	+1
2	O	S	CH_3	0	+1	0	0	+2	+2	+2	+3
3	O	S	C_2H_5	+1	+1	+3	+3	0	+2	+2	+1
4	O	S	C_3H_7	+1	+2	+3	+3	0	+1	+1	0
5	O	S	C_4H_9	0	+2	+3	+2	0	+1	+1	0
6	O	S	C_5H_{11}	0	+2	+3	+1	0	0	0	0
7	O	S	C_6H_{13}	0	0	+1	0	0	0	0	0
8	O	S	C_7H_{15}	0	0	0	0	0	0	0	0
9	O	S	C_8H_{17}	0	0	0	0	0	0	0	0
10	O	S	C_9H_{19}	0	0	0	0	0	0	0	0
11	O	S	$C_{10}H_{21}$	0	0	0	0	0	0	0	0
12	O	S	$C_{11}H_{23}$	0	0	0	0	0	0	0	0
13	O	S	$C_{12}H_{25}$	0	0	0	0	0	0	0	0
14	O	S	Isopropyl	0	+1	+3	+2	0	0	0	0
15	O	S	Allyl	0	+1	+3	+1	0	+1	+1	0
16	O	S	1-Methylpropyl	0	+1	+3	+1	0	+1	+1	0
17	O	S	2-Methylpropyl	0	+1	+3	+1	0	0	0	0
18	O	S	Cyclohexyl	0	0	0	0	0	0	0	0
19	O	S	2-Pyridylmethyl	0	0	0	0	+1	+2	+2	0
20	O	S	3-Pyridylmethyl	0	+1	0	0	+1	+1	+1	0
21	O	S	4-Pyridylmethyl	0	0	0	0	0	+1	+1	0
22	O	S	2-N-Piperidinoethyl	0	+3	0	0	+3	+1	+1	0
23	O	S	Tetrahydrofurfuryl	0	+2	+1	+1	+1	−1	−1	−1
24	O	S	*p*-Fluorobenzoylpropyl	0	+1	0	0	+3	−1	−1	0
25	O	S	2-N-Morpholinoethyl	0	0	0	0	+1	−1	−1	0
26	O	S	2-N-Pyrrolidinoethyl	0	+1	0	0	+3	+3	+2	−1
27	O	S	3-Hydroxypropyl	+1	+1	+3	+2	0	+1	+1	0
28	O	S	2-Hydroxypropyl	0	+1	+2	0	0	+1	+1	0
29	O	S	2-Aminoethyl	0	+1	0	0	+1	+2	+1	0
30	O	S	3-N-Ethylpiperidino	0	+1	0	0	+3	+3	+3	−2
31	O	S	2-Thienyl	0	0	+1	0	0	0	0	0
32	O	S	2-N,N-Dimethylaminoethyl	0	0	0	0	+2	+3	+2	−1
33	O	S	1-Methylbutyl	+1	+1	+3	+3	0	−1	+1	0
34	O	S	1-Methylpentyl	0	+1	+2	+1	0	−1	0	0
35	O	S	Benzyl	0	+1	+2	0	0	+1	0	0
36	O	S	1-Ethylbutyl	0	+2	+2	+1	0	−1	+1	0
37	O	S	1-Methylheptyl	0	0	+1	0	0	0	0	0
38	O	S	3-Methylbutyl	0	+1	+2	+1	0	+1	+1	0
39	O	S	3,3-Dimethylbutyl	0	0	+1	0	0	0	0	0
40	O	S	2-Ethylhexyl	0	0	0	0	0	0	0	0
41	O	S	2-Ethylbutyl	0	0	0	0	0	0	0	0
42	O	S	2-N,N-Diethylaminoethyl	0	+1	0	0	+3	+2	+3	−2
43	O	S	2-N-Phthalimidoethyl	0	0	0	0	0	0	0	0
49	O	S	Cyclopentyl	0	0	0	0	0	0	0	0
50	O	S	4-Methylcyclohexyl	0	0	0	0	0	0	0	0
51	S	O	H	0	+1	0	0	+1	+1	+1	+1
52	S	O	CH_3	0	+1	0	0	+1	+2	+2	+1
53	S	O	C_2H_5	0	+2	+1	0	0	+1	+1	0
54	S	O	C_3H_7	0	+2	+2	0	0	+1	+1	0
55	S	O	C_4H_9	0	+1	+1	0	0	0	0	0
56	S	O	C_5H_{11}	0	0	0	0	0	0	0	0
57	S	O	C_6H_{13}	0	0	0	0	0	0	0	0
58	S	O	C_7H_{15}	0	0	0	0	0	0	0	0
59	S	O	C_8H_{17}	0	0	0	0	0	0	0	0
60	S	O	C_9H_{19}	0	0	0	0	0	0	0	0
61	S	O	$C_{10}H_{21}$	0	0	0	0	0	0	0	0
62	S	O	$C_{11}H_{23}$	0	0	0	0	0	0	0	0
63	S	O	$C_{12}H_{25}$	0	0	0	0	0	0	0	0
64	S	O	Cyclohexyl	0	0	0	0	0	1	0	0

Table VI (*Continued*)

No.	X	Y	R	Activity[a] Anal	Ataxia	Sed	Hypn	Stim	Resp	Heart rate	Vasodil
65	S	O	2-Pyridylmethyl	0	+2	+1	0	0	−1	0	0
66	S	O	3-Pyridylmethyl	0	+1	+1	0	0	0	0	0
67	S	O	4-Pyridylmethyl	0	+1	+1	0	0	+1	0	0
68	S	O	2-N-Piperidinoethyl	0	+1	0	0	+2	+1	+1	0
69	S	O	2-N-Morpholinoethyl	0	0	0	0	0	0	0	0
70	S	O	2-Aminoethyl	0	0	0	0	0	0	0	0
71	S	S	H	0	+1	0	0	+1	+2	+2	0
72	S	S	CH_3	0	+3	+1	0	+2	+3	+2	+2
73	S	S	C_2H_5	0	+1	+3	+3	0	+2	+1	0
74	S	S	C_3H_7	0	+2	+2	+2	0	+1	+1	0
75	S	S	C_4H_9	0	+2	+2	+2	0	0	0	0
76	S	S	C_5H_{11}	0	+2	+1	0	0	0	0	0
77	S	S	C_6H_{13}	0	0	+1	0	0	0	0	0
78	S	S	C_7H_{15}	0	0	0	0	0	0	0	0
79	S	S	C_8H_{17}	0	0	0	0	0	0	0	0
80	S	S	C_9H_{19}	0	0	0	0	0	0	0	0
81	S	S	$C_{10}H_{21}$	0	0	0	0	0	0	0	0
82	S	S	Cyclohexyl	0	0	0	0	0	0	0	0
94	O	O	Cyclohexyl	0	0	0	0	0	0	0	0

[a] Anal = analgetic, Sed = sedative, Hypn = hypnotic, Stim = stimulating, Resp = effect on respiration, Vasodil = vasodilatory; 0 = normal, +1 = slight increase, +2 = moderate increase, +3 = large increase, −1 = slight decrease, −2 = moderate decrease, −3 = large decrease.

Table VII

Diuretic Action of Some Thiated Theophyllines

No.	Derivative of theopylline	T/C[a] 6 hr	24 hr
1	8-Mercapto-6-thio	2.26	0.95
2	8-Methylthio-6-thio	0.16	1.21
3	8-Ethylthio-6-thio	0.89	1.47
39	8-Mercapto-2-thio	0.93	0.93
40	8-Methylthio-2-thio	3.85	1.72
41	8-Ethylthio-2-thio	9.35	3.07
42	8-Propylthio-2-thio	0.73	2.75
71	2,6-Dithio-8-mercapto	0.65	1.63
72	2,6-Dithio-8-methylthio	2.28	0.63
73	2,6-Dithio-8-ethylthio	3.86	2.03
Theophylline		9.85	2.16
Chlorthiazide		2.17	1.57

[a] Compounds were given intraperitoneally, 50 mg/kg, as the sodium salt. T/C = volume of urine of test animals/volume of urine of control animals.

normal saline. Because of the variation of urine output from day to day a control group was run with each test group and a T/C value was obtained by the ratio of the volume for the control. The T/C values were compared to those obtained from chlorthiazide and theophylline (a potent diuretic in rats) (Table VII).

Hypnotic Effect.—In compounds that produced a loss of the righting reflex the time required for loss of this reflex was recorded as the induction time, and the time from the loss of righting to regaining it was recorded as the sleeping time. The compounds were administered in doses of 100 mg/kg ip to groups of 10 male albino rats. The induction times and sleeping time were compared to those produced by thiopental and pentobarbital (Table VIII).

Effect on Smooth Muscle Studies *in vitro*.—A small strip of intestine was removed from the rabbit and suspended in oxygenated Ringer–Lock solution maintained at a constant temperature of 37.5°. Movements of the smooth muscle were recorded kymographically by way of the attachment of the tissue to isotonic gravity levers. Test procedures were for the most part conventional and have been described previously.[5] No significant effects were observed for any of the selected compounds tested.

(5) P. M. Lish, K. W. Dungan, and E. L. Peters, *J. Pharmacol. Exptl. Therap.*, **129**, 191 (1960).

Convulsant Effect.—In compounds that produced excessive stimulation the time for onset of tremors, the duration of tremors and the type of tremors are recorded in Table IX.

Discussion

While testing these compounds two major effects became apparent: CNS depressant activity and CNS stimulant activity. From the time of onset of hypnosis and length of sleeping time a correlation between the structure and activity of these compounds was deduced. From the data in Table VIII it can be seen that the greatest activity lies in the unbranched alkyl derivatives. Activity decreases after propyl with the length of the carbon chain. Unsaturated groups are less active then saturated ones. As branching increases the activity decreases. Hydroxylation or other substituents on the chain also decreases activity. The 6-thiotheophylline series is more active than the 2,6-dithiotheophylline series, while the 2-thiotheophyllines are inactive as hypnotics.

For CNS stimulant activity an amino group separated from the sulfur atom in the 8-position by two carbon atoms is required. The activity increases as the amine hydrogens are replaced by longer alkyl chains. The amine nitrogen may be part of a ring system, but this system must be saturated. The activity is greater in the 6-thiotheophylline series than in the 2-thiotheophylline series.

The most active compound pharmacologically was 8-ethylthio-6-thiotheophylline. It showed activity as a sedative–hypnotic. The activity of this compound, intraperitoneally, compared very favorably with thiopental and pentobarbital, while being less toxic (ED_{50} = 25 mg/kg in rats, LD_{50} = 162 mg/kg in rats) and not depressing the respiration as do the barbiturates. The pharmacology of this compound will be published elsewhere when complete. Of the compounds tested 8-ethylthio-2-thiotheophylline possessed the greatest diuretic activity. 8-(2-N,N-Diethylaminoethyl)thio-6-

TABLE VIII

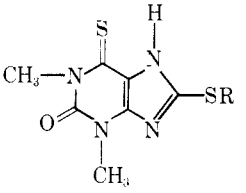
HYPNOTIC EFFECT OF SOME 8-ALKYLTHIO-6-THIOTHEOPHYLLINE AND 2,6-DITHIO-8-ALKYLTHIOTHEOPHYLLINE

No.	Derivative of theophylline	Dose, mg/kg[a]	Induction time, sec	Sleeping time, min
3	8-Ethylthio-6-thio	50	75 ± 5[b]	48 ± 2
	8-Ethylthio-6-thio	100	80 ± 10	159 ± 11
4	8-Propylthio-6-thio	100	123 ± 16	167 ± 11
5	8-Butylthio-6-thio	100	185 ± 22	45 ± 10
6	8-Pentylthio-6-thio	100	240 ± 35	20 ± 4
14	8-Isopropylthio-6-thio	100	125 ± 10	16 ± 1
15	8-Allylthio-6-thio	100	139 ± 8	11 ± 2
16	8-(1-Methylpropyl)thio-6-thio	100	140 ± 8	4 ± 0.5
17	8-(2-Methylpropyl)thio-6-thio	100	240 ± 18	3.5 ± 0.5
23	8-Tetrahydrofurfurylthio-6-thio	100	135 ± 10	5 ± 0.5
27	8-(3-Hydroxypropyl)thio-6-thio	100	189 ± 11	8 ± 1.5
33	8-(1-Methylbutyl)thio-6-thio	100	155 ± 9	35 ± 7
34	8-(1-Methylpentyl)thio-6-thio	100	300 ± 20	6 ± 1
36	8-(1-Ethylbutyl)thio-6-thio	100	360 ± 30	2 ± 0.5
38	8-(3-Methylbutyl)thio-6-thio	100	340 ± 30	3.5 ± 1
72	2,6-Dithio-8-methylthio	100	300 ± 35	2 ± 0.5
73	2,6-Dithio-8-ethylthio	100	89 ± 8	45 ± 2
74	2,6-Dithio-8-propylthio	100	100 ± 11	38 ± 2
75	2,6-Dithio-8-butylthio	100	121 ± 12	30 ± 1.5
Pentobarbital		50	177 ± 11	40 ± 2
Pentobarbital		100	104 ± 10	All died
Thiopental		50	101 ± 5	35 ± 2
Thiopental		100	93 ± 5	All died

[a] Sodium salt. [b] One standard deviation.

TABLE IX

CONVULSANT PROPERTIES OF SOME 8-ALKYLTHIO-6-THIOTHEOPHYLLINES



No.	R	Onset, min	Duration, min	Type of convulsions
24	*p*-Fluorobenzoylpropyl	2	10, death	Tonic and clonic
22	2-N-Piperidinoethyl	1	5, death	Tonic and clonic
25	2-N-Morpholinoethyl	3	5	Tremors
26	2-N-Pyrrolidinoethyl	2	13, death	Tonic and clonic
29	2-Aminoethyl	2	10	Tremors
30	3-N-Ethylpiperidino	1.5	5.5, death	Tonic and clonic
32	2-N,N-Dimethylaminoethyl	2	10	Tremors
42	2-N,N-Diethylaminoethyl	1	2, death	Tonic and clonic

thiotheophylline was the most potent stimulant causing tonic and clonic convulsions in less than 60 sec and death within 2 min at 100 mg/kg in rats. In all this is a very active series possessing many and varied pharmacologic effects and provides the opportunity for further research.