352. *The Synthesis of Some 6-Thioxanthines.*

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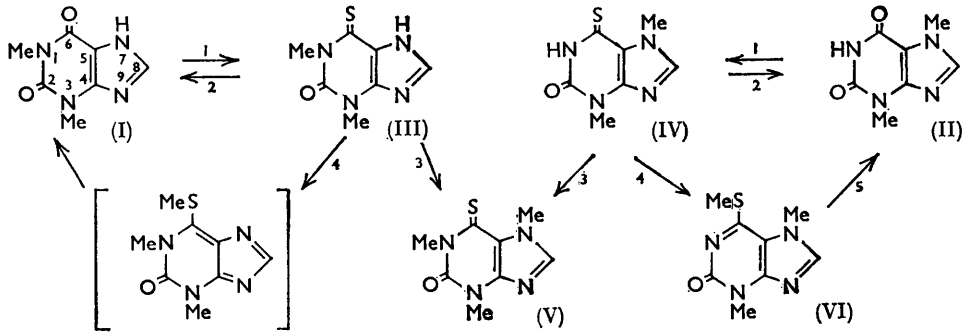
A series of 1,3- and 3,7-disubstituted 6-thioxanthines, of interest as broncho- and coronary dilators, has been prepared by selective thionation of the corresponding xanthines with phosphorus pentasulphide in pyridine. 1,3,7-Trialkyl-6-thioxanthines could not be prepared in this way but were readily obtained from 1,3-dialkyl-6-thioxanthines.

Xanthine (2,6-dihydroxypurine) reacts selectively in the 6-position with phosphorus pentasulphide in pyridine to give the corresponding thio-compound.[1] We have found that this replacement also takes place with 1,3- and 3,7-dialkylxanthines, but not with 1,3,7-trialkylxanthines, giving a series of 6-thioxanthines of interest as broncho- and

[1] Beaman, *J. Amer. Chem. Soc.*, 1954, **76**, 5633.

coronary dilators. Thus, theophylline (I) and theobromine (II) gave 6-thiotheophylline (III) and 6-thiotheobromine (IV), respectively, in almost quantitative yield, whereas caffeine (1,3,7-trimethylxanthine) was recovered after prolonged treatment with the reagent. This difference is understandable if thionation depends on enolisation of the oxygen atom in position 6. Caffeine is firmly fixed in the diketonic configuration by the methyl groups, but the formulæ oı theobromine (II) and theophylline (I) may be written in enolic forms.

The structure of 6-thiotheophylline (III) was confirmed by reconversion into theophylline with dilute nitric acid and by direct comparison with authentic 2-thiotheophylline synthesised by Traube's method.[2] The ultraviolet absorption spectra of the two compounds showed marked differences. Again, on methylation with methyl sulphate, both 6-thiotheophylline and 6-thiotheobromine gave 6-thiocaffeine (V), a compound previously obtained, together with 2,6-dithiocaffeine, by treating caffeine with phosphorus trisulphide in kerosene.[3] Under milder methylation conditions, 6-thiotheobromine gave the *S*-methyl derivative (VI) as the main product, but the corresponding compound from 6-thiotheophylline was unstable and decomposed to give methanethiol and theophylline. The interrelations in this series are shown in the chart.



Reagents: 1, P_2S_5 in pyridine. 2, 50% Nitric acid. 3, Methyl sulphate at 40°. 4, MeI at 20°. 5, Dilute hydrochloric acid.

The ultraviolet absorption data for the thioxanthines are collected in Table 1. Replacement of the 2-oxygen atom of theophylline by sulphur led to a relatively small bathochromic displacement (17 mμ) in neutral solution,[4] comparable to the difference between

TABLE 1.

Ultraviolet absorption spectra of thioxanthines.

	Chloroform solution		Phosphate buffer at pH 11·5	
Compound	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
6-Thiotheophylline (III)	276, 341, 350	15,190, 5200, 4785	231, 260, 345	12,900, 7850, 22,600
6-Thiotheobromine (IV)	346, 355	5110, 5190	216, 289, 328	14,800, 10,000, 18,200
6-Thiocaffeine	276, 341, 350	2220, 8225, 8015		
S-Methyl-6-thiotheobromine (VI)	275, 327	15,770, 16,200	217, 278, 322	12,900, 9150, 7350
2-Thiotheophylline	289	10,900	240, 294	20,000, 18,350

semicarbazones and thiosemicarbazones.[5] On the other hand, the 6-thioxanthines showed a much larger displacement (70—80 mμ) with characteristic bands at 340—350 mμ, which may be attributed to the partial chromophore –N·C:C·C:S.[6]

[2] Traube, *Ber.*, 1900, **33**, 3035.
[3] Khaletskii and Eshman, *Zhur. obshchei Khim.*, 1948, **18**, 2116.
[4] Bergmann and Dikstein, *J. Amer. Chem. Soc.*, 1955, **77**, 691.
[5] Braude, *Ann. Reports*, 1945, **42**, 105.
[6] Cf. Cavalieri, Fox, Stone, and Chang, *J. Amer. Chem. Soc.*, 1954, **76**, 1119.

Many homologues have been prepared, by the standard thionation procedure, for pharmacological evaluation (Tables 2—4). Water-soluble choline salts of the most active 1,3-dialkyl-6-thioxanthines were also prepared (Table 5).[7] A full account of the pharmacology of these compounds is published elsewhere.[8]

Since this work was completed, a note has appeared [9] describing 6-thiotheobromine and its *S*-methyl derivative. Although the spectral data quoted are not inconsistent with ours, the purity of these compounds is doubtful since our products melt respectively 26° and 40° higher.

Experimental

1,3-*Dimethyl*-6-*thioxanthine* (III).—Theophylline (50 g., 0·277 mole), phosphorus pentasulphide (100 g., 0·450 mole) and dry pyridine (1 l.) were refluxed with stirring for 8 hr. The mixture was cooled, water was (2 l.) added with stirring during 1 hr., and the whole concentrated to about 1/3 volume. The solid from the cooled mixture was dissolved in 2N-sodium hydroxide, and the solution filtered and acidified with dilute hydrochloric acid, to give *6-thiotheophylline* (51 g., 94%), m. p. 315—320° (decomp.). Crystallisation from ethanol or water gave pale yellow needles, m. p. 323—325° (decomp.) (Found: C, 42·9; H, 4·2; N, 28·7; S, 16·6. $C_7H_8N_4OS$ requires C, 42·9; H, 4·1; N, 28·6; S, 16·3%).

3,7-*Dimethyl*-6-*thioxanthine* (IV).—Similar treatment of 6-thiotheobromine (75 g., 0·415 mole) with phosphorus pentasulphide (150 g., 0·675 mole) gave *6-thiotheobromine* (72 g., 88%), m. p. 300—301° (Found: C, 42·8; H, 3·9; N, 28·5; S, 16·3%).

1,3-*Dimethyl*-2-*thioxanthine*.—*NN'*-Dimethylthiourea [10] (79 g.) was added portionwise in 30 min. to a stirred solution of cyanoacetic acid (65 g.) in acetic anhydride (156 g.) and acetic acid (200 ml.) at 65°. After 2 hr. at 65°, the mixture was concentrated at 60—65° under reduced pressure, to give an orange gum. This was stirred with water (200 ml.) at 50° and the pH adjusted to 10 by addition of 50% sodium hydroxide solution. *6-Amino-1,3-dimethyl-2-thiouracil* (65 g.), m. p. 278—281°, separated. Recrystallisation from ethanol (charcoal) gave white prisms, m. p. 286—288° (Found: C, 42·2; H, 5·4; N, 24·6; S, 18·4. $C_6H_9N_3OS$ requires C, 42·1; H, 5·3; N, 24·6; S, 18·7%). The crude product was suspended in water (6000 ml.) containing sodium nitrite (25·5 g.) at 80—90° and acetic acid (50 ml.) added during 15 min. The mixture was stirred at 80—90° for a further 15 min., then cooled in ice, to give crude 6-amino-1,3-dimethyl-5-nitroso-2-thiouracil as a blue-green amorphous solid, m. p. 215—216° (decomp.). This was added in 5-g. portions to water (2·5 l.) at 70—80° together with sufficient sodium dithionite to discharge the colour of the nitroso-compound. On cooling, crude 5,6-diamino-1,3-dimethyl-2-thiouracil, m. p. 230—234°, separated, and was immediately added to 2N-sulphuric acid (500 ml.) to give the sulphate (57 g.). The sulphate was boiled with formamide (500 ml.) for 30 min. and the solution diluted with water (250 ml.) and cooled. The yellow solid was dissolved in hot 17% aqueous ammonia (300 ml.), and the solution filtered (charcoal) and acidified to pH 4 with acetic acid, to give *1,3-dimethyl-2-thioxanthine* (47 g., 63% from 6-amino-1,3-dimethyl-2-thiouracil), m. p. 344—348° (Found: C, 43·3; H, 4·2; N, 28·6; S, 16·3. $C_7H_8N_4OS$ requires C, 42·9; H, 4·1; N, 28·6; S, 16·3%).

1,3,7-*Trimethyl*-6-*thioxanthine* (*6-Thiocaffeine*).—*Method I.* Methyl sulphate (25·2 g., 0·20 mole) was added dropwise in 15 min. to a stirred mixture of 1,3-dimethyl-6-thioxanthine (35 g., 0·18 mole) and 2N-sodium hydroxide (100 ml.) at 40°. After a further 30 min. at 40°, the mixture was cooled and the solid filtered off and washed with dilute sodium hydroxide and water. Crystallisation from ethanol (charcoal) gave the product (15 g., 40%) as yellow prisms, m. p. 246—247° (Khaletskii and Eshman [3] give m. p. 240·5—245°).

Method II. Similar treatment of 3,7-dimethyl-6-thioxanthine (17·5 g., 0·09 mole) with methyl sulphate (42·5 g., 0·34 mole) gave 1,3,7-trimethyl-6-thioxanthine (1 g.), m. p. 247—249°, undepressed on admixture with the compound obtained by method I.

1,2,3,6-*Tetrahydro*-3,7-*dimethyl*-1-*methylthio*-2-*oxopurine* (VI).—3,7-Dimethyl-6-thioxanthine (10 g., 0·051 mole) in 0·5N-sodium hydroxide (125 ml.) was stirred with methyl iodide (10·7 g., 0·076 mole) for 2 hr. at room temperature. White needles of *1,2,3,4-tetrahydro-3,7-dimethyl-1-methylthiopurine* (6·7 g., 63%), m. p. 299—302°, were collected and washed with

[7] Armitage and Wooldridge, *Nature*, 1960, **188**, 1107.
[8] Armitage, Boswood, and Large, *Brit. J. Pharmacol.*, 1961, **16**, 59; 1961, **17**, 196.
[9] Kalmus and Bergmann, *J.*, 1960, 3679.
[10] Moore and Crossley, *Org. Synth.*, 1941, **21**, 81.

water. Crystallisation from water (charcoal) gave needles, m. p. 300—303° (Found: C, 45·7; H, 4·8; N, 26·5; S, 15·5. $C_8H_{10}N_4OS$ requires C, 45·7; H, 4·8; N, 26·6; S, 15·3%).

Alkylxanthines.—The xanthines were mostly obtained from the appropriate urea by the Traube synthesis [2] or later modifications of it.[11] It was sometimes more convenient to formylate and cyclise the intermediate 5,6-diaminouracils by treatment with ethyl orthoformate and acetic anhydride.[12] *Xanthines* not previously described in the literature are listed in Table 2.

TABLE 2.

Xanthines.

Subst. at position					Found (%)			Required (%)		
1	3	7	M. p.	Formula	C	H	N	C	H	N
H	Bu^i	H	299—301°	$C_9H_{12}N_4O_2$	51·7	6·1	27·6	51·9	5·8	26·9
H	Bu^i	Me	239—241	$C_{10}H_{14}N_4O_2$	54·2	6·4	24·8	54·1	6·3	25·2
Me	MeO·[CH$_2$]$_3$	H	166—168	$C_{10}H_{14}N_4O_3$	50·5	6·0	23·8	50·4	5·9	23·5
Me	Furfuryl	H	255—258	$C_{11}H_{10}N_4O_3$	53·5	4·2	22·5	53·6	4·1	22·8
Et	Bu^i	H	195—197	$C_{11}H_{16}N_4O_2$	56·1	6·9	23·8	55·9	6·8	23·7
Pr^n	Bu^i	H	189—192	$C_{12}H_{18}N_4O_2$	57·6	7·3	22·4	57·6	7·3	22·4
Bu^n	Me	H	207—210	$C_{10}H_{14}N_4O_2$	54·4	6·4	25·4	54·1	6·3	25·2

Alkyl-6-thioxanthines.—The procedure for the preparation of the homologues of 6-thiotheophylline and 6-thiotheobromine (see Tables 3 and 4) is illustrated by the following example:

3-Isobutyl-1-methyl-6-thioxanthine. Phosphorus pentasulphide (600 g., 2·70 moles) was added to 3-isobutyl-1-methylxanthine (482 g., 2·16 mole) in dry pyridine (4·2 l.), and the mixture was stirred under reflux for 9 hr. The solution was cooled to *ca.* 40° and water (3 l.) added, the first 300—400 ml. dropwise in 2 hr. The mixture was concentrated to *ca.* 2·5 l. and water (3·5 l.) added to give crude product. This was dissolved in warm N-sodium hydroxide (2·5 l.), and the solution was filtered and acidified to pH 4 with concentrated hydrochloric acid, giving the thioxanthine (426 g., 82%), m. p. 169—172°. Crystallisation from ethanol gave yellow prisms, m. p. 170—172°.

TABLE 3.

Homologues of 6-thiotheophylline.

Subst. at position				Yield		Found (%)				Required (%)			
1	3	8	M. p.	(%)	Formula	C	H	N	S	C	H	N	S
Me	Me	H	323—325°	94	$C_7H_8N_4OS$	42·9	4·2	28·7	16·6	42·9	4·1	28·6	16·3
Me	Me	Me	294—295	75	$C_8H_{10}N_4OS$	45·5	4·5	26·7	15·8	45·7	4·8	26·6	15·3
Me	Me	Et	218—219	76	$C_9H_{12}N_4OS$	48·1	5·4	24·6	14·4	48·2	5·4	25·0	14·3
Me	Me	SH	240 *	83	$C_7H_8N_4OS_2$	37·1	3·7	24·1	28·5	36·8	3·5	24·6	28·1
Me	Et	H	235—237	79	$C_8H_{10}N_4OS$	45·3	4·8	26·6	15·2	45·7	4·8	26·6	15·3
Me	Pr^n	H	164—167	63	$C_9H_{12}N_4OS$	48·5	5·2	24·9	14·2	48·2	5·4	25·0	14·3
Me	Bu^n	H	156—158	73	$C_{10}H_{14}N_4OS$	50·7	5·9	23·8	13·7	50·4	5·9	23·5	13·5
Me	n-Pentyl	H	169—170	50	$C_{11}H_{16}N_4OS$	51·9	6·4	22·2	12·5	52·4	6·4	22·2	12·7
Me	n-Hexyl	H	167—174	78	$C_{12}H_{18}N_4OS$	54·2	6·9	21·0	11·9	54·1	6·8	21·0	12·0
Me	Bu^i	H	169—172	82	$C_{10}H_{14}N_4OS$	50·6	5·9	23·4	13·7	50·4	5·9	23·5	13·5
Me	i-Pentyl	H	156—160	50	$C_{11}H_{16}N_4OS$	52·1	6·4	21·3	13·3	52·4	6·4	22·2	12·7
Me	MeO·[CH$_2$]$_3$	H	150—152	50	$C_{10}H_{14}N_4O_2S$	47·5	5·6	21·9	12·8	47·2	5·6	22·0	12·6
Me	Allyl	H	152—156	81	$C_9H_{10}N_4OS$	48·7	4·7	25·4	14·6	48·6	4·5	25·2	14·4
Me	Methallyl	H	195—198	47	$C_{10}H_{12}N_4OS$	51·2	5·2	23·8	13·5	50·8	5·1	23·7	13·6
Me	CH_2Ph	H	213—215	84	$C_{13}H_{12}N_4OS$	56·8	4·6	20·2	11·8	57·3	4·4	20·6	11·8
Me	Ph·[CH$_2$]$_2$	H	198—199	63	$C_{14}H_{14}N_4OS$	58·7	5·1	19·8	11·3	58·7	4·9	19·6	11·2
Me	Furfuryl	H	184—186	15	$C_{11}H_{10}N_4O_2S$	50·5	3·7	22·0	12·1	50·4	3·9	21·4	12·2
Et	Me	H	235—239	76	$C_8H_{10}N_4OS$	45·6	4·8	26·3	15·5	45·7	4·8	26·6	15·3
Et	Et	H	256—258	72	$C_9H_{12}N_4OS$	48·2	5·3	24·1	14·0	48·2	5·4	25·0	14·3
Et	Bu^n	H	175—178	74	$C_{11}H_{16}N_4OS$	52·4	6·4	21·9	12·7	52·4	6·4	22·2	12·7
Et	Bu^i	H	180—183	39	$C_{11}H_{16}N_4OS$	52·3	6·4	22·0	13·0	52·4	6·4	22·2	12·7
Et	Allyl	H	210—212	49	$C_{10}H_{12}N_4OS$	50·8	5·0	23·4	13·4	50·8	5·1	23·7	13·6
Pr^n	Pr^n	H	212—215	89	$C_{11}H_{16}N_4OS$	52·1	6·2	22·2	12·6	52·4	6·4	22·2	12·7
Bu^n	Me	H	195—198	84	$C_{10}H_{14}N_4OS$	50·5	6·1	23·4	13·2	50·4	5·9	23·5	13·5
Bu^n	Bu^n	H	183—186	72	$C_{13}H_{20}N_4OS$	55·7	7·4	19·8	11·8	55·7	7·2	20·0	11·4

* With decomp.

[11] Speer and Raymond, *J. Amer. Chem. Soc.*, 1953, **75**, 114; U.S.P. 2,602,795, 2,673,848.
[12] Montgomery, *J. Amer. Chem. Soc.*, 1956, **78**, 1928.

TABLE 4.

Homologues of 6-thiotheobromine and 6-thiocaffeine.

Subst. at position					Found (%)				Required (%)			
1	3	7	M. p.	Formula	C	H	N	S	C	H	N	S
H	Bu^i	H	269—274°	$C_9H_{12}N_4OS$	48·2	5·7	25·0	14·2	48·2	5·4	25·0	14·3
H	Me	Me	300—301	$C_7H_8N_4OS$	42·8	3·9	28·5	16·3	42·9	4·1	28·6	16·3
H	Bu^n	Me	200—203	$C_{10}H_{14}N_4OS$	50·7	5·8	23·6	13·6	50·4	5·9	23·5	13·5
H	Bu^i	Me	228—230	$C_{10}H_{14}N_4OS$	50·3	6·1	24·0	13·6	50·4	5·9	23·5	13·5
Me	Me	Et	136—138	$C_9H_{12}N_4OS$	47·9	5·2	25·0	14·0	48·2	5·4	25·0	14·3
Me	Me	CH_2Ac	208—210	$C_{10}H_{12}N_4O_2S$	47·8	5·0	22·3	12·5	47·6	4·8	22·2	12·7
Me	Me	$NEt_2{\cdot}[CH_2]_2$	52—54	$C_{13}H_{21}N_5OS$	53·0	7·2	23·5	10·6	52·9	7·2	23·7	10·9
Me	Bu^i	$NEt_2{\cdot}[CH_2]_2$ [a]	120 [b]	$C_{36}H_{43}N_5O_9S$	60·0	6·2	—	4·1	59·9	6·0	—	4·4
Me	Bu^i	CH_2Ac	170—174	$C_{13}H_{18}N_4O_2S$	53·5	6·0	19·1	10·6	53·0	6·2	19·0	10·9
Me	Me	2-Oxo-4-piperidinobutyl [c]	189—195	$C_{16}H_{24}ClN_5O_2S$			18·0	8·7			18·2	8·3
Bu^n	Me	Me	118—119	$C_{11}H_{16}N_4OS$	52·4	6·3	22·4	12·4	52·4	6·4	22·2	12·7

[a] The compound was obtained as the (−)-di-(*p*-toluoyl)-D-tartrate. [b] With decomp. [c] Hydrochloride (Found: Cl, 8·9. Required: Cl, 9·2%).

The 6-thiocaffeine derivatives were prepared as follows:

7-Acetonyl-1,3-dimethyl-6-thioxanthine. 1,3-Dimethyl-6-thioxanthine (42 g.) was added to sodium hydroxide (8·6 g.) in water (150 ml.) at room temperature and stirred for 30 min. The sodium salt of 1,3-dimethyl-6-thioxanthine (44 g., 96%) was collected from the cooled solution, washed with ethanol, and dried at 60°. It was dissolved in dimethylformamide (200 ml.), and redistilled chloroacetone (18·6 g.) was added with stirring during 15 min. at room temperature. The solution was diluted with iced water (300 ml.) after being stirred for a further 30 min. and the white solid filtered off and washed with 2N-sodium hydroxide and then with water. Crystallisation from ethanol gave yellow needles of the acetonyl derivative, *7-acetonyl-1,3-dimethyl-6-thioxanthine* (21·3 g., 42%), m. p. 208—210°.

1,3-Dimethyl-7-(2-oxo-4-piperidinobutyl)-6-thioxanthine Hydrochloride.—7-Acetonyl-1,3-dimethyl-6-thioxanthine (21 g.) was added to paraformaldehyde (2·69 g.), piperidine hydrochloride (11·9 g.), and boron trifluoride–ether complex (1·6 ml.) in dry dioxan (200 ml.), and the mixture heated at 100° with stirring for 7 hr. The product was collected from the cooled mixture and recrystallised from dry ethanol to give yellow-brown prisms (23·0 g., 72%), m. p. 197—200°.

Choline Salts of 6-Thioxanthines.—A typical procedure (see Table 5) is given below.

TABLE 5.

Choline salts of 6-thioxanthines.

Subst. at position				Yield		Found (%)				Required (%)			
1	3	8	M. p.	(%)	Formula	C	H	N	S	C	H	N	S
Me	Me	H	145—147°	47	$C_{12}H_{21}N_5O_2S$	47·8	7·0	22·7	10·5	48·1	7·1	23·4	10·7
Me	Me	Me	175—176	65	$C_{13}H_{23}N_5O_2S$	49·3	7·4	22·3	10·3	49·8	7·4	22·4	10·2
Me	Me	SH	209—211	70	$C_{12}H_{21}N_5O_2S_2$	43·8	6·2	21·1	19·5	43·5	6·4	21·1	19·4
Me	Et	H	157—159	72	$C_{13}H_{23}N_5O_2S$	50·2	7·5	21·6	10·2	49·8	7·4	22·4	10·2
Me	Pr^n	H	145—150	72	$C_{14}H_{25}N_5O_2S$	51·1	7·4	21·1	9·6	51·4	7·7	21·4	9·8
Me	Bu^n	H	133—135	88	$C_{15}H_{27}N_5O_2S$	53·1	7·9	20·5	9·4	52·8	8·0	20·5	9·4
Me	n-Pentyl	H	150—153	93	$C_{16}H_{29}N_5O_2S$	53·6	8·1	19·2	9·3	54·1	8·2	19·7	9·0
Me	n-Hexyl	H	55—57	94	$C_{17}H_{31}N_5O_2S$	54·9	8·4	18·7	8·3	55·3	8·5	19·0	8·7
Me	Bu^i	H	148·5—149·5	92	$C_{15}H_{27}N_5O_2S$	52·9	8·1	20·3	9·4	52·8	8·0	20·5	9·4
Me	i-Pentyl	H	125—128	90	$C_{16}H_{29}N_5O_2S$	53·6	8·4	19·7	8·8	54·1	8·2	19·7	9·0
Me	Allyl	H	172—175	73	$C_{14}H_{23}N_5O_2S$	51·7	7·3	21·4	10·0	51·7	7·1	21·5	9·7
Me	Methallyl	H	145—151	80	$C_{15}H_{25}N_5O_2S$	52·6	7·8	20·3	9·0	53·1	7·4	20·6	9·4
Me	CH_2Ph	H	166—171	80	$C_{18}H_{25}N_5O_2S$	57·2	6·7	18·5	8·5	57·6	6·7	18·7	8·5
Me	$Ph{\cdot}[CH_2]_2$	H	173—175	80	$C_{19}H_{27}N_5O_2S$	58·4	7·3	18·1	8·0	58·6	7·0	18·0	8·2
Et	Me	H	157—158	70	$C_{13}H_{23}N_5O_2S$	50·2	7·7	22·4	10·3	49·8	7·4	22·4	10·2
Et	Et	H	142—147	92	$C_{14}H_{25}N_5O_2S$	51·0	7·6	21·1	9·7	51·4	7·7	21·4	9·8
Et	Bu^n	H	115—118	79	$C_{16}H_{29}N_5O_2S$	53·9	8·3	19·3	9·0	54·1	8·2	19·7	9·0
Pr^n	Pr^n	H	114—118	57	$C_{16}H_{29}N_5O_2S$	53·9	8·0	19·6	9·0	54·1	8·2	19·7	9·0
Bu^n	Me	H	105—109	62	$C_{15}H_{27}N_5O_2S$	53·4	8·3	19·9	9·4	52·8	8·0	20·5	9·4

Choline salt of 3-*isobutyl*-1-*methyl*-6-*thioxanthine*. Choline chloride (3·4 g., 2·25 moles) in hot propan-2-ol (900 ml.) was treated with 85% potassium hydroxide (150 g., 2·25 moles) in anhydrous methanol (600 ml.) with stirring. The mixture was cooled to 0° and potassium chloride (159 g.; 95% of theor.) filtered off and washed with propan-2-ol (2 × 100 ml.). 3-Isobutyl-1-methyl-6-thioxanthine (500 g., 2·10 moles) was added to the filtrate and the whole was warmed for a few minutes to give a cloudy, black solution. This was concentrated under reduced pressure to a viscous syrup which was dissolved in hot propan-2-ol (1 l.), treated with charcoal, and filtered. The filtrate was treated with anhydrous ether (1 l.). The *choline salt* of 3-isobutyl-1-methyl-6-thioxanthine slowly crystallised from the cooled solution as pale yellow prisms (548 g.), m. p. 145—149°. The mother-liquor was concentrated to a syrup, dissolved in water, and acidified to pH 4 with hydrochloric acid to give 3-isobutyl-1-methyl-6-thioxanthine (8 g.), m. p. 166—171°.

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