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STRUCTURE-ACTIVITY RELATIONSHIPS IN A SERIES OF 6-THIOXANTHINES WITH BRONCHODILATOR AND CORONARY DILATOR PROPERTIES

BY

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The bronchodilator activity of 47 compounds on the isolated guinea-pig tracheal ring preparation and the coronary dilator activity on the dog heart–lung preparation is described. 1,3-Disubstituted xanthines and 6-thioxanthines (theophyllines and 6-thiotheophyllines) were more active as bronchodilators and as coronary dilators than were 3,7-disubstituted 6-thioxanthines (6-thiotheobromines) or 1,3,7-trisubstituted 6-thioxanthines (6-thiocaffeines). None of the 6-thioxanthines was of any interest as a diuretic and none of the 6-thiocaffeines was of any interest as a central stimulant. Structure-activity requirements for potent bronchodilator and coronary dilator activity are discussed.

The potent bronchodilator and coronary dilator properties of the choline salt of 3-isobutyl-1-methyl-6-thioxanthine (M&B 5924) have already been described (Armitage & Wooldridge, 1960 ; Armitage, Boswood & Large, 1961). In the present paper, the *in vitro* bronchodilator activity of 1,3- and 3,7-disubstituted and 1,3,7-trisubstituted 6-thioxanthines on the guinea-pig tracheal ring preparation and the coronary dilator activity on the dog heart–lung preparation are reported. For brevity these three classes of compounds will be referred to as 6-thiotheophyllines, 6-thiotheobromines and 6-thiocaffeines respectively. Results on various theophyllines, that is, non-thio-analogues, are also included. In the light of these results, structure-activity relationships among 6-thioxanthines are discussed. The synthesis and chemical properties of the compounds discussed in this paper will be published elsewhere (Slack & Wooldridge).

METHODS

Bronchodilator and coronary dilator activity. The methods used for estimating bronchodilator activity on the isolated guinea-pig tracheal ring preparation and coronary dilator activity on the dog heart–lung preparation were fully described by Armitage *et al.* (1961). The tracheal chain preparation was found to work much more satisfactorily if the cartilage of each ring in the chain was cut, as described by Akçasu (1959).

Other methods used in the present study and described in our earlier paper include the estimation of *in vivo* bronchodilator activity, which was assessed by determining whether the

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compounds when given intraperitoneally or orally would protect guinea-pigs against broncho-constrictor aerosols. Several of the compounds were tested for diuretic activity in conscious rats and for their effects on the voluntary motor activity of mice by the light-box method of Dews (1953). Intravenous and oral LD50 values in albino mice were also determined.

Emetic properties of some of the more active 6-thiotheophyllines and theophyllines were studied in cats and dogs.

Effects on respiration of anaesthetized rabbits. The method used was that described by Burn (1952). Rabbits of either sex were anaesthetized with urethane and respiratory movements were recorded with a kymograph. Respiration was usually depressed by intravenous injection of 4 mg morphine sulphate. In some of the experiments, blood pressure was stabilized as described by Burn & Rand (1960).

RESULTS

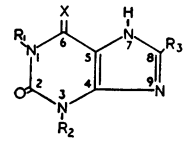
6-Thiotheophyllines

Bronchodilator and coronary dilator activity of 6-thiotheophyllines. The structures of the 6-thiotheophyllines tested are shown in Table 1 and their molar activity ratios in Table 2. These figures have been calculated as the ratio of the molar dose or molar concentration of choline theophyllinate required to cause a given relaxation of the guinea-pig tracheal muscle or a given increase in coronary blood flow in the dog heart–lung preparation, to the molar dose of 6-thiotheophylline required to produce a similar effect. It should be stressed that these estimates of activity, particularly coronary dilator activity, were for many of the compounds only approximate, the main object of the experiments being to ascertain which compound was the most active. The number of experiments was often small and the data have not been subjected to any statistical tests. Included for each compound in Table 2 are the mean activity ratio, the number of experiments and the highest and lowest activity observed in all the experiments. Activities have been calculated to the nearest whole number. Compounds were not always compared directly with choline theophyllinate but with a compound whose activity relative to choline theophyllinate had been determined in previous experiments. It will be seen that compounds 6, 19, 21 and 23 were the most active bronchodilators and compound 6 was the most active coronary dilator. In the dog heart–lung preparation, compound 23 caused predominantly coronary constriction as shown in Fig. 1.

The *in vivo* bronchodilator activity of 6 compounds (1, 2, 5, 15, 25 and 27) was investigated on 8 guinea-pigs for each compound, the animals being exposed 20 min after intraperitoneal injection to either a 2% histamine or 4% acetylcholine aerosol. Activity relative to choline theophyllinate was invariably less than on the guinea-pig tracheal ring preparation, compounds 2, 5 and 15 being only 1 to 2 times as active as choline theophyllinate, compounds 1 and 27 being equiactive and compound 25 being inactive and causing convulsions in a dose of 100 mg/kg salt. Experiments were also performed with compounds 1a, 5a, 6a, 19, 19a and 21 to see if, when given orally, they subsequently protected guinea-pigs from the convulsant effects of a 4% acetylcholine aerosol and for approximately how long the protection lasted. Choline theophyllinate and compound 21 were the least effective, 5a was about 3 times as active, and 19 and 19a were both about twice as active as choline theophyllinate. Activity was estimated as the ratio of the doses

TABLE 1

CHEMICAL STRUCTURES AND TOXICITY VALUES OF THEOPHYLLINES AND 6-THIOTHEOPHYLLINES



Compound no.	M&B no.	R_1	R_2	R_3	X	Salt	Mol. wt.	Oral LD50/ intravenous LD50 (mg/kg active component in mice)
1 (Choline 6-thiotheophyllinate)	4926A	CH_3–	CH_3–	H–	S	Choline	299	260/39=7
1a (Choline theophyllinate)	—	CH_3–	CH_3–	H–	O	Choline	283	337/74=4
1b (Aminophylline)	—	CH_3–	CH_3–	H–	O	Ethylenediamine dihydrate	456/2	250/150=1–2
2	5656	CH_3–	C_2H_5–	H–	S	Choline	313	244/47=5
3	6020	CH_3–	n–C_3H_7–	H–	S	Choline	327	250/63=4
4	6138	CH_3–	CH_2:CH.CH_2–	H–	S	Choline	325	260/48=5
5	5777	CH_3–	n–C_4H_9–	H–	S	Choline	341	364/55=7
5a	6052	CH_3–	n–C_4H_9–	H–	O	Choline	325	129/66=2
6	5924	CH_3–	i–C_4H_9–	H–	S	Choline	341	163/51=3
6a	6139	CH_3–	i–C_4H_9–	H–	O	Sodium	244	75/42=1–2
7	6375	CH_3–	CH_2:C(CH_3).CH_2–	H–	S	Choline	339	142/47=3
8	5955	CH_3–	n–C_5H_{11}–	H–	S	Choline	355	294/58=5
8a	6986	CH_3–	n–C_5H_{11}–	H–	O	Sodium	258	77/54=1–2
9	6340	CH_3–	$CH_3O.CH_2.CH_2.CH_2$–	H–	S	Sodium	276	345/132=3
9a	6847	CH_3–	$CH_3O.CH_2.CH_2.CH_2$–	H–	O	Base	238	210/130=1–2
10	6082	CH_3–	i–C_5H_{11}–	H–	S	Choline	355	425/51=8
11	5937	CH_3–	n–C_6H_{13}–	H–	S	Choline	369	>430/34=>12
12	6051	CH_3–	$C_6H_5.CH_2$–	H–	S	Choline	375	360/51=7
13	6522	CH_3–	$C_6H_5.CH_2.CH_2$–	H–	S	Choline	389	955/46=>20
14	6557	CH_3–	Furfuryl	H–	S	Sodium	284	460/135=3
14a	6761	CH_3–	Furfuryl	H–	O	Sodium	268	420/96=4
15	5722	C_2H_5–	CH_3–	H–	S	Choline	313	234/63=4
16	5861	C_2H_5–	C_2H_5–	H–	S	Choline	327	503/54=9
17	6511	C_2H_5–	CH_2:CH.CH_2–	H–	S	Sodium	258	450/110=4
18	5904	C_2H_5–	n–C_4H_9–	H–	S	Choline	355	510/68=7
19	6783	C_2H_5–	i–C_4H_9–	H–	S	Sodium	274	405/138=3
19a	6775	C_2H_5–	i–C_4H_9–	H–	O	Sodium	258	150/125=1–2
20	6510	CH_2:CH.CH_2–	C_6H_5–	H–	S	Sodium	306	1,450/130=11
21	6154	n–C_3H_7–	n–C_3H_7–	H–	S	Choline	355	>565/46=>12
22	5962	n–C_4H_9–	CH_3–	H–	S	Choline	341	>550/54=>10
22a	6985	n–C_4H_9–	CH_3–	H–	O	Sodium	244	235/140=1–2
23	6164	n–C_4H_9–	n–C_4H_9–	H–	S	Sodium	302	>500/21=>24
24	5829	CH_3–	CH_3–	CH_3–	S	Choline	313	193/66=3
25	5609	CH_3–	CH_3–	C_2H_5–	S	Choline	327	109/45=2
25a	6189	CH_3–	CH_3–	C_2H_5–	O	Sodium	230	180/130=1–2
26	5812	CH_3–	CH_3–	HS–	S	Choline	331	>2,000/69=>29

TABLE 2

STRUCTURE-ACTIVITY OF 6-THIOTHEOPHYLLINES, BRONCHODILATOR ACTIVITY (BDA), CORONARY DILATOR ACTIVITY (CDA), EXPRESSED RELATIVE TO CHOLINE THEOPHYLLINATE

Compound no.	Mean relative molar BDA	Range of BDA and no. of expts. in parentheses	Mean relative molar CDA	Range of CDA and no. of expts. in parentheses	Thioxanthine/xanthine activity BDA	Thioxanthine/xanthine activity CDA
1	5	3–7 (5)	3	2–5 (6)	5	3
1a	1	1 by definition	1	1 by definition		
1b	1–2	1–2 (6)	1–2	1–2 (2)	3	2
2	20	8–25 (7)	5	3–6 (8)		
3	44	39–60 (3)	7	— (1)		
4	13	10–15 (5)	7	3–10 (7)		
5	53	23–108 (17)	10	5–15 (11)	0·4	0·4
5a	134	75–214 (10)	22	12–37 (7)		
6	72	24–122 (15)	18	10–29 (14)	0·7	0·9
6a	102	54–183 (9)	20	20 (3)		
7	36	24–44 (3)	12	11–14 (3)		
8	59	44–83 (5)	10	7–14 (4)	0·5	0·4
8a	110	46–174 (3)	25	16–32 (3)		
9	20	11–28 (3)	7	7 (3)	2	2
9a	11	7–15 (2)	3	— (1)		
10	54	23–83 (3)	5	4–8 (3)		
11	23	23 (2)	4	3–5 (2)		
12	29	24–35 (3)	1	— (1)		
13	22	13–30 (3)	4	4–5 (3)		
14	10	— (1)	7	7 (2)	0·6	0·6
14a	16	16 (2)	12	4–16 (3)		
15	9	2–21 (7)	3	3 (3)		
16	36	32–41 (3)	5	4–5 (2)		
17	18	13–26 (4)	4	4 (3)		
18	69	42–93 (4)	4	— (1)		
19	143	102–208 (5)	6	6 (3)	0·4	0·7
19a	342	246–407 (5)	9	4–14 (5)		
20	49	37–53 (3)	<1	— (1)		
21	143	72–254 (5)	5	2–8 (6)		
22	4	3–6 (2)	2	— (1)	0·1	0·5
22a	32	— (1)	4	— (1)		
23	202	94–290 (4)	Constrictor	— (2)		
24	5	5 (2)	3	2–4 (4)		
25	11	7–24 (5)	4	2–7 (8)	2	2
25a	5	3–8 (3)	2	1–3 (4)		
26	Constrictor	— (1)	Not tested	—		

giving about equal protection of between 50 and 100%. Compound 6a was toxic to guinea-pigs in doses as low as 20 mg/kg, this dose killing 6 out of 32 guinea-pigs. At 10 mg/kg, compound 6 offered less than 50% protection, but as much protection as choline theophyllinate at 100 mg/kg. None of the compounds tested for *in vivo* bronchodilator activity was found to have more than slight antihistamine or anti-acetylcholine activity on the guinea-pig ileum.

Other properties of 6-thiotheophyllines. The pharmacological properties of M&B 5924 (compound 6) have already been described in detail (Armitage *et al.*, 1961). Further experiments have been made on some other 6-thioxanthines, and in general the only differences observed have been quantitative.

Diuretic activity in rats. These experiments were of a qualitative nature only. Rats were given by stomach tube 25 ml./kg 0.9% saline containing the appropriate

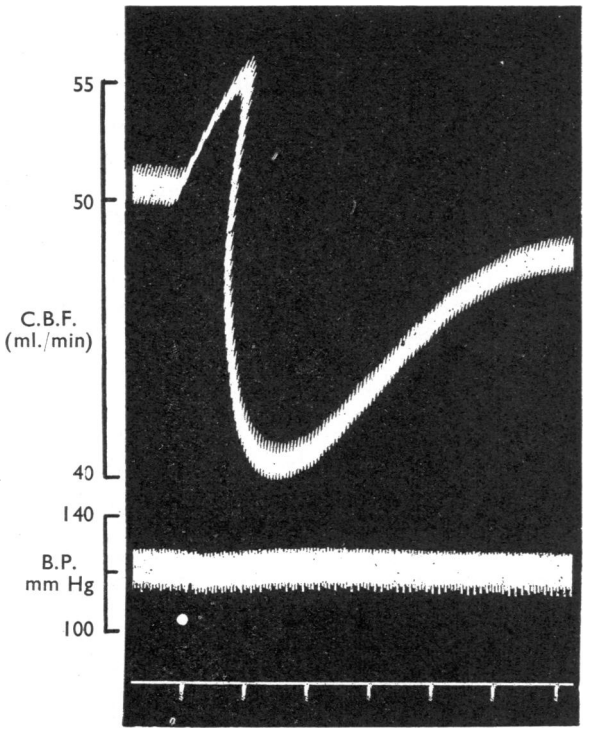


Fig. 1. Dog heart–lung preparation, showing coronary blood flow (upper record) and blood pressure (lower record). Time marker=60 sec. At the white dot, 0.5 mg compound 23 was injected close to the superior vena cava. Note the unusual effect in this series of compounds of coronary constriction following a small initial dilatation.

amount of compound to give doses up to 40 mg/kg. Urine was collected for 5 hr. Compounds 1, 2, 3, 5, 5a, 6, 8, 10, 11, 15, 18, 22 and 25 were all much less active than choline theophyllinate and were therefore of no interest as diuretics.

Effects on the voluntary motor activity of mice. In doses up to 20 mg/kg choline theophyllinate increased the motor activity of mice, a 50% increase being produced by 12 mg/kg theophylline. All the other theophyllines and 6-thiotheophyllines, however, in doses up to 80 mg/kg either decreased motor activity or had no effect, the dose causing a 50% decrease usually being in the range 20 to 50 mg/kg.

Emetic properties in cats and dogs. The results of the experiments on two of the most active pairs of theophyllines and 6-thiotheophyllines are shown in Table 3. The drugs were administered by injection into the saphenous vein and orally in gelatin capsules. Vomiting and retching sometimes occurred within a minute of intravenous injection, but recovery was usually complete within 1 or 2 hr. In cats, but not in dogs, salivation and laboured respiration were sometimes observed. Compound 19a caused emesis in cats and dogs in much lower doses than the other compounds. Compounds 4, 5, 5a and 7 were also given orally to dogs, and all caused vomiting at much lower doses than choline theophyllinate and aminophylline.

TABLE 3
EMETIC PROPERTIES OF THEOPHYLLINES AND 6-THIOTHEOPHYLLINES IN CATS AND DOGS

Compound no.	Dose (mg/kg active component)	Route	No. of dogs which vomited	No. of cats which vomited
6	2	Intravenous	2/5	—
(M&B 5924)	4	Intravenous	—	0/2
	5	Oral	0/2	—
	8	Intravenous	—	0/2
	10	Oral	2/2	0/2
6a	1	Intravenous	0/2	—
(M&B 6139)	2	Intravenous	2/5	0/2
	4	Intravenous	2/3	2/2
	5	Oral	2/2	—
	10	Oral	2/2	0/2
19	2	Intravenous	0/4	0/1
(M&B 6783)	4	Intravenous	4/4	0/1
	6	Intravenous	—	0/1
	10	Oral	0/1	0/1
	20	Oral	—	0/1
19a	0·25	Intravenous	1/1	—
(M&B 6775)	0·5	Intravenous	7/7	—
	2	Oral	2/2	2/2
	5	Oral	4/4	2/2

Acute toxicity in mice. Approximate acute intravenous and oral LD50 values were determined for each compound with up to 30 mice for each determination. The ratio of the two LD50 determinations is shown in Table 1, and for most of the compounds the value was below 6. A low value for this ratio is generally taken to indicate that oral absorption is good.

2-Thiotheophyllines

One compound only of this series was tested, namely, choline 2-thiotheophyllinate, and it was less active as a bronchodilator and as a coronary dilator than the 6-thio-analogue.

6-Thiotheobromines

The chemical structures of the compounds tested, other than theophyllines and 6-thiotheophyllines, are shown in Table 4. Three compounds only of this series were tested, and, although slightly more active than choline theophyllinate as coronary dilators and as bronchodilators, they were much less active than the closely related 1,3-dialkyl-6-thiotheophyllines (Table 5). Choline 6-thiotheobrominate (compound 27), like choline 6-thiotheophyllinate (compound 1), was a relatively poor diuretic. Toxicity data are also shown in Table 5.

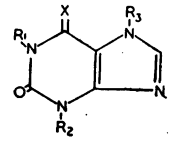
6-Thiocaffeines

The 6-thiocaffeines were tested for bronchodilator and coronary dilator activity and also compared with caffeine as central stimulants in the mouse motor activity test and for ability to stimulate the respiration of the anaesthetized rabbit depressed by morphine.

TABLE 4

CHEMICAL STRUCTURES OF 6-THIOTHEOBROMINES AND 6-THIOCAFFEINES

In column 8, Sal=dissolved in 25% sodium salicylate solution, Sal′=an equimolecular mixture of caffeine and sodium salicylate dissolved in water



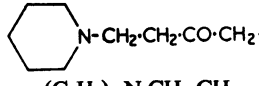
Compound no.	M&B no.	R_1	R_2	R_3	X	Salt	Solvent	Mol. wt.
27	4390A	H–	CH_3–	CH_3–	S	Choline	H_2O	299
28	6436	H–	n-C_4H_9–	CH_3–	S	Sodium	H_2O	260
29	6266	H–	i-C_4H_9–	CH_3–	S	Sodium	H_2O	260
30	6287	H–	i-C_4H_9–	H–	S	Sodium	H_2O	246
31	6227	CH_3–	CH_3–	CH_3–	S	—	Sal	210
31a	—	CH_3–	CH_3–	CH_3–	O	Citrate	H_2O	386
31b	—	CH_3–	CH_3–	CH_3–	O	—	Sal′	194
32	6231	CH_3–	CH_3–	C_2H_5–	S	—	Sal	224
33	6194	CH_3–	CH_3–	$(C_2H_5)_2N.CH_2.CH_2$–	S	Hydrochloride	H_2O	331
34	6316	CH_3–	CH_3–	$(C_2H_5)_2N.CH_2.CH_2$–	S	Methiodide	H_2O	437
35	6254	CH_3–	CH_3–	$CH_3.CO.CH_2$–	S	—	Sal	252
36	6496	CH_3–	CH_3–		S	Hydrochloride	H_2O	385
37	6464	CH_3–	i-C_4H_9–	$(C_2H_5)_2.N.CH_2.CH_2$–	S	(−)-Di(*p*-toluoyl)-D-tartrate	H_2O	723

TABLE 5

STRUCTURE-ACTIVITY OF 6-THIOTHEOBROMINES AND 6-THIOCAFFEINES, BRONCHODILATOR ACTIVITY (BDA), AND CORONARY DILATOR ACTIVITY (CDA), EXPRESSED RELATIVE TO CHOLINE THEOPHYLLINATE

Compound no.	Mean relative molar BDA and no. of expts. in parentheses	Mean relative molar CDA and no. of expts. in parentheses	Oral LD50/ intravenous LD50 (mg/kg active component in mice)	Respiration
27	2–3 (1)	2 (4)	340/40=8	Not tested
28	16 (1)	1–2 (1)	>400/30=>13	Not tested
29	12 (3)	2 (1)	560/50=11	Not tested
30	19 (2)	3 (4)	177/79=2	Not tested
31	<1 (1)	1 (1)	960/—	+
31a	0·5 (2)	0·5 (2)	356/49=7	++
31b			312/—	
32	<1 (1)	2 (1)	515/—	+
33	5 (3)	1 (3)	228/19=12	++
34	Constrictor (1)	≪1 (1)	>420/14=>30	+
35	<1 (1)	1 (1)	—/—	+
36	2 (1)	1 (1)	472/34=14	++
37	<1 (1)	Not tested	>1,000/—	Not tested
Nikethamide	Not tested	Not tested	Not determined	+++

Bronchodilator and coronary dilator activity. Three of the 6-thiocaffeines (Table 4, compounds 31, 32 and 35) were soluble only in 25% (w/v) sodium salicylate solution, and some of the bronchodilatation and coronary dilatation caused by solutions of these compounds was due to the sodium salicylate content. Nevertheless, the bronchodilator activity of these compounds was low ; as coronary dilators they were more active than caffeine, but very much less active than the 6-thiotheophyllines.

Motor activity in mice. Caffeine citrate in doses of 20 to 40 mg/kg increased the voluntary motor activity of mice up to a maximum of 40% above the control count. None of the 6-thiocaffeines tested had any stimulant effects on mice, although high doses (80 mg/kg) sometimes caused sedation.

Effects on respiration. It was not easy to compare quantitatively the stimulant effects of 6-thiocaffeines, and for this reason the results shown in Table 5 are expressed merely in a qualitative way. For example, a dose of compound which at the beginning of an experiment caused perhaps 30% stimulation of the rate was sometimes without effect later in the experiment. The degree of stimulation varied according to the initial rate of respiration, the level of anaesthesia and blood pressure, in experiments in which blood pressure was not stabilized.

All the compounds were tested except 37. Compounds 31, 32 and 35 all caused stimulation of the respiration, most of which was shown to be due to the sodium salicylate solvent. Of the other compounds, there appeared to be little difference in the stimulant properties of 33, 36 and caffeine (31a, 31b). Some of these stimulant effects are shown in Fig. 2. Nikethamide and caffeine caused similar stimulation whether the blood pressure was stabilized or not, but the 6-thiocaffeines, which caused large falls in blood pressure in the normal preparation, were usually less effective stimulants when the blood pressure was stabilized. Compound 34 was

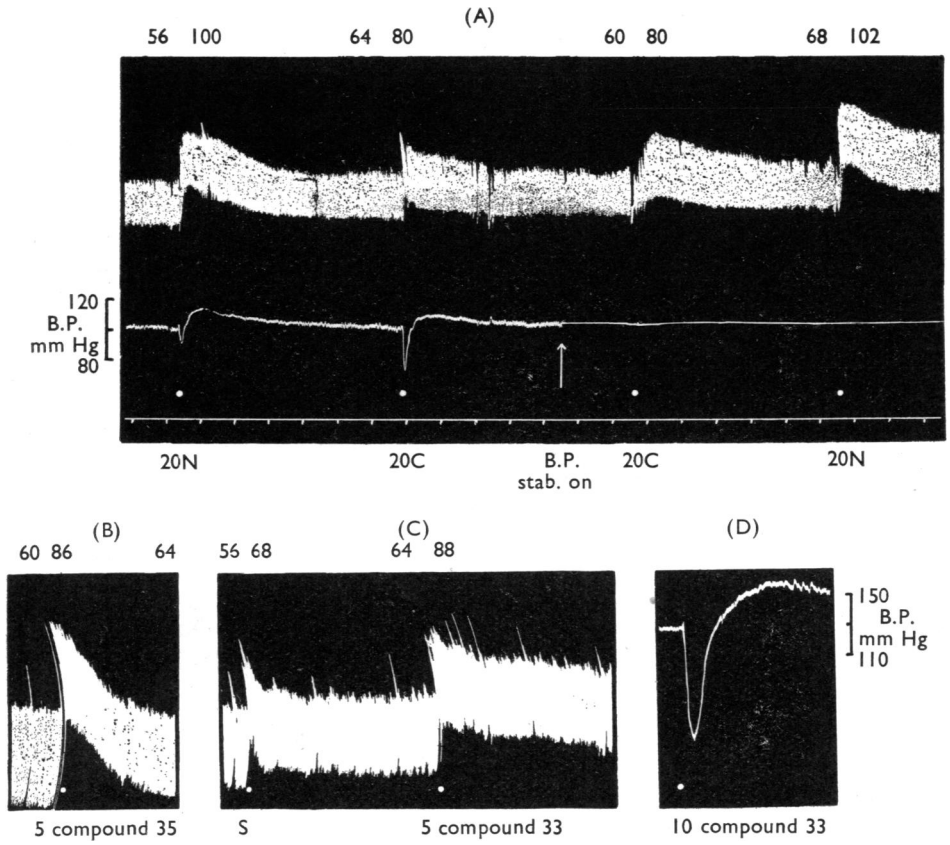


Fig. 2. Rabbits, urethane anaesthesia. Records of respiration and blood pressure in (A), respiration in (B) and (C) and blood pressure in (D). Respiration rates are shown at the top of each tracing. C=caffeine citrate, N=nikethamide, S=0·4 ml. sodium salicylate solution (25% w/v). Time marker in (A)=60 sec, also the same for (B), (C), and (D). The values with C, N, compound 35 and compound 33 refer to doses in mg/kg injected intravenously. In (A) are shown the effects of caffeine citrate and nikethamide on respiration before and after stabilizing the blood pressure. In contrast to the 6-thiocaffeines, caffeine citrate and nikethamide caused only small changes in blood pressure and blood pressure stabilization did not affect the respiratory response. In another experiment shown in (B) and (C), in which the blood pressure was stabilized at 100 mm Hg, compounds 35 and 33 had similar effects on respiration, part of which in the case of compound 35 was due to the high concentration of sodium salicylate (S). Time interval between (B) and (C)=35 min. In (D) is shown the typical effect on blood pressure of high doses of the 6-thiocaffeines, in this case compound 33, when the blood pressure was not stabilized.

less active than compound 33. All these compounds were active in the range 5 to 10 mg/kg, although 10 mg/kg of 33 and 36 killed one rabbit each. The dose required to stimulate respiration was not much less than the dose which caused convulsions and a profound fall in blood pressure. Nikethamide, on the other hand, could safely be given in doses up to 30 mg/kg without any pronounced effects on the blood pressure.

DISCUSSION

As far as we are aware, most of the 6-thioxanthines described in this paper are new compounds, the only other reference to compounds of this type being a paper by Quimby, Aviado & Schmidt (1958) on the effects of xanthines and some unspecified 6-thioxanthines on the pulmonary circulation of the dog. The first compound we tested was choline 6-thiotheophyllinate, which was more than twice as active as choline theophyllinate as a bronchodilator and as a coronary dilator. This suggested that 6-thiotheophyllines might be more active than theophyllines, but this generalization is clearly incorrect, and with several higher members of the series the theophyllines were more active than the 6-thio-analogues (Table 2, column 6). Some compounds were tested as their sodium salts when it was not possible to prepare the choline salts, and activities have accordingly been quoted in Tables 2 and 4 on a molar basis. Le Roy & Speer (1940) found that there was a difference in the coronary dilator activity of different salts of certain xanthines; in particular the sodium acetate salt of theobromine was five times as active as the sodium salt. Such a large discrepancy is difficult to understand. The only compound we have tested as two salts is theophylline itself; aminophylline, the ethylenediamine salt, was consistently about 1.5 times as active as the choline salt. Of several mono-, di-, and tri-alkylxanthines reported by Le Roy & Speer (1940), none was more active than aminophylline as a coronary dilator. These experiments were made in the anaesthetized dog, and so differences in the activity of 1,3-diethyl- and 1,3-dibutyl-xanthine compared with our results are not surprising. The latter was reported to cause no effect on coronary flow in two out of three experiments, whereas in two experiments we found it to cause coronary constriction.

1,3-Dialkylxanthines are emetic (Kattus, Newman & Franklin, 1951), as we have also found, and it is probably because of their poor tolerance that these compounds have not found use in man. 1-Ethyl-3-isobutylxanthine (compound 19) caused emesis in cats and dogs, both orally and intravenously, even when administered in very low doses (Table 3). It would appear that with alkyl groups larger than methyl in the 1- and 3- positions activity increases at the expense of tolerance. Some of the newer 7-hydroxyalkyl- and 7-aminoalkyl-theophylline derivatives are less acutely toxic than theophylline, but are no more active and apparently no better tolerated than existing preparations (McColl, Parker & Ferguson, 1956; Jourdan & Faucon, 1958; Roth, Winbury & Govier, 1957). The fact that the theophyllines and thiotheophyllines caused vomiting when administered intravenously as well as when administered orally indicated that vomiting was not solely due to gastric irritation.

Although we do not wish to place too much emphasis on the relative activities quoted in Tables 2 and 4, our results clearly illustrate some of the factors essential for bronchodilator and coronary dilator activity in these series of compounds.

Goodman & Gilman (1955) state that theophylline is more active as a bronchodilator and as a coronary dilator than theobromine and that theobromine is more active than caffeine. The same relationship exists for the 6-thio-analogues, 6-thiotheophylline being more active than 6-thiotheobromine or 6-thiocaffeine. So far as 6-thiotheophyllines are concerned, maximum bronchodilator activity was achieved with a relatively large alkyl group in the 3-position. Among 1-methyl-6-thiotheo-

phyllines, the 3-isobutyl derivative was the most active compound tested, though the n-butyl, n-pentyl and isopentyl derivatives were not much less active. With larger or smaller groups than these, however, activity was considerably reduced. In this series of compounds, coronary dilator activity generally ran closely parallel with bronchodilator activity, and the 3-isobutyl derivative was again the most active compound. It is interesting to note that compounds with an unsaturated group in the 3-position (for example, allyl, methylallyl, compounds 4 and 7 respectively) or compounds with a substituted alkyl group (for example, methoxypropyl, compound 9) were less effective as bronchodilators than the equivalent saturated or non-substituted compounds, 3, 6 and 8 respectively. The coronary dilator properties of the pairs of compounds, however, were very similar. From spatial considerations, a furfuryl group is theoretically equivalent to a 4-atom chain, but 3-furfuryl-1-methyl-6-thioxanthine (compound 14) was much less active as a bronchodilator and slightly less active as a coronary dilator than the 3-n-butyl derivative (compound 5).

Among 1-ethyl-6-thiotheophyllines, the 3-isobutyl derivative was the most active compound tested, being more active than the 1-methyl homologue as a broncho-dilator, though less active as a coronary dilator. This relationship was observed with all the 1-ethyl-6-thiotheophyllines. Only 4 compounds were tested with groups larger than ethyl in the 1-position, and 1,3-di-n-propyl-6-thioxanthine (compound 21) and 1,3-di-n-butyl-6-thioxanthine (compound 23) were exceptionally active as bronchodilators. Compound 23 also had the interesting property of first dilating, then constricting, the coronary vessels of the dog heart–lung preparation, and, although some 6-thioxanthines were almost inactive as coronary dilators, this was the only compound tested that caused the opposite of the expected action. It is possible that higher members of the series might be pure coronary constrictors. The other 1-n-butyl derivative (compound 22) was the reverse analogue of the active compound 5 and was only feebly active, indicating the importance of a small alkyl group in the 1-position. It should be noted that compounds 20, 21, 22 and 23 all had a high oral : intravenous LD50 ratio in mice, indicating that their oral absorption was poor. Of the three 8-substituted 6-thiotheophyllines tested, none had more than moderate bronchodilator or coronary dilator activity.

From these results it appears that a 1-methyl group is essential for high coronary dilator activity. Bronchodilator activity, however, was increased in compounds with relatively large groups in both the 1- and 3-positions, though with large groups in the 1-position oral absorption was probably reduced. It is also concluded that unsubstituted alkyl groups in the 3-position are essential for high bronchodilator activity as measured on the guinea-pig tracheal ring preparation, but are of less importance for coronary dilator activity. No conclusions can be drawn concerning structure-activity requirements for diuretic activity, since all the compounds tested had similar low activity. With the advent of the chlorothiazide-like diuretics, theophylline itself has become almost obsolete and it seems doubtful if 6-thioxanthines will be of any interest as diuretics. Of the dialkylxanthines, we tested only compound 5a for diuretic activity ; it was half as active as choline theophyllinate and slightly more active than its thio-analogue. Several dialkylxanthines, in

particular 1,3-diethylxanthine, were reported to be more active than theophylline as diuretics (Kattus *et al.*, 1951).

The 6-thiotheobromines and 6-thiocaffeines were all of little interest as bronchodilators and coronary dilators. Transfer of the methyl group from the 1- to the 7-position in compounds 28 and 29 greatly reduced activity, and the introduction of extra groups in the 7-position (6-thiocaffeines) also reduced activity. It is clearly only the 1,3-dialkyl-6-thioxanthines which are potent bronchodilators and coronary dilators.

The 6-thiocaffeines in contrast to caffeine did not show any stimulant properties in increasing the voluntary motor activity of mice, and although they did stimulate the respiration of the anaesthetized rabbit they were less effective than caffeine and nikethamide. The observation that they were less effective stimulants when the blood pressure was stabilized indicates that part of the stimulation is reflex in origin. Nikethamide, however, even in high doses, did not cause any undesirable vascular effects.

Of all the 6-thioxanthines, only the 6-thiotheophyllines are of any potential therapeutic interest. They are highly active bronchodilators and coronary dilators on the pharmacological preparations used, and there is some evidence in cats and dogs that they have less effect in producing emesis than their oxygen analogues.

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