SUBSTITUTED THIOCARBAMIDE DERIVATIVES OF SULPHANILAMIDE*

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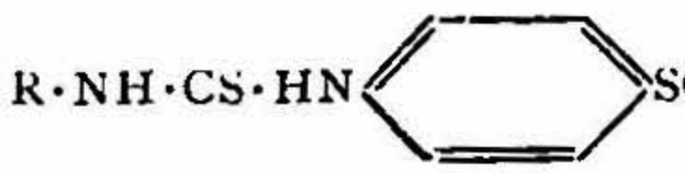
Mayer[1] has shown that phenyl sulphonamido thiocarbamide and sulphanilamido thiocarbamide are very active against experimental avian and human tubercle bacilli. Nao Uyei *et al.*,[2] have also found that of the few sulphanilamides that are effective against *B. tuberculosis* and *Staphylococcus aureus*, only the thiocarbamide derivative has a powerful effect. Though thiocarbamide has proved to have effect on the tubercle bacillus,[3] it has the disadvantage of high toxicity. However, the toxicity can be decreased by the introduction of a sulphonamide group.[2] Substitution of both the nitrogen atoms by thiocarbamide has minimised the toxicity.[4]

Roth and Degering[5] have prepared a series of compounds (type A) to study the bacteriostatic properties and to explore the further possibilities of the N^4-substituted thiocarbamide derivatives of sulphanilamide. But the results of pharmacological trials are not available even to-day.



$R \cdot NH \cdot CS \cdot HN$ ⟨benzene⟩ SO_2NH_2 (Type A)

R = methyl, ethyl, propyl, butyl, amyl and allyl;
phenyl, α-naphthyl, and *o*-tolyl.

The present investigation has therefore been taken up in line with the work of Roth and Degering[5] on the N^4-thiocarbamide derivatives of sulphanilamide, with a view to studying the effect of substitution of aryl- and alkyl-thiocarbamides at the N^4-position of sulphanilamide. It will thus be possible to see the difference in activity of these compounds with that of the metanilamide derivatives[6] and to find the effect of isomerism in these two types of compounds where the same groups have been attached to the *meta*- and *para*-positions with respect to the sulphonamide group.

Accordingly fourteen compounds of type A (Table I) have been prepared by reacting one mole of sulphanilamide with one mole of the corresponding isothiocyanate. Although Roth and Degering[5] have reported the

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TABLE I

(Type A)

No.	R	m.p. °C.	m.p. °C. reported	Method of prepn.	Crystallised from	Structural formula	Percentage of			
							Nitrogen		Sulphur	
							Found	Calcd.	Found	Calcd.
1	C_6H_5–	189·5–90	190–91[5] 198·8[2]	I	Aqueous acetone	$C_{13}H_{13}O_2N_3S_2$	13·29	13·68	..	..
2	*p*-ClC_6H_4–	180–80·5	..	II	do	$C_{13}H_{12}O_2N_3ClS_2$	12·39	12·30	19·34	18·74
3	*p*-BrC_6H_4–	185–86	..	do	do	$C_{13}H_{12}O_2N_3BrS_2$	10·76	10·88	17·28	16·58
4	*p*-IC_6H_4–	183·5–84·5	..	do	do	$C_{13}H_{12}O_2N_3IS_2$	9·80	9·70	..	..
5	*p*-$CH_3C_6H_4$–	186·5–87·5	..	III	do	$C_{14}H_{15}O_2N_3S_2$	13·44	13·08	19·58	19·94
6	*o*-$CH_3C_6H_4$–	194–95	215–16	I	do	$C_{14}H_{15}O_2N_3S_2$	13·35	13·08	..	..
7	*m*-$CH_3C_6H_4$–	209·5–10·5	..	do	do	$C_{14}H_{15}O_2N_3S_2$	12·93	13·08	..	..
8	*p*-$CH_3·O·C_6H_4$–	175–76	..	III	do	$C_{14}H_{15}O_3N_3S_2$	12·32	12·46	..	..
9	2: 4$(CH_3)_2C_6H_3$–	210–11	..	IV	do	$C_{15}H_{17}O_2N_3S_2$	12·40	12·54	..	..
10	2:5$(CH_3)_2C_6H_3$–	209–11	..	V	do	$C_{15}H_{17}O_2N_3S_2$	12·71	12·54	..	..
11	*m*-ClC_6H_4–	209–10	..	IV	do	$C_{13}H_{12}O_2N_3ClS_2$	12·79	12·30	..	..
12	CH_3–	195·96	205–6[5]	VI	do	$C_8H_{11}O_2N_3S_2$	17·32	17·14	26·32	26·12
13	CH_2–CH–CH_2–	183–84	189–90[5]	do	90% ethanol	$C_{10}H_{13}O_2N_3S_2$	16·07	15·50	..	..
14	$(CH_3)_2$CH–	193–94	..	do	Dilute alcohol	$C_{10}H_{15}O_2N_3S_2$	15·00	15·38	23·68	23·44

preparation of methyl, allyl, phenyl and *o*-tolyl derivatives, certain discrepancies have been observed in their analytical data for the methyl and allyl derivatives.

All these compounds have been tested *in vitro* for their anti-bacterial and anti-tubercular activity. While eight of these compounds have shown slight inhibitory activity against *M. tuberculosis*, only two have shown slight anti-bacterial activity against *S. aureus*. In general the anti-bacterial and anti-tubercular activities are less in the thiocrabamide derivatives of sulphanilamide than in those of metanilamide.[6] Details of these tests will be published separately.

Experimental

One typical experiment detailing each of the six methods employed in the preparation and isolation of the fourteen compounds listed in the table is given below.

Method I

1-(p-*Sulphamyl phenyl*)-3-*phenyl-thiocarbamide* (1).—Phenyl-isothiocyanate (1·35 g.) was added to a solution of sulphanilamide (1·72 g.) in alcohol (20 c.c.) and the mixture was refluxed for two hours. The product which separated on cooling was filtered off, washed with a little alcohol and dried. Yield—2·4 g. (crude). More of the product (0·4 g.) was obtained on concentrating the solution. The product was crystallised from aqueous acetone to get white shining leaflets; m.p., 189·5–190°. It is soluble in dioxane and dilute alkali; sparingly soluble in alcohol and insoluble in water and benzene [Found: N, 13·29; $C_{13}H_{13}O_2N_3S_2$ requires N, 13·68 per cent.].

Method II

1-(p-*Sulphamyl phenyl*)-3-(p-*chlorophenyl*)-*thiocarbamide* (2).—To a boiling solution of sulphanilamide (1·72 g.) in alcohol (40 c.c.) *p*-chlorophenyl-isothiocyanate (1·7 g.) was added and the hot reaction mixture was left at room temperature for a day. By then, white shining leaflets had separated out which were filtered, washed with cold alcohol and dried. Yield—2·8 g. (crude). The product was recrystallised twice from acetone-water (3 : 1) mixture. White shining leaflets were obtained; m.p., 180–180·5°. It is soluble in acetone, dioxane and dilute alkali; sparingly soluble in alcohol; insoluble in water and benzene [Found: N, 12·39; S, 19·34; $C_{13}H_{12}O_2N_3ClS_2$ requires N, 12·30; S, 18·74 per cent.].

Method III

1-(p-*Sulphamyl phenyl*)-3-(p-*tolyl*)-*thiocarbamide* (5).—*p*-Tolyl-isothiocyanate (1·49 g.) was refluxed for twenty minutes with sulphanilamide (1·72 g.)

in alcohol (40 c.c.) and the mixture left at room temperature for 36 hours. The white crystalline product that had separated by then, was filtered, washed and dried. Yield—2·1 g. (crude). The product was purified by dissolving in 85 per cent. aqueous acetone (80 c.c.), filtering and diluting with water (40 c.c.). This procedure was repeated once when the product came out in a fine crystalline form, m.p., 186·5–187–5°. It is soluble in dioxane, dilute alkali and 85 per cent. aqueous acetone; very sparingly soluble in acetone and alcohol; insoluble in water and benzene [Found: N, 13·44; S, 19·58; $C_{14}H_{15}O_2N_3S_2$ requires, N, 13·08; S, 19·94 per cent.].

Method IV

1-(p-*Sulphamyl phenyl*)-3-(2 : 4-*dimethyl phenyl*) *thiocarbamide* (9).—This was obtained by refluxing a mixture of sulphanilamide (1·72 g.) 2:4-dimethyl-phenyl-isothiocyanate (1·63 g.) and alcohol (25 c.c.) for 22 hours, cooling, collecting the solid by filtration. washing with alcohol and drying; yield—0·6 g.; m.p. 209–10°. It was purified as described under method III. m.p. 210–11°. Its solubility is the same as that of compound 5. [Found: N, 12·40; $C_{15}H_{17}O_2N_3S_2$ requires N, 12·54 per cent.].

Method V

1-(p-*Sulphamyl phenyl*)-3-(2 : 5-*dimethyl phenyl*)-*thiocarbamide* (10).—A mixture of 2:5-dimethyl phenyl isothiocyanate (0·85 g.), sulphanilamide (0·86 g.) and alcohol (15 c.c.) were heated under reflux at 60–70° for three hours. White crystals began to separate. Heating at 60–70° was continued for 15 hours and the product was filtered off, washed and dried; yield—0·5 g. (crude). It was purified as described under method III. Its solubility is also similar to that of compound 5 [Found: N, 12·71; $C_{15}H_{17}O_2N_3S_2$ requires N, 12·54 per cent.].

Method VI

1-(p-*Sulphamyl phenyl*)-3-*methyl thiocarbamide* (12).—Methyl-isothiocyanate (0·73 g.) was refluxed with sulphanilamide (1·72 g.) and alcohol (20 c.c.) for six hours. After cooling overnight the white crystalline product was filtered, washed with cold alcohol and dried; yield—1·7 g. Three recrystallisations from dilute acetone (*cf.* method III) gave colourless rhombic plates; m.p., 195–96°. It resembles compound 5 in its solubility. [Found: N, 17·32; S, 26·32; $C_8H_{11}O_2N_3S_2$ requires N, 17·14; S, 26·12 per cent.].

SUMMARY

The preparation and properties of fourteen aryl- and alkyl-substituted thiocarbamide derivatives of sulphanilamide have been described. All of them have been tested for their anti-bacterial and anti-tubercular activity.

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