SUBSTITUTED THIOUREA DERIVATIVES OF METANILAMIDE

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Summary

The preparation and properties of fourteen substituted thiourea derivatives of metanilamide are described in this paper. All of them have been tested for their antibacterial activity. Some of them have indicated antitubercular activity in 1 : 100,000 concentration.

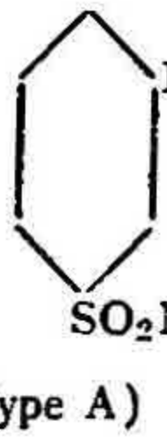
Interest in the field of substituted thiourea derivatives was aroused by the reported chemotherapeutic properties of thioureas, simple[1] as well as substituted.[2, 3] Thiourea has got a marked inhibitory action on the development and vitality of pathogenic organisms[4] like *Staphylococcus aureus* and *albus*.[5] Mayer[6] had found during the determination of antibacterial, antimycotic and antitubercular action of many compounds containing sulphur, that sulphanilamido thiourea, phenyl sulphonamidothiourea and mercapto benzothiazole were highly active towards avian and human tubercle bacilli.

It can be seen from the reports of Jimenez Vargas and Monche Escubos[7] that disubstituted thioureas show much less toxicity as compared to monosubstituted ones. Toxicity tests carried out by oral administration methods by Nao Uyei *et al.*,[3] have shown that compounds with $C_{10}H_8$ and guanidine derivatives had almost no toxicity, and acetyl and $CONH_2$ groups lowered the toxicity to a remarkable extent. They have also observed that phenyl thiourea which was highly toxic, when substituted with a sulphonamide group, became less toxic.

Metachloridine and 2-metanilamido-pyrimidine, the corresponding meta analogues of 2-sulphanilamido-5-chloro-pyrimidine and sulphadiazine were prepared by English *et al.*,[8] to study the effects of isomerism. They were reported to be highly active against sporozoite induced and blood induced *Plasmodium gallinacium* infections in chicks, metachloridine being sixteen times as active as quinine in this type of blood induced infections. The metanilamides are in good contrast to the sulphanilamides both in their lack

of antibacterial property and in the more restricted nature of the N^1 substituents associated with antimalarial property. It was probably this fact coupled with the close relation of the antibacterial and antimalarial action of sulphanilamides, which discouraged an earlier examination of compounds in the metanilamide series. The N^1 derivatives of 6-methyl metanilamide were claimed to be active against pneumococcal and brucella infections in the patent literature.[9] Such activity, if verified, would be interesting to current theories of mechanism of chemotherapeutic action and the future development in this field.

Bearing in mind the aforesaid literature about therapeutic activities of metanilamide and thiourea derivatives, as also the researches done in this laboratory about thioureas, guanidines, biguanides, cyanoguanidines, bisguanidines, tri and tetraguanides, dithiobiurets, etc., and their association with *para*-sulphanilamides,[10] it was considered desirable to study the above types of compounds with metonilamide. In this part, the first of this series, 1-(*m*-sulphonamidophenyl)-3-thioureas of type A have been synthesised and their antibacterial properties studied.



(R = H, alkyl, aryl and substituted aryl groups)

(Type A)

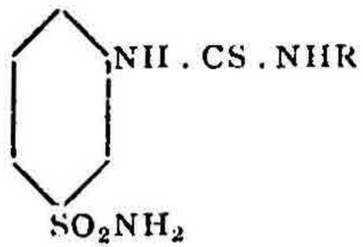
The compounds tabulated below (Table I) were prepared by the condensation of metanilamide with the corresponding mustard oils in alcohol.

The details for the preparation of metanilamide are not available thoroughly in the literature.[11, 12, 13] These details have now been worked out and described under experimental part. The overall yield of metanilamide, starting from nitrobenzene, has been 27 to 30 per cent.

The aryl mustard oils were prepared from the corresponding amines by the method due to Dains, Brewster and Olander.[14] But we were able to obtain yields twice as much as was reported. The percentage yields, melting points and boiling points are given in Table II.

The compounds were tested against micro-organisms like *Staphylococcus aureus*, *B. coli* and *Microbacterium tuberculosis* to evaluate their chemotherapeutic properties and the results are given in Table III.

TABLE I



No.	R	M.P. ° C.	Yield %	Method	Duration of reaction in hours	Crystal-lised from	Structural formula	Percentage			
								Nitrogen		Sulphur	
								Found	Calcd.	Found	Calcd.
1	H-	.. 164–166·5	90	II	..	dil. alc. (3 : 2)	$C_7H_9O_2N_3S_2$	19·00	18·18	28·09	27·71
2	C_6H_5-	.. 161·5	89	IV	24	alcohol	$C_{13}H_{13}O_2N_3S_2$	13·29	13·68	..	..
3	*p*-Cl.C_6H_4-	.. 162·5–163	97·6	IV	24	dil. alc.	$C_{13}H_{12}O_2N_3ClS_2$	12·38	12·30	18·22	18·74
4	*m*-Cl.C_6H_4	.. 181–82	52	V	*cf.* Expt.	dil. alc.	$C_{13}H_{12}O_2N_3ClS_2$	12·66	12·30	..	..
5	*p*-Br.C_6H_4-	.. 168·5	85·5	IV	12	dil. alc. (1 : 1)	$C_{13}H_{12}O_2N_3BrS_2$	10·87	10·88	16·23	16·58
6	*p*-I.C_6H_4-	.. 186	86	IV	12	dil. acetone (1 : 1)	$C_{13}H_{12}O_2N_3IS_2$	9·59	9·70	..	..
7	*p*-CH_3.C_6H_4-	.. 160·5–161	87	IV	24	dil. alc. (3 : 2)	$C_{14}H_{15}O_2N_3S_2$	13·10	13·08	19·68	19·94
8	*p*-CH_3.O.C_6H_4-	.. 155·5–156	83·9	IV	12–20	alcohol	$C_{14}H_{15}O_3N_3S_2$	12·79	12·46	..	..
9	2 : 5 $(CH_3)_2C_6H_3$-	.. 156·5–157	77·6	IV	48	dil. alc. (2 : 1)	$C_{15}H_{17}O_2N_3S_2$	12·31	12·54	..	..
10	2 : 4 $(CH_3)_2C_6H_3$-	.. 155–155·5	80·6	IV	48	dil. alc. (1 : 1)	$C_{15}H_{17}O_2N_3S_2$	12·66	12·54	..	..
11	α-$C_{10}H_7$	.. 170	82	IV	12	dil. acetone (4 : 3)	$C_{17}H_{15}O_2N_3S_2$	11·92	11·76	..	..
12	$CH_2 = CH\text{-}CH_2$-	.. 142–43	83	VIII	*cf.* Expt.	dil. alc. (1 : 1)	$C_{10}H_{13}O_2N_3S_2$	15·28	15·50	23·88	23·61
13	CH_3-	.. 156·5–157	75	VI	*cf.* Expt.	dil. alc. (1 : 3)	$C_8H_{11}O_2N_3S_2$	17·41	17·14	..	..
14	$(CH_3)_2CH$-	.. 154	60	VII	*cf.* Expt.	dil. alc. (1 : 2)	$C_{10}H_{15}O_2N_3S_2$	15·31	15·38	..	..

TABLE II

$R - N = C = S$

No.	R	M.P. °C.	B.P. °C.	Method	Yield per cent.	Reference
1	C_6H_5-	..	95/12 mm.	III *a*	77	14
2	*p*-Cl.C_6H_4-	46–47	..	III *b*	58·5	14
3	*p*-Br.C_6H_4-	60–61	..	III *b*	60	14
4	*p*-I.C_6H_4-	75–76*	..	III *b*	32	14, 17, 18, 19
5	*o*-$CH_3C_6H_4$- ..	..	138/68 mm.	III *b*	33	..
6	*m*-$CH_3C_6H_4$- ..	..	189–91/220 mm.	III *b*	41	..
7	*p*-$CH_3C_6H_4$- ..	..	178–81/200 mm.	III *b*	33	..
8	*p*-CH_3.O.C_6H_4- ..	18	158–59/25 mm.	III *b*	44	..
9	*p*-$(CH_3)_2C_6H_3$- ..	..	146–47/29 mm.	III *b*	30	..
10	α-$C_{10}H_7$-	59	..	III *b*	35	..
11	CH_3-	34	114/684 mm.	VI	16	15
12	$(CH_3)_2CH$-	..	134/684 mm.	VII	28·5	16

* Crowther, Curd *et al.*[17] give the m.p. 76–77°, while Losanitsch[18] gives m.p. as 65° and Dyson and George[19] give the m.p. as 63°.

TABLE III

Antibacterial Activity of the Compounds

No.	Name of the compound	Minimum inhibitory concentration against		
		E. coli	*Staph. aureus*	*M. tuberculosis*
1	*m*-Sulphamyl phenyl thiourea	—ve	1 : 1,000	1 : 1,000
2	1-Phenyl-3-R	1 : 1,000	1 : 1,000	1 : 1,000
3	1-(*p*-Chloro-phenyl)-3-R ..	—ve	1 : 10,000	1 : 10,000
4	1-(*m*-Chloro-phenyl)-3-R ..	—ve	1 : 1,000	1 : 1,000
5	1-(*p*-Bromo-phenyl)-3-R ..	—ve	1 : 10,000	1 : 100,000
6	1-(*p*-Iodo-phenyl)-3-R ..	—ve	1 : 10,000	1 : 100,000
7	1-(*p*-Tolyl)-3-R	—ve	1 : 1,000	1 : 100,000
8	1-(*p*-Anisyl)-3-R	—ve	1 : 1,000	1 : 1,000
9	1-(*p*-Xylyl)-3-R	1 : 1,000	1 : 1,000	1 : 10,000
10	1-(*m*-Xylyl)-3-R	1 : 1,000	1 : 1,000	1 : 10,000
11	1-(α-Naphthyl)-3-R ..	—ve	1 : 10,000	1 : 100,000
12	1-(Allyl)-3-R	1 : 1,000	1 : 1,000	1 : 1,000
13	1-Methyl-3-R	1 : 1,000	1 : 1,000	1 : 1,000
14	1-Isopropyl-3-R	1 : 1,000	1 : 1,000	1 : 1,000

R = (*m*-sulphamyl phenyl) thiourea

EXPERIMENTAL

m-Nitrobenzene sulphonyl chloride (I a)[11]

Prepared from nitrobenzene (123 g.) and chlorosulphonic acid (350 g.) following the method due to Hodgson and Whitehurst.[11] It can be preserved longer without decomposition by keeping in a vacuum desiccator.

m-Nitrobenzene sulphonamide (I b)[12]

m-Nitrobenzene sulphonyl chloride (125 g.) was added gradually under stirring to a mixture of liquor ammonia (200 c.c.–0·895 s.g.) and water (150 c.c.). The mixture was refluxed for 15 minutes and concentrated to a small bulk (Ca. 50 c.c.) filtering the solid from time to time to avoid severe bumping. The solid finally was filtered, washed with a little cold water and dried in the air. Yield of the crude product: 105 g., m.p. 162–63°. The compound came out as a shining crystalline powder from alcohol, m.p. 163–64°. The crude product was sufficiently pure for the next stage.

m-Aminobenzene sulphonamide (*Metanilamide*) (*I c*)[13]

m-Nitrobenzene sulphonamide (104 g.) was dissolved in a mixture of alcohol (400 c.c.) and liquor ammonia (350 c.c.). The solution was saturated with hydrogen sulphide, when the solution turned orange yellow in colour. It was concentrated to one-fourth its volume under vacuo and filtered hot to separate the precipitated sulphur. The filtrate was left overnight when the compound crystallised out. It was collected by filtration, washed with water and dried. Yield 50 g., m.p. 139–41°. Dissolved the product in dilute sodium hydroxide (10 per cent.), treated with a little (2–3 g.) norite in the cold, filtered, and washed with a little water, cooled the clear filtrate in an ice-bath and gradually neutralised with dilute acetic acid (1 : 1). The separated product was filtered, washed thoroughly with small quantities of ice-cold water, drained well and dried in the air. Yield: 45 g. (53 per cent.). Calculated on *m*-nitrobenzene sulphonamide. Recrystallisation from alcohol gave white prismatic needles melting at 142° (Found: N, 16·28; S, 18·24; $C_6H_8O_2N_2S$ requires N, 16·28; S, 18·61 per cent.).

m-Sulphamyl phenyl thiourea (*II*)

Potassium sulphocyanide (1·45 g.) was added to a mixture of metanilamide (1·72 g.), water (10 c.c.) and concentrated hydrochloric acid (1 c.c.) at 100° C. The solution was evaporated to dryness on the water-bath. The residue was treated with some water (10 c.c.) and again evaporated to dryness. The solid left behind was recrystallised from dilute alcohol (3 parts alcohol: 2 parts water) in white shining needles, m.p. 164–166·5°, yield: 2 g. (Found: N, 19·0; S, 28·09; $C_7H_9O_2N_3S_2$ requires N, 18·12; S, 27·71 per cent.).

Phenyl Isothiocyanate (III a)[14]

Prepared by the method due to Dains *et al.*

p-Bromo phenyl isothiocyanate (III b)[14]

p-Bromo aniline (60 g.) was dissolved in alcohol (54 c.c.–95 per cent.) and carbon disulphide (32 c.c.) was dropped into it. The mixture was cooled in an ice-bath to about 10° and liquor ammonia (55 c.c.–0·895 s.g.) was added to that gradually under shaking during 20 minutes. The temperature of the reaction mixture was not allowed to rise above 25° by keeping in the ice-bath. It was left overnight and next morning it was filtered, washed with a little ether and dried in the air. Dissolved this in water (4 litres). A solution of lead nitrate (110 g.) in water (250 c.c.) was slowly added to the above solution under stirring and the stirring was continued for 20 minutes more. It was then steam-distilled, the distillate (11 litres) being collected in 20 c.c. of N sulphuric acid. The solidified oil was washed with a little water and dried in a desiccator, yield 60 per cent. (45 g.), m.p. 60–61°.

On repeating the same experiment with small quantity of *p*-bromo aniline (4·5 g.), the yield came upto 73 per cent. (4·1 g.).

Rest of the aryl isothiocyanates (Table II) were prepared by the same method. Only a very small amount of the intermediate ammonium dithiocarbamate separated out during the preparation of the *o*-tolyl- and *p*-xylyl isothiocyanates. Hence the whole of the reaction mixture was diluted with water, treated with lead nitrate solution and steam distilled, collecting the distillate as usual in 20 c.c. N sulphuric acid. Extracted it with benzene, washed the extract, dried over anhydrous sodium sulphate, removed the benzene and fractionated the mustard oil under reduced pressure.

1-(*m-Sulphamyl phenyl*)-3-*phenyl-thiourea* (*IV*)

Metanilamide (1·72 g.–0·01 mole) was dissolved in hot alcohol (15 c.c.). A solution of phenyl isothiocyanate (1·35 g.–0·01 mole) in alcohol (5 c.c.) was added to the warm solution and the mixture was left at room temperature. After about 12 hours white crystals started separating out. It was left as such for 12 more hours and filtered. Washed the product with a little cold alcohol (5 c.c.) and dried. Yield of the crude product was 89 per cent. (2·72 g.). After two recrystallisations from alcohol white shining needles were obtained, m.p. 166·5° (Found: N, 13·29, $C_{13}H_{13}O_2N_3S_2$ requires N, 13·68 per cent.).

In the case of *p*-bromo, *p*-iodo and α-naphthyl analogues of the series (Nos. 5, 6 and 11 of Table I) the final products separated out within 30, 5

and 10 minutes respectively after the addition of the corresponding isothiocyanates to the hot solution of metanilamide. The reaction mixture was, however, kept overnight and the products were isolated and purified as described under (IV).

1-(*m-Sulphamyl phenyl*)-3-(*m-chlorophenyl*) *thiourea* (*V*)

To a warm alcoholic solution of metanilamide (1·72 g. in 15 c.c.) was added a solution of *m*-chlorophenyl isothiocyanate (1·69 g.) in alcohol (5 c.c.). It was left at laboratory temperature for two days and then refluxed on a water-bath for 15 hours. Unreacted isothiocyanate was then removed by steam. The white solid residue was washed with water and dried. This was dissolved in dilute sodium hydroxide (10 per cent.), filtered to remove the suspended impurities and gradually acidified with dilute acetic acid, under ice-cooling. The separated solid was filtered off, washed well with cold water and dried. This on repeated crystallisations from alcohol gave slender shining white needles, m.p. 181–82° (Found: N, 12·66; $C_{13}H_{12}O_2N_3ClS_2$ requires N, 12·30 per cent.).

This method did not work for *o*-tolyl and *m*-tolyl analogues.

1-(*m-Sulphamyl phenyl*)-3-*methyl thiourea* (*VI*)

Methyl isothiocyanate was prepared by the method due to Bremer.[15] To a warm alcoholic solution of metanilamide (1·72 g.) in alcohol (20 c.c.) methyl isothiocyanate (0·73 g.) was added. The reaction mixture was left at room temperature for 24 hours. Then it was refluxed for 3 hours more and again kept at room temperature for one day, when the product separated out in shining nodules. Filtered, washed with dilute alcohol and dried. Yield, 75% (1·8 g.). It formed white crystalline powder from dilute alcohol (1 part alcohol : 3 parts water), m.p. 156–57° (Found: N, 17·41; $C_8H_{11}O_2N_3S_2$ requires N, 17·14 per cent.).

1-(*m-Sulphamyl phenyl*)-3-*isopropyl thiourea* (*VII*)

Iso-propyl isothiocyanate was prepared following the method of John[16] (*cf.* Table II).

The clear solution, formed by the addition of isopropyl isothiocyanate (1·01 g.) in alcohol (5 c.c.) to metanilamide (1·72 g.) in alcohol (15 c.c.), was left overnight at room temperature and refluxed for 3 hours. It was further kept for one day more, concentrated to half the volume, diluted with twice the quantity of water, heated to form a clear solution, treated with a little of norite and filtered hot. The filtrate on cooling deposited white shining leaflets. Yield, 60 per cent. (1·2 g.). Recrystallisation from dilute alcohol (1 : 2) gave white glistening leaflets, m.p. 154° (Found: N, 15·31, $C_{10}H_{15}O_2N_3S_2$ requires N, 15·38 per cent).

1-(*m-Sulphamyl phenyl*)-3-*allyl thiourea* (*VIII*)

Proceeded as described under (IV) from metanilamide (1·72 g.), alcohol (30 c.c.) and allyl mustard oil (0·99 g.). But in this case, after leaving it overnight at room temperature, it was refluxed for one hour and cooled. The product separated out in white shining needles. Filtered, washed with a little alcohol and dried. Yield, 83 per cent. (2·25 g.). Recrystallisation from alcohol yielded thin shining needles, m.p. 142–43° (Found: N, 15·28; $C_{10}H_{13}O_2N_3S_2$ requires N, 15·50 per cent.).

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