N^1, N^3-BIS-(ARYL- AND ALKYL-THIOCARBAMYL)-METANILAMIDES*

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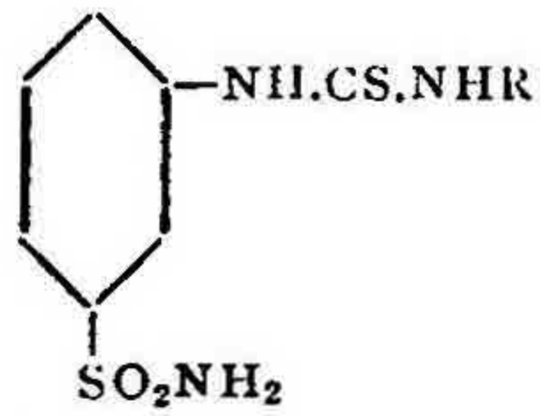
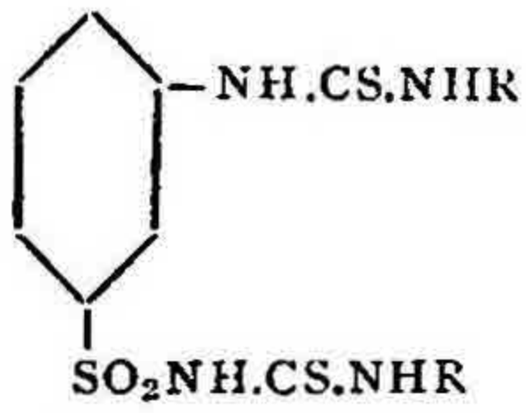
The preparation and properties of twelve N^1, N^3-*bis*-(aryl- and alkyl-thiocarbamyl) metanilamides have been described in this paper. All of them have been tested for their anti-bacterial and anti-tubercular activity.

Although metanilamide has been reported to be devoid of anti-bacterial properties,[1-3] Viswanathan *et al.*[4, 5] have reported that the *p*-bromophenyl, *p*-iodophenyl, *p*-tolyl, and α-naphthyl thiourea derivatives of metanilamide (type A) have shown promising anti-tubercular activity. They have also found that the *p*-chlorophenyl thiourea derivative of the series showed slight suppressive antimalarial activity when tested against blood-induced *P. gallinaceum* infections in chicks.



(Type A)



(Type B)

where R = aryls and alkyls

In the light of the above observations as also of the chemotherapeutic properties of thioureas,[6-8] it was thought desirable to extend this line of work by preparing metanilamides (type B) substituted both in its N^1 and N^3 positions by aryl and alkyl thiocarbamyl residues, for pharmacological study.

Accordingly 12 new compounds (type B) given in Table I have been prepared by condensing 1 mole of metanilamide with 2 moles of the corresponding isothiocyanate in presence of 1 mole equivalent of N. sodium hydroxide in acetone medium at a temperature of 60–70° C., following the method due to Siegfried Peterson.[9] All these compounds have been isolated as described under experimental part and purified by recrystallisation from

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dilute alcohol or acetone. In most cases the compounds were obtained in beautiful crystalline form.

EXPERIMENTAL

One typical experiment detailing each of the 4 methods employed in the preparation and isolation of the 12 compounds listed in the table is given below.

Metanilamide, and the aryl- and alkyl-isothiocyanates have been prepared as already reported.[5]

Method I

N^1, N^3-Bis-(phenyl thiocarbamyl)-metanilamide (1). — Metanilamide (1·72 g; 0·01 mole) was dissolved in N. sodium hydroxide (10 c.c.) and acetone (4 c.c.) and a solution of phenyl isothiocyanate (2·7 g.; 0·02 mole) in acetone (6 c.c.) was added to it. The mixture was heated at 60–65° under reflux. In about 6 hours fine crystals began to separate. The heating was continued for 42 hours more to complete the reaction and cooled to room temperature. The crystals were filtered, washed with water, then with a little alcohol and dried, m.p. 150–51°. Yield 1·3 g. (crude). Two recrystallisations from dilute alcohol (1 : 1) yielded thin white shining flakes, m.p. 151°. It is soluble in alcohol, acetone, and dioxane; insoluble in benzene and water. (Found: N, 12·73; $C_{20}H_{18}O_2N_4S_3$ requires N, 12·67 per cent.).

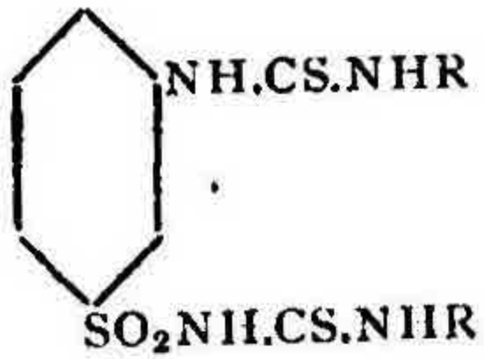
Method II

N^1, N^3-Bis-(p-*iodophenyl thiocarbamyl)-metanilamide* (4).—To a solution of metanilamide (1·72 g.; 0·01 mole) in N. sodium hydroxide solution (10 c.c.) and acetone (5 c.c.), *p*-iodophenyl isothiocyanate (5·22 g.; 0·02 mole) in acetone (15 c.c.) was added and the mixture was just heated at 60–65° for 5 minutes, shaken well and kept aside. In about 5 minutes crystals started separating out. It was left at room temperature for 24 hours, filtered, washed with water, then with alcohol and dried. Yield 2·70 g. (crude). The mother liquor, after heating for 24 hours at 60–65°, yielded 0·4 g. more of the product. The product came out in fine crystalline needles from aqueous acetone, m.p. 181–82°. It is soluble in acetone and dioxane; very sparingly soluble in alcohol; insoluble in benzene and water. (Found: N, 8·06; $C_{20}H_{16}O_2N_4I_2S_3$ requires N, 8·07 per cent.)

Method III

N^1, N^3-Bis-(methyl thiocarbamyl)-metanilamide (10).—Methyl isothiocyanate (1·46 g.; 0·02 mole) was added to a solution of metanilamide (1·72 g.; 0·01 mole) in acetone (10 c.c.) and N. sodium hydroxide (10 c.c.).

TABLE I



(Type B)

No.	R	m.p. ° C.	Method of preparation	Duration of reaction in hours	Crystallised from	Crystalline form	Structural formula	Percentage of nitrogen	
								Calc.	Found
1	C_6H_5—	151	I	48	dil. alcohol (1 : 1)	shining flakes	$C_{20}H_{18}O_2N_4S_3$	12·67	12·73
2	*p*-Cl·C_6H_4—	171–72	,,	28	alcohol 80%	long plates	$C_{20}H_{16}O_2N_4Cl_2S_3$	10·96	10·66
3	*p*-Br·C_6H_4—	183·5–84·5	,,	28	,,	,,	$C_{20}H_{16}O_2N_4Br_2S_3$	9·33	9·32
4	*p*-I·C_6H_4—	181–82	II	24	dil. acetone	needles	$C_{20}H_{16}O_2N_4I_2S_3$	8·07	8·06
5	*p*-CH_3·C_6H_4—	176–77	I	28	dil. alcohol (1 : 1)	prisms	$C_{22}H_{22}O_2N_4S_3$	11·94	11·84
6	*p*-CH_3·O·C_6H_4—	186–87	,,	28	alcohol 80%	flakes	$C_{22}H_{22}O_4N_4S_3$	11·15	10·93
7	2 : 5$(CH_3)_2C_6H_3$—	144–44·5	,,	43	dil. alcohol (1 : 1)	thin needles	$C_{24}H_{26}O_2N_4S_3$	11·25	11·16
8	2 : 4$(CH_3)_2C_6H_3$—	148–49·5	,,	60	first from 90% ethanol and then from rectified spirit	thick prisms	$O_{24}H_{26}O_2N_4S_3$	11·25	11·37
9	α-$C_{10}H_7$—	195–96	,,	43	dil. acetone	microscopic needles	$C_{28}H_{22}O_2N_4S_3$	10·33	9·94
10	CH_3—	171–71·5	III	25	dil. acetone	thick prisms	$C_{10}H_{14}O_2N_4S_3$	17·61	17·77
11	CH_2=CH·CH_2—	127–28	IV	40	dil. alcohol (1 : 1)	glistening flakes	$C_{14}H_{18}O_2N_4S_3$	15·14	14·99
12	$(CH_3)_2$CH—	154·5–56	,,	40	dil. alcohol (1 : 1)	plates	$C_{14}H_{22}O_2N_4S_3$	14·97	14·80

The mixture was heated under reflux at 60–65° for 25 hours. The mixture was then treated with a little norite and filtered hot. The filtrate was diluted with an equal volume of water and made slightly acidic with dilute acetic acid. The precipitate was filtered, washed with water and dried. Yield, 1·64 g. (crude). It formed thick prisms from aqueous acetone, m.p. 171–71·5° (decomposition). It is soluble in acetone and dioxane; very sparingly soluble in alcohol; insoluble in benzene and water. (Found: N, 17·77; $C_{10}H_{14}O_2N_4S_3$ requires N, 17·61 per cent.)

Method IV

N^1, N^3-Bis-(allyl thiocarbamyl)-metanilamide (11).—This has been prepared by heating at 60–65° for 40 hours a mixture of metanilamide (1·72 g.; 0·01 mole), N. sodium hydroxide (10 c.c.), acetone (10 c.c.) and allyl isothiocyanate (1·98 g.; 0·02 mole). The reaction mixture was then diluted with twice the quantity of water, treated with norite and filtered off. The light yellow clear filtrate was made slightly acidic with dilute acetic acid when an oily material separated which solidified on scratching and chilling. This solid was filtered, washed with water and dried. Yield 1·5 g. (crude). Three recrystallisations from dilute alcohol after treatment with norite gave white glistening flakes, m.p. 127–28°. It is soluble in alcohol, acetone and dioxane; insoluble in benzene and water. (Found: N, 14·99; $C_{14}H_{18}O_2N_4S_3$ requires N, 15·14 per cent.)

All these compounds have been tested *in vitro* for their antibacteria and antitubercular activity. Two typical compounds have been tested for their antimalarial activity. Details of these tests will be published separately.

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