

THIOUREA DERIVATIVES FROM SULPHA BIGUANIDES

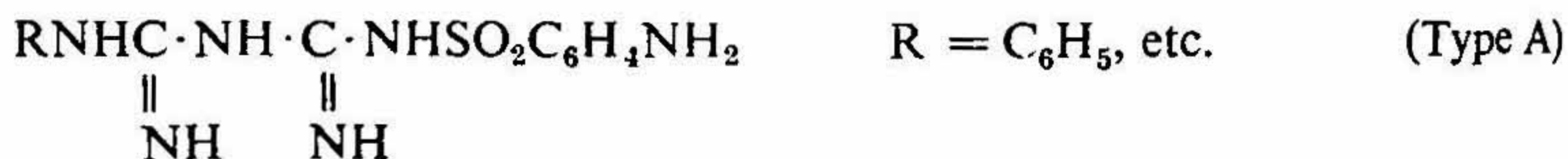
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The synthesis of eight new thioureido derivatives from sulphabiguanide is described in this paper. Some typical compounds were tested for their antimalarial activity but none of them showed any activity.

Starting their work on the chemically versatile pyrimidine ring and making various alterations in the molecule Curd and Rose arrived at paludrine which is a substituted biguanide derivative.¹ Suffice it to say that paludrine is the drug of choice in the chemotherapy of malaria. Rose² prepared sulphabiguanides of the type A



which possess strong antiseptic properties and are useful as therapeutic agents in the treatment of bacterial infections. A number of sulphabiguanides has been prepared in our laboratory and some of them possessed suppressive antimalarial activities.³⁻⁶ A reference to literature reveals thioureas, substituted or otherwise, as chemotherapeutically active compounds. They inhibit the growth of pathogenic organisms⁷ and also suppress the growth of several pathogenic fungi.⁸ Thioureas have activity in several other bacterial infections.⁹⁻¹¹ Humberto *et al.*,¹² and R. L. Meyer¹³ describe the usefulness of thioureas, substituted or otherwise, in the chemotherapy of mycoses and of tuberculosis.

Having in mind the considerations detailed above, it was thought to be of interest to synthesize compounds wherein the thioureido moiety is attached to the sulphabiguanide chain (type B) for pharmacological examinations.

Accordingly, eight thiourea derivatives (*vide* Table I) have been prepared by reacting phenyl; *p*-chloro, bromo, iodo phenyl; allyl; *o*, *m* and *p*-tolyl mustard oils with *N'*-*p*-chlorophenyl-*N*⁵-(*p*-aminobenzenesulphonyl)

biguanide in an alcohol-acetone medium. These compounds (type B) have been tabulated below:

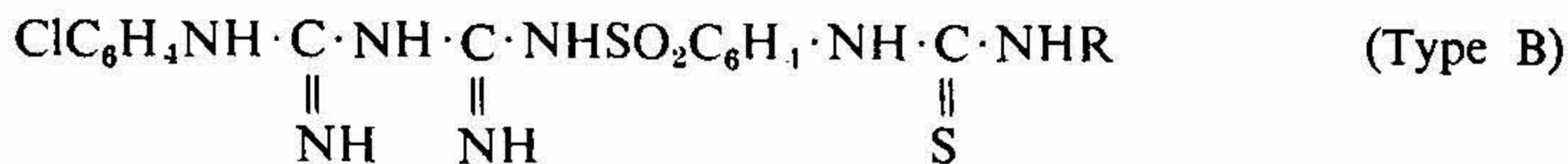


TABLE I
Thiourea Derivatives from Sulphabiguanide

No.	R	M.P.	% of N ₂ required	% of N ₂ found
1	C ₆ H ₅ -	108° C.	19.54	19.67
2	<i>p</i> -ClC ₆ H ₄ -	140° C.	18.28	18.38
3	<i>p</i> -BrC ₆ H ₄ -	132° C.	16.89	17.04
4	<i>p</i> -IC ₆ H ₄	138° C.	15.62	15.42
5	CH ₂ =CH-CH ₂ -	105° C.	21.05	20.73
6	<i>o</i> -CH ₃ C ₆ H ₄ -	115° C.	19.01	18.93
7	<i>m</i> -CH ₃ C ₆ H ₄ -	94° C.	19.01	19.02
8	<i>p</i> -CH ₃ C ₆ H ₄ -	102° C.	19.01	19.29

EXPERIMENTAL

The compounds were prepared by taking the sulphabiguanide and the respective mustard oil in alcohol-acetone medium and heating under reflux for 2-3 hours on a water-bath. Then the contents were steam-distilled to remove excess of mustard oil. The product left behind after the removal of the mustard oil was dissolved in dilute alkali and filtered. From the filtrate the thiourea derivative was precipitated by the addition of dilute hydrochloric acid. The precipitate was washed free from acid and crystallised from dilute alcohol. A typical experiment is detailed below.

Preparation of N'-p-chlorophenyl-N⁵-p-(p-chlorophenyl-p-thioureido phenyl) sulphonyl-biguanide: (Compound 2 in Table I)

N'-*p*-chlorophenyl-N⁵-(*p*-aminobenzene sulphonyl) biguanide (0.916 g., 0.0025 Mol.) and *p*-chlorophenyl mustard oil (0.5 g., a little more than 0.0025 Mol.) were taken in alcohol (20 c.c.) and acetone (5 c.c.) and heated

under reflux for 2 hours on a water-bath. The contents were then steam-distilled to remove the excess of *p*-chlorophenyl mustard oil. The product left behind after the removal of mustard oil was dissolved in dilute sodium hydroxide and filtered. The filtrate was acidified with dilute hydrochloric acid. The precipitate was washed several times with water to remove the adhering acid and recrystallised from alcohol. Yield: 0.8 g. M.p. 140° C. (% of N₂ required: 18.28, % of N₂ found: 18.38).

The different mustard oils for the synthesis of the compounds listed in Table I were prepared by the general method of preparation of mustard oils,^{14, 15} viz., treating the different amines with carbon disulphide and ammonia, getting the dithiocarbamate which in turn is treated with lead nitrate and steam-distilled to yield the mustard oils.

PHARMACOLOGICAL TESTS

Five of the eight compounds of the series were tested for their anti-malarial activity against *P. gallinaceum* in chicks not more than six weeks old.

TABLE II

No.	R		Dosage in mgm./100 g. body weight	Activity
1	C ₆ H ₅ -	..	10	..
2	<i>p</i> -ClC ₆ H ₄ -	..	10	..
3	<i>p</i> -BrC ₆ H ₄ -	..	10	..
4	<i>p</i> -IC ₆ H ₄ -	..	10	..
5	<i>o</i> -CH ₃ C ₆ H ₄ -	..	10	..

None of these compounds has shown any suppressive antimalarial activity.

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