METACHLORIDINE SUBSTITUTED ARYL- AND ALKYL-THIOCARBAMIDES*

By K. V. Viswanathan and B. H. Iyer

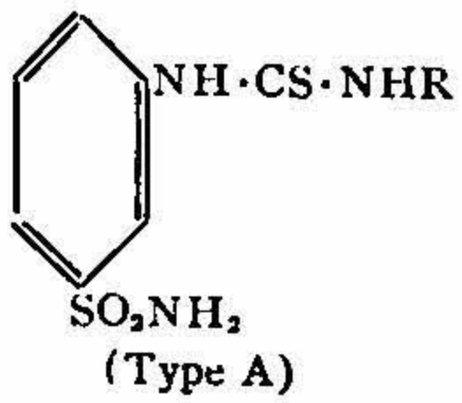
(*Department of Organic Chemistry, Indian Institute of Science, Bangalore-3*)

Received July 15, 1953

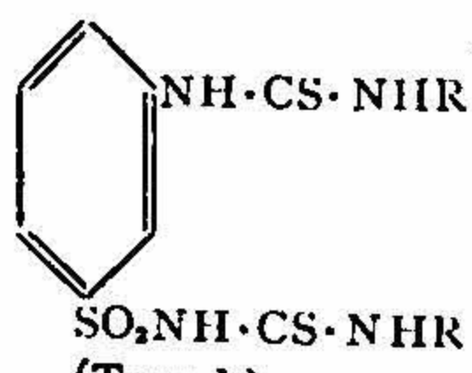
The preparation and properties of eight metachloridine substituted aryl- and alkyl-thiocarbamides are described. All of them have been tested for their anti-bacterial and anti-tubercular activity.

In an effort to obtain sulphonamides more active than sulphadiazine in experimental malaria, 2-sulphanilamido-5-chloro pyrimidine and its bromo analogue were developed.[1] These two compounds behave differently from the other sulphonamides in the sense that their antimalarial activity is only partially inhibited by *p*-amino-benzoic acid. This new behaviour induced English *et al.*[2] to investigate the effect of isomerism of 2-sulphanilamido-5-chloro pyrimidine, culminating in the discovery of 2-metanilamido-5-chloro pyrimidine (Metachloridine—SN 11,437).[3] Although metachloridine is effective in the different forms of malaria, it has no prophylactic or curative action.[2-5]

Of the many substituted thiocarbamide derivatives (type A and type B) that have been prepared and studied by Viswanathan *et al.*[6, 7] only the *p*-chlorophenyl thiocarbamide derivative (type A) has shown slight suppressive antimalarial activity against *P. gallinaceum* infections in chicks.[8] Some of them have shown encouraging anti-bacterial and anti-tubercular activity.[6, 8]



(Type A)



(Type B)

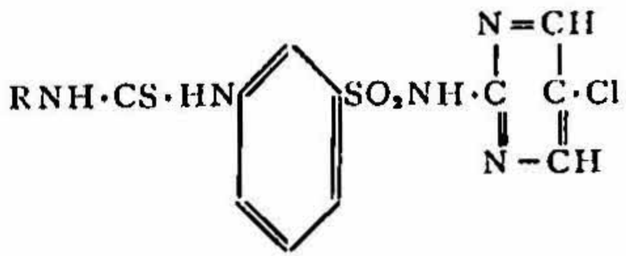
R = aryl- or alkyl-group.

The introduction of a *p*-chlorophenyl thiocarbamyl residue at the N^3-position of metanilamide has resulted in an active compound. On the same lines it can be expected that the introduction of such residues at the nuclear

---

* Extracted from a thesis submitted to the University of Bombay by K. V. Viswanathan for the Degree of Master of Science, May 1953.

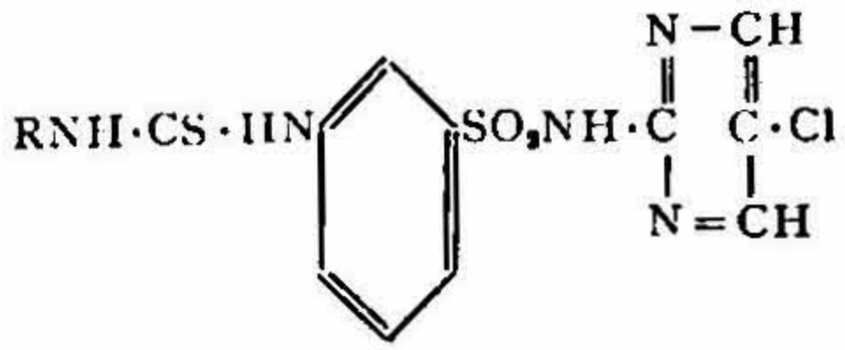
TABLE I



(Type C)

No.	R	m.p. °C.	Method of preparation	Crystallised from	Structural formula	Percentage of			
						Nitrogen		Sulphur	
						Calcd.	Found	Calcd.	Found
1	C_6H_5	182-83	I	aqueous acetone	$C_{17}H_{14}O_2N_5ClS_2$	16·69	16·03	15·29	15·32
2	p-Cl·C_6H_4-	183–84 (decomp.)	II	aqueous dioxane	$C_{17}H_{13}O_2N_5Cl_2S_2$	15·42	15·28	14·09	14·07
3	p-Br·C_6H_4-	184–85 ,,	,,	,,	$C_{17}H_{13}O_2N_5ClBrS_2$	14·05	14·04	..	..
4	p-I·C_6H_4-	180–81 ,,	,,	,,	$C_{17}H_{13}O_2N_5ClIS_2$	12·83	12·97	..	..
5	p-CH_3·O·C_6H_4-	169·5–70	I	,,	$C_{18}H_{16}O_3N_5ClS_2$	15·57	15·89	..	..
6	CH_3-	195–95·5	III	alcohol	$C_{12}H_{12}O_2N_5ClS_2$	19·58	19·78	..	..
7	$(CH_3)_2CH$·	194–95 (decomp.)	,,	95% ethanol + water	$C_{14}H_{16}O_2N_5ClS_2$	18·16	18·79	..	..
8	$CH_2=CH-CH_2$-	185–86	,,	aqueous ethanol	$C_{14}H_{14}O_2N_5ClS_2$	18·25	18·10	..	..

amino group of metachloridine, which in itself is an active molecule, may produce results of considerable interest. With this end in view, it was thought worthwhile to investigate a series of compounds of type C.



(Type C)

R = aryl- or alkyl-group.

Eight new thiocarbamides (type C, Table I) have been prepared by condensing one mole of metachloridine with one mole of the corresponding isothiocyanate in solvents like alcohol or a mixture of alcohol and dioxane.

The compounds are insoluble in water, but are soluble in dilute sodium hydroxide. It is interesting to note that compounds 2 to 5 (Table I), while being insoluble in water and while being sparingly soluble in dioxane, are readily soluble in 85 to 90 per cent. aqueous dioxane. This property of the compounds was made use of for their purification. Similar observation was made for acetone-water mixture.

All the compounds have been tested *in vitro* for their anti-bacterial and anti-tubercular activity. While all of them indicated varying degrees of inhibitory action against *M. tuberculosis*, only the first four (Table I) showed slight anti-bacterial activity. Two typical compounds (Nos. 2 and 7, Table I) that have been tested, showed marked suppressive antimalarial activity. Full details of these tests will be published separately.

Experimental

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

Method I

N^3-(*phenylthiocarbamyl*)-*metachloridine* (1).—Phenyl isothiocyanate (0·68 g.) was added to a hot solution of metachloridine (1·42 g.) in alcohol (150 c.c.) and the mixture was allowed to react at room temperature for 20 hours. The product that had separated by then was filtered, washed with alcohol and dried (0·68 g.). The mother liquor after keeping for 2 days at room temperature was concentrated to one-fifth its volume under reduced

pressure and the separated product was filtered off, washed and dried (1·15 g.). The compound was purified by recrys.allising it twice from aqueous acetone (2 : 3). It shrinks at 181° and melts at 182–3° to an orange liquid. It is soluble in dioxane and dilute alkali; sparingly in acetone and hot alcohol; insoluble in water and benzene (Found: N, 16·03; S, 15·23; $C_{17}H_{14}O_2N_5ClS_2$ requires N, 16·69; S, 15·29 per cent.).

Method II

N^3-(p-chlorophenylthiocarbamyl)-metachloridine (2).—*p*-Chlorophenyl isothiocyanate (0·85 g.) was added to a solution of metachloridine (1·42 g.) in alcohol (5 c.c.) and dioxane (20 c.c.). The mixture was heated for 7 hours at 60–65° and kept overnight. It was then diluted with water (20 c.c.) and stirred well. The product which separated as a white powder was filtered off, washed with a little alcohol and dried. Yield 2 g. (crude). The product was taken in a mixture of dioxane (30 c.c.) and water (5 c.c.), heated gently to form a clear solution and diluted with hot water (25 c.c.). On cooling the compound separated in a pure form. This was filtered, washed with a little alcohol and dried. The process was repeated once. m.p. 183–4° (decomposition). It is sparingly soluble in acetone and dioxane; very sparingly in alcohol. It is soluble in 85 per cent. aqueous dioxane and dilute alkali while it is insoluble in water and benzene (Found: N, 15·28; S, 14·07; $C_{17}H_{13}O_2N_5Cl_2S_2$ requires N, 15·42; S, 14·09 per cent.).

Method III

N^3-(methylthiocarbamyl)-metachloridine (6).—A mixture of metachloridine (2·84 g.), methyl isothiocyanate (0·73 g.) and alcohol (150 c.c.) was refluxed on a water-bath for 18 hours and concentrated to one-fourth its volume. It was treated with norite and filtered hot. On cooling overnight white crystalline product separated which was filtered, washed and dried. Yield 2·35 g. (crude), m.p. 192–4°. The compound formed white crystalline powder from alcohol, m.p. 195–95·5°. It is soluble in acetone, dioxane and dilute alkali; sparingly soluble in alcohol; insoluble in water and benzene (Found: N, 19·78; $C_{12}H_{12}O_2N_5ClS_2$ requires N, 19·58 per cent.).

Our grateful thanks are due to Messrs. American Cyanamid Company, New York, U.S.A., for a gift of metachloridine.

Our thanks are also due to Dr. M. Sirsi, Dr. A. S. Ramaswamy and Dr. K. P. Menon and to Messrs. T. K. Wadhwani and R. Rama Rao for the pharmacological examination of these compounds.

References

1. English, J. P., Clark, J. H., Clapp, J. W., Doris Seeger and Ebel, R. H. — *J. Amer. Chem. Soc.*, 1946, **68**, 453.
2. ———, ———, Shepherd, R. G., Marson, H. W., Krapcho, J. and Roblin, R. O., Jr. .. *Ibid.*, 1039.
3. Wiselogle, F. Y. .. *A Survey of Antimalarial Drugs*, 1941–45, 1946, **1**, 294.
4. Brackett, S. and Waletsky, E. .. *J. Parasitol.*, 1946, **32**, 325.
5. Huges, Carrie and Brackett .. *Ibid.*, 340.
6. Viswanathan, K. V., Raghavan, M. and Guha, P. C. .. *J. Indian Inst. Sci.*, 1953, **35A**, 251.
7. ——— and Iyer, B. H. .. *Ibid.*, 1953, **35A**, 315.
8. (Personal communication)