STUDIES IN ANTIMALARIALS

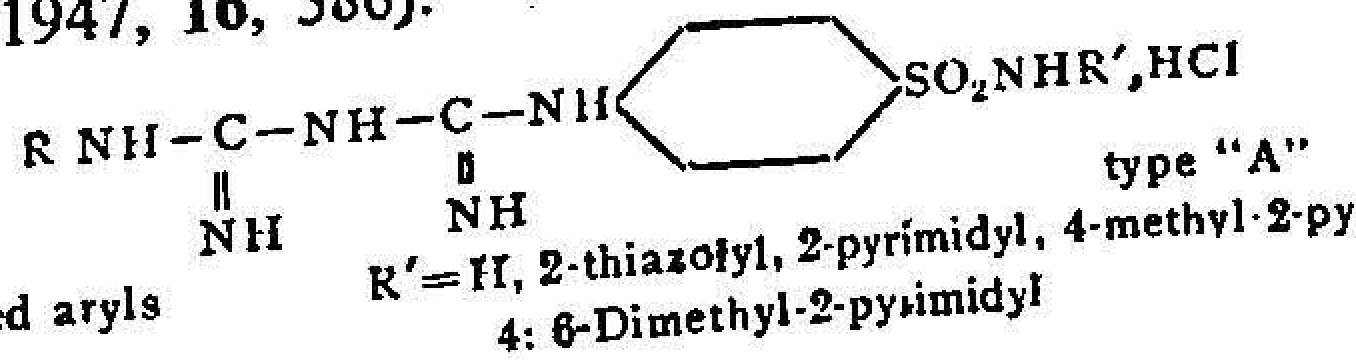
Part VII. Metachloridine Substituted Arylbiguanides

By H. L. Bami, B. H. Iyer and P. C. Guha

Metanilamides have been reported to be *devoid* of antibacterial activity (Northey, E. H., *Chem. Rev.*, 1940, **27**, 182) and this fact along with the parallel nature of antimalarial and antibacterial property of sulphanilamides (Marshall, E. K., *J. Pharmacol. and Exptl. Therap.*, 1942, **75**, 89; Mair, J., and Riley, E., *Proc. Soc. Exptl., Biol. and Med.*, 1942, **50**, 152) had discouraged research in the field of metanilamides as possible antimalarials. Recently, English, *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 453) discovered enhanced antimalarial activity in the case of 2-sulphanilamido-5-chloro pyrimidine and found it to be only slightly affected by the presence of para-amino-benzoic acid. This gave a new lead and in order to investigate the effect of isomerism, various compounds were prepared out of which 2-metanilamido-5-chloro-pyrimidine (Metachloridine, SN 11437) was found to be highly effective both in sporozoite induced *P. gallinaceum* infection in chicks (6 times as active as sulphadiazine) as well as in blood induced infection of the same strain (16 times as active as quinine) (English, *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1039). It was also shown to prevent sporozoite induced infections of *P. cathemerium* in canaries, an infection against which other sulphas are not effective. Metachloridine is also not affected by the presence of para-aminobenzoic acid and possibly has a double mode of action, one due to chloropyrimidine ring and the other due to the metanilamide molecule (English, *et al.*, *loc. cit.*).

In human malarias metachloridine has proved to be a good suppressive but the drug is still under clinical trial (Brackett, S., and Waletsky, E., *J. Parasitol.*, 1946, **32**, 325; Huges, Carrie and Brackett, *ibid*, 340; "A survey of antimalarial drugs, 1941-45" Wiselogle, Vol. I, 294).

Previously Bami, Iyer and Guha (*J. Indian Inst. of Sci.*, 1947, **29 A**, 15, *ibid.*, 1948, **30 A**, 1) have reported a number of sulphabiguanide derivatives of type (A), some of which have shown to be active against blood induced *P. gallinaceum* infection in young chicks (Bami, Iyer and Guha, *Current Science*, 1947, **16**, 386).

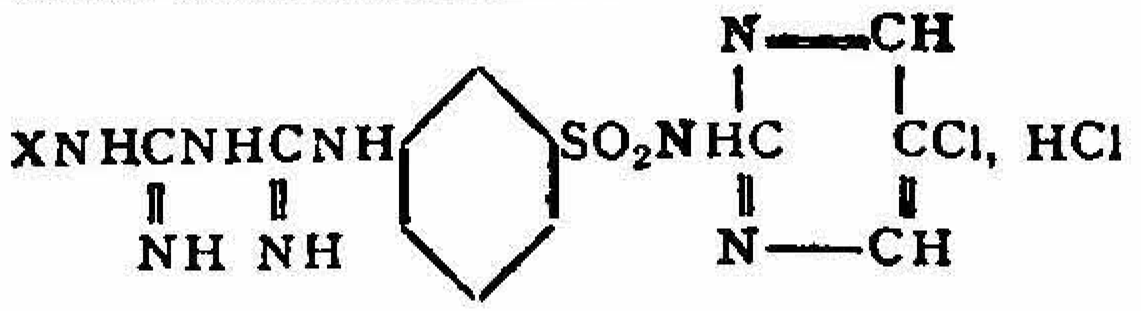


type "A"

R′ = H, 2-thiazolyl, 2-pyrimidyl, 4-methyl-2-pyrimidyl and 4: 6-Dimethyl-2-pyrimidyl

R = Substituted aryls

Metachloridine is a definite advancement in the field of sulphonamides as regards their usefulness as antimalarials and hence it was thought of interest to investigate the compounds of type ' B ' where the sulphonamido grouping of compounds of type " A " has been replaced by a metanilamide group derived from metachloridine.



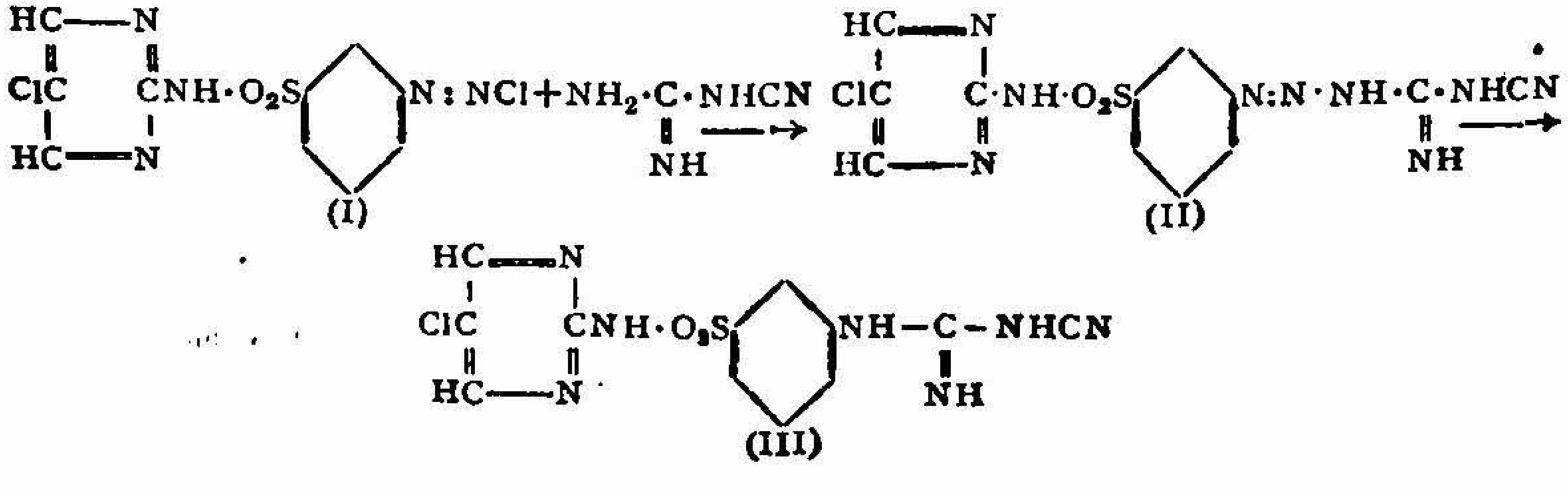
type "B"

X = Substituted aryl groups

Compounds of type " A " have shown some antibacterial activity also when tested, *in vitro* against coccal infections (Bami and Natarajan, *Current Science*, 1947, **16**, 156) and due to reasons discussed above, replacement of sulphanilamide part by a metanilamide group is anticipated to increase the antimalarial activity of the compounds of type " A ".

For the preparation of compounds of type " B ", metachloridine was reacted with the required aryl cyanoguanidines in 90 per cent. ethanol having enough hydrochloric acid to form the amino hydrochloride, yielding the corresponding hydrochloride salts of N^1-aryl-N^5-meta-(5-chloro-2-pyrimidyl) phenyl sulphonamide-biguanide hydrochlorides (type " B "). The hydrochloride salts were crystallised from dilute acetone, dioxane, alcohol or ethylacetate. The free bases were generated by neutralising a dilute alcoholic solution of the hydrochloride with dilute sodium hydroxide solution. Free bases were crystallised from alcohol. Both the salts and the bases were white crystalline powders (except the nitro derivatives which were light yellow) with high melting points. These compounds were insoluble in water but formed soluble sodium salts as in the case of previous sulphabiguanide derivatives (Bami, *et al.*, *loc. cit.*).

Attempts to convert the meta-amino group of metachloridine into a cyanoguanidine group by coupling its diazonium salt (I) with dicyandiamide and subsequent denitrogenation failed. The triazine (II) could not be denitrogenated to give (III) by methods already employed for this purpose (Bami, Iyer and Guha, *J. Indian Inst. Sci.*, 1947, **29 A**, p. 1).



This observation is similar to that observed in the case of previous sulphanilamides which also could not be denitrogenated by following the above method to yield the corresponding cyanoguanidines (Bami, Iyer and Guha, *loc. cit.*). The detailed discussion of these results shall be reported in a later communication.

For the reason already advanced (Bami, Iyer and Guha, *J. Indian Inst. Sci.*, 1947, **29** A, 1) it was attempted to prepare the copper chelates of the present series of compounds (type " B ") but found them to be of a non-chelating type. The failure of these compounds, as well as the sulphabiguanides reported previously, to chelate, may be explained on the basis of the increased electronegative nature of the substituents at N^1 and N^5 positions of the biguanide molecule.

Experimental

N^1-Phenyl-N^5-meta-(5-Cl-2-pyrimidyl)-phenylsulphonamide-biguanide hydrochloride (type " B "; X = phenyl) (I).—Phenylcyanoguanidine (1·6 g.) and metachloridine (2·8 g.) were refluxed together for 6 hours in a mixture of alcohol (10 c.c.) and hydrochloric acid (1 c.c.). A solid separated out, which was filtered off after chilling. The product was orystallised from dilute acetone by using a little norite for decolourisation. White crystalline powder, m.p. 232° C. Yield, 2·6 grams. (Found: N, 23·29; $C_{18}H_{18}O_2N_8Cl_2S$ requires N, 23·28 per cent.).

Free Base (II).—The hydrochloride salt (I) (1·0 g.) was dissolved in dilute alcohol (50%; 15 c.c.) and neutralised with sodium hydroxide solution (5%). The product was filtered after chilling and crystallised from dilute alcohol. White crystalline powder, m.p. 234° (slight decomposition). Yield 0·7 g. (Found: N, 24·68; $C_{18}H_{17}O_2N_8ClS$ requires N, 25·19 per cent.).

N^1-p-Chlorophenyl-N^5-meta-(5-Cl-2-pyrimidyl)-phenyl sulphonamide-biguanide hydrochloride (type B; X = *p*-chlorophenyl) (III).—*p*-Chlorophenylcyanoguanidine (2 g.) and metachloridine (2·9 g.) were refluxed together in a mixture of alcohol (12 c.c.) and hydrochloric acid (1 c.c.) for 6 hours. The separated solid was filtered and crystallised from dilute acetone. White amorphous powder, m.p. 235°. Yield 1·5 g. (Found: N, 21·29; $C_{18}H_{17}O_8N_2ClS$ require N, 21·72 per cent.).

Free Base (IV).—The hydrochloride (III) was neutralised and the base obtained as detailed for (II). White crystalline powder, m.p. 239°. Found: 23·37; $C_{18}H_{16}O_2N_8Cl_2S$ requires N, 23·38 per cent.).

N^1-2:4-Dichlorophenyl-N^5-meta-(5-Cl-2-pyrimidyl)-phenylsulphonamide-biguanide hydrochloride (type B); X = 2:4-dichlorophenyl) (V).—2:4-Dichlorophenylcyanoguanidine (2·1 g.) and metachloridine (2·9 g.) were refluxed together in alcohol (12 c.c.), hydrochloric acid (1 c.c.) mixture for six hours. The separated solid was collected by filtration and crystallised from dilute dioxane. White amorphous powder, m.p. 256°. Yield 3 g. (Found: N, 20·59; $C_{18}H_{16}O_2N_8Cl_4S$ requires N, 20·36 per cent.).

Free Base (VI).—The hydrochloride (V) was neutralised and the base obtained as detailed under (II). White crystalline powder m.p. 234°. (Found: N, 21·97; $C_{18}H_{15}O_2N_8Cl_3S$ requires N, 21·81 per cent.).

*N^1-*p*-Bromo-phenyl-N^5-meta-(5-cl-2-pyrimidyl)-phenylsulphonamide-biguanide hydrochloride* (type B; X = *p*-bromophenyl) (VII).—*p*-Bromophenylcyanoguanidine (2·4 g.) and metachloridine (2·9 g.) were refluxed together in alcohol (12 c.c.), hydrochloric acid (1 c.c.) mixture for 6 hours. No solid separated. The mixture was diluted with water and the resulting semisolid washed repeatedly with water and dried. It could not be crystallised from alcohol or acetone and was crystallised from ethyl acetate. White crystalline product, m.p. 227 (slight decomposition). Yield 2 g. (Found: N, 19·53; $C_{18}H_{17}O_2N_2Cl_8BrS$ requires N, 20·0 per cent.).

Free Base (VIII).—Obtained from (VII) as described under (II). White amorphous powder, m.p. 243° (slight decomposition). (Found: N, 21·39; $C_{18}H_{16}O_2N_8ClBrS$ requires N, 21·35 per cent.).

*N^1-*p*-Iodophenyl-N^5-meta-(5-chloro-2-pyimidyl)-phenylsulphonamide-biguanide hydrochloride* (type B; X = *p*-iodophenyl) (IX).—Metachloridine (2·9 g.) and *p*-iodophenylcyanoguanidine (2·9 g.) were reacted together in alcoholic hydrochloric acid and product obtained as under (VII). White crystalline product, m.p. 208° (decomp.). Yield 3 g. (Found: N, 18·45; $C_{18}H_{17}O_2N_8Cl_2IS$ requires N, 18·45 per cent.).

Free Base (X).—The hydrochloride (IX) was neutralised and product obtained as under (II). White crystalline product, m.p. 239°. (Found: N, 20·03; $C_{18}H_{16}O_2N_8ClIS$ requires N, 19·59 per cent.).

*N^1-*p*-Methylphenyl-N^5-meta-(5-Cl-2-pyrimidyl)-phenylsulphonamide-biguanide hydrochloride* (type B; X = *p*-methylphenyl) (XI).—Metachloridine (2·9 g.) and *p*-methyl-phenylcyanoguanidine (1·7) were reacted together in alcoholic hydrochloric acid and the product obtained as under (I). White crystalline powder, m.p. 237°. Yield 3 g. (Found: N, 22·18; $C_{19}H_{20}O_2N_8Cl_2S$ requires N, 22·62 per cent.).

Free Base (XII).—Obtained from (XI) as described under (II). White powder, m.p. 233° (slight decomp.). Found: N, 24·26; $C_{19}H_{19}O_2N_8ClS$ requires N, 24·42 per cent.).

N^1-2:3-*Dimethylphenyl-N*^{5}-*meta*-(5-*Cl*-2-*pyrimidyl*)-*phenylsulphonamide-biguanide hydrochloride* (type B; X = 2:3-dimethylphenyl) (XIII).—2:3-dimethylphenylcyanoguanidine (1·9 g.) and metachloridine (2·9) were reacted together in alcoholic hydrochloric acid and the product obtained as under (I). White crystalline powder, m.p. 246°. Yield 3 g. (Found: N. 21·81; $C_{19}H_{20}O_2N_8Cl_2S$ requires N, 22·00 per cent.).

Free Base (XIV).—Obtained from (XII) by the procedure detailed for (II). White crystalline solid, m.p. 232–234°. (Found: N, 23·86; $C_{20}H_{21}O_2N_8ClS$ requires N, 23·70 per cent.).

N^1-p-*Methoxyphenyl*-N^5-*meta*-(5-*Cl*-2-*pyrimidyl*)-*phenylsulphonamide-biguanide hydrochloride* (type B; X = *p*-methoxyphenyl) (XV).—*p*-Methoxyphenylcyanoguanidine (1·9 g.) and metachloridine (2·9 g.) were reacted together in alcoholic hydrochloric acid and the product obtained as detailed under (I). White crystalline solid, m.p. 202°. Yield 3 g. (Found: N, 21·85; $C_{19}H_{20}O_3N_8Cl_2S$ requires N, 21·91 per cent.).

Free Base (XVI).—Obtained from (XV) by procedure detailed for (II). White crystalline powder, m.p. 236° (slight decomp.). (Found: N, 24·01; $C_{19}H_{19}O_3N_8ClS$ requires N, 23·60 per cent.).

N^1-p-*Nitrophenyl*-N^5-*meta*-(5-*Cl*-2-*pyrimidyl*)-*phenylsulphonamide-biguanide hydrochloride* (type B; X = *p*-nitrophenyl) (XVII).—*p*-Nitrophenylcyanoguanidine (2 g.) and metachloridine (2·9 g.) were reacted together and the product isolated as under (I). Light yellow powder, m.p. 252°. Yield 2·5 g. (Found: N, 24·29; $C_{18}H_{17}O_4N_9Cl_2S$ requires N, 23·95 per cent.).

Free Base (XVIII).—Obtained from (XVII) by method detailed for (II). Light yellow powder, m.p. 237° C. (Found: N, 25·65; $C_{18}H_{16}O_4N_9ClS$ requires N, 25·74 per cent.).

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