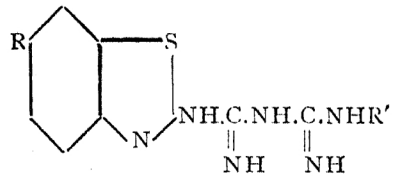
SOME 2-BENZOTHIAZOLYL BIGUANIDES AS POSSIBLE ANTI-MALARIALS

As a part of extensive programme of research, in the chemotherapy of malaria, that has been undertaken in our laboratory to study the effects of different substitutions at either end of the tautomeric biguanide structure, a number of biguanide derivatives having the heterocyclic ring, benzothiazole, attached to the end nitrogen atom of N′-aryl biguanides have been made. In earlier attempts to study the anti-plasmodial activity of compounds, changes have been brought about by the replacement of the sub-

stituents in the paludrine molecule by introducing various pyridyl,[1] quinolyl,[2-4] phenanthryl[5] and acridyl[6,7] rings in place of either *p*-chlorophenyl group or isopropyl group of paludrine. Excepting a few, almost all of these compounds proved to be inactive when tested against experimental malaria using different plasmodia.

Benzothiazole derivatives[8-14] having various substitutions at different positions are being tried since long, for their chemotherapeutic properties. 1-(2-benzothiazolyl)-2-thiourea was found to possess a quinine equivalent of one when tested for suppressive activity against duck malaria.[15] It, therefore, appears that proper substitutions at the proper places in benzothiazole are likely to produce potential chemotherapeutic agents.

In view of the immense possibilities now being offered by the biguanide structure, it was considered to be of interest to synthesise and study the anti-malarial properties of the compounds possessing the heterocyclic ring and the essential features of paludrine, and as such compounds of the type A have now been synthesised.



Type A

R=H. Cl, CH_3 or CH_3O
R'= Various aryl groups

Compounds of the above type will offer tautomeric possibilities which are said to be responsible for anti-malarial activity of the compound. It will also be noticed that the benzothiazole nucleus can be considered structurally related to the therapeutically active quinoline nucleus in a way where two $-CH=$ groups are replaced by a sulphur atom and also that the nuclear nitrogen atom is in *para*-position to the methoxy group (as in one particular type) as in plasmochin or atebrin; the only difference being that the new 'conductophoric' group has been introduced into 2-position of the heterocyclic part of the ring.

For the synthesis of the compounds of type A as noted below, a number of routes could be suggested, but the most practical and direct one which was successfully employed consisted in reacting the 2-aminobenzothiazolyl hydrochloride with the appropriate arylcyanoguanidine in suitable solvents. The biguanides were isolated as stable crystalline monohydrochlorides with low solubility in alcohol or acetone. The free base was isolated by treating the hydrochlorides with dilute sodium hydroxide solution, which were purified by recrystallisation from dilute alcohol.

Compounds of Type A

No.	R	R'	M.P. °C.	
1	H	C_6H_5-	104-5	Base
2	H	p-ClC_6H_4-	198-199	HCl
3	H	p-$CH_3OC_6H_4$	193-194	HCl
4	H	p-$CH_3C_6H_4$	128	Base
5	Cl	C_6H_5-	196-198	HCl
6	Cl	p-ClC_6H_4	206	HCl
7	OCH_3	C_6H_5-	195	HCl
8	OCH_3	p-ClC_6H_4-	199-200	HCl
9	OCH_3	p-$CH_3C_6H_4-$,	124-125	HCl
10	CH_3	p-ClC_6H_4-	203-204	HCl
11	CH_3	p-$CH_3C_6H_4-$	194-195	HCl
12	CH_3	p-$CH_3OC_6H_4$	187	HCl

On testing some of the compounds of the above series for their suppressive activity against *gallinaceum* malaria in laboratory-bred-chicks, none showed any activity against chick malaria.

The authors' thanks are due to Dr. S. S. Guha and Dr. A. C. Roy for their interest in this investigation.

Dept. of Organic Chemistry, J. R. GUHA.
Indian Inst. of Science, P. C. GUHA.
Bangalore-3,
October 13, 1952.

1. Roy, Guha, *J. Sc. Ind. Res.*, 1950, V, **9B**, No. 10, 262. 2 Gupta and Guha, *Curr. Sci.*, 1948, **17**, 185. 3. May, *J. Org. Chem.*, 1947, **12**, 437, 443. 4. Basu, *et al.*, *J. Sc. Ind. Res.*, 1950, V, **9B**, 57. 5. May, *et al.*, *J. Org. Chem.*, 1947, **12**, 869. 6. Gupta and Guha, *Sc. and Cult.*, 1950-51, **16**, 257. 7. —, *Ibid.*, 1950-51, **16**, 475. 8. Knunyants and Benevolenskayr, *J. Sc. Chem. (U.S.S.R.)*, 1937, **7**, 2471; *cf. C.A.*, 1938, **32**, 2119. 9. Fox and Bogert., *J. Am. Chem. Soc.*, 1939, **61**, 2103. 10. Ishii, *Japan Med. J.*, 1948, **1**, 30. 11. Rose, *et al.*, *Pharm. Arch.*, 1940, **11**, 81. 12. Mayer, *Rev. Medical. Franch.*, Nov-Dec., 1941, 3-19; *cf. C.A.*, **36**, 5199. 13. Kaufmann and Buckmann, *Arch. Pharm.*, 1941, 279, 194. *Chem. Zent.*, 1941, **11**, 2934. 14. Sewell and Hauking, *Brit. J. Pharmacol.*, 1950, **5**, 239. 15. Wiselogle, *A Survey of Antimalarial Drugs*, 1946.