STUDIES IN ANTIMALARIALS—SOME SULPHA-BIGUANIDE DERIVATIVES

AMONG sulphanilamides[1-3] sulphadiazine is the most effective and possesses a slight but definite prophylactic action[4] in malaria. Metachloridine,[3] a recent suppressive antimalarial drug of the sulpha-group, is also a pyrimidine derivative.

Considering the activity of sulphadiazine, Curd and Rose[5] prepared at first its sulphur-free analogues of phenyl-substituted pyramidine type and their later work culminated in the discovery of paludrine,[5,7] which is a substituted biguanide derivative.

Compounds of the type (I) have not shown appreciable antimalarial activity[6] which might be partly due to lack of any potential substituent in the aromatic nucleus at N^5-position of the biguanide molecule. Hence it was thought of interest to prepare compounds of type (II) where "SO_2NH_2" or substituted "SO_2NH_2" radical is introduced in the aromatic nucleus at N^5-position, and for this purpose only potent sulpha compounds, sulphanilamide, sulphathiazole and sulphadiazine were selected. It may be mentioned that compounds of the type (III) have already been patented[8,9] as therapeutic agents.

$$R\cdot C_6H_4\cdot \overset{1}{NH}\cdot \overset{2}{C}(=\overset{3}{NH})\cdot \overset{4}{NH}\cdot \overset{5}{C}(=NH)\cdot NH\cdot R'HCl \quad \text{(I)}$$

R = alkyl, halo, nitro. etc. R′ = phenyl or naphthyl

$$p\text{-}R\cdot C_6H_4\cdot NH\cdot C(=NH)\cdot NH\cdot C(=NH)\cdot NH\cdot C_6H_4\cdot SO_2NHX\cdot HCl \quad \text{(II)}$$

(*a*) X=H and R=H, m.p. 228°; R=Cl, m.p. 233°; R=Br, m.p. 245-6°; R=NO_2, m.p. 217°; R=CH_3, m.p. 231°; R=CH_3O, m.p. 234°.

(*b*) X=2-thiazolyl and R=H, m.p. 225°; R=Cl, m.p. 219°; R=Br, m.p. 197° (with

decomp.); R=NO_2, m.p. 267°; R=CH_3, m.p. 189–190° (with decomp.); R=CH_3O, m.p. 176° (with decomp.).

(c) X=2-pyrimidyl and R=H, m.p. 238°; R=Cl, m.p. 189°; R=Br, m.p. 202°; R=NO_2, m.p. 246°; R=CH_3, m.p. 232° (with decomp.); R=CH_3O, m.p. 210–212° (with decomp.)

$R \cdot C_6H_4 \cdot SO_2NH \cdot C(=NH) \cdot NH \cdot C(=NH) \cdot NHR'$ .. (III)

R=NO_2, AcNH, NH_2, etc. R'=H, alkyl or aryl.

The eighteen new compounds indicated above have been synthesised by the interaction of the hydrochloride of the required sulpha-derivative and the corresponding para-substituted-phenyl-cyanoguanidine in boiling aqueous dioxan medium. The compounds were obtained as their hydrochloride salts and crystallised from dilute alcohol or water. The substituted phenyl-cyanoguanidines were obtained after denitrogenating the corresponding substituted phenyl-azocyanoguanidines and the report of a systematic study of the denitrogenation of similar triazines will be communicated later. These compounds which are fairly soluble in water and bitter in taste are being tested against bird malaria (*P. gallanaceum*) for their activity as antimalarials.

Further work on substituted biguanides as possible antimalarials is in progress. Full paper will be published elsewhere.

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