STUDIES IN ANTIMALARIALS—SOME SULPHA-BIGUANIDE DERIVATIVES

Among sulphanilamides¹-³ sulphadiazine is the most effective and possesses a slight but definite prophylactic action⁴ in malaria. Meta-chloridine,³ a recent suppressive antimalarial drug of the sulpha-group, is also a pyrimidinc derivative.

Considering the activity of sulphadiazine, Curd and Rose⁵ prepared at first its sulphur-free analogues of phenyl-substituted pyramidine type and their later work culminated in the discovery of paludrine⁶,⁷ which is a substituted biguanide derivative.

Compounds of the type (I) have not shown appreciable antimalarial activity⁶, which might be partly due to lack of any potential substituent in the aromatic nucleus at N⁵-position of the biguanide molecule. Hence it was thought of interest to prepare compounds of type (II) where "SO₂NH₂" or substituted "SO₂NH₂" radical is introduced in the aromatic nucleus at N⁵-position, and for this purpose only potent sulpha compounds, sulphonlamide, sulphathiazole and sulphadiazine were selected. It may be mentioned that compounds of the type (III) have already been patented⁸,⁹ as therapeutic agents.

\[
\begin{align*}
R \cdot C₆H₄ \cdot NH \cdot C(=NH) \cdot NH \cdot C(=NH) \cdot NH \cdot R' \cdot HCl \\
\end{align*}
\]

\[
\begin{align*}
1 & \quad 2 & \quad 3 & \quad 4 & \quad 5 \\
\end{align*}
\]

\[ (I) \]

\[ R = \text{alkyl, halo, nitro. etc.} \quad R' = \text{phenyl or naphthyl} \]

\[ p\cdot R \cdot C₆H₄ \cdot NH \cdot C(=NH) \cdot NH \cdot C(=NH) \cdot NH \cdot SO₂NH \cdot HCl \]

\[ (II) \]

(a) \[ X = H \quad \text{and} \quad R = H, \text{ m.p. } 228°; R = Cl, \text{ m.p. } 233°; R = Br, \text{ m.p. } 245-6°; R = NO₂, \text{ m.p. } 217°; R = CH₃, \text{ m.p. } 231°; R = CH₃O, \text{ m.p. } 234°. \]

(b) \[ X = 2\text{-thiazolyl and } R = H, \text{ m.p. } 225°; R = Cl, \text{ m.p. } 219°; R = Br, \text{ m.p. } 197° (\text{with} \]

\]
decomp.); \( R = \text{NO}_2 \), m.p. 267°; \( R = \text{CH}_3 \), m.p. 189-190° (with decomp.); \( R = \text{CH}_2\text{O} \), m.p. 176° (with decomp.).

(c) \( X = \text{2-pyrimidyl} \) and \( R = \text{H} \), m.p. 238°; \( R = \text{Cl} \), m.p. 189°; \( R = \text{Br} \), m.p. 202°; \( R = \text{NO}_2 \), m.p. 246°; \( R = \text{CH}_3 \), m.p. 232° (with decomp.); \( R = \text{CH}_2\text{O} \), m.p. 210-212° (with decomp.)

\[ \text{R} \cdot \text{C}_2\text{H}_4\cdot \text{SO}_2\cdot \text{NH} \cdot \text{C}(=\text{NH}) \cdot \text{NH} \cdot \text{C}(=\text{NH}) \cdot \text{NHR} \]  

(III)

\( \text{R} = \text{NO}_2, \text{AcNH}, \text{NH}_2, \text{etc.} \quad \text{R'} = \text{H}, \text{alkyl or aryl} \)

The eighteen new compounds indicated above have been synthesised by the interaction of the hydrochloride of the required sulpho-derivative and the corresponding para-substituted-phenylcyanoguanidine in boiling aqueous dioxan medium. The compounds were obtained as their hydrochloride salts and crystallised from dilute alcohol or water. The substituted phenylcyanoguanidines were obtained after denitrogenating the corresponding substituted phenylazo-cyanoguanidines 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 (\textit{P. gallinaceum}) 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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3. Bami, Iyer and Gaha, "Recent advances in the chemistry of synthetic antimalarials."
6. --, \textit{Ibid.}, 720.