# SULPHABIGUANIDE DERIVATIVES

By K. Raman, M. Raghavan and P. C. Guha

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

## Summary

The synthesis and properties of twenty-four $N^1$–$N^5$-substituted biguanides are described in this paper. The compounds have been screened for antimalarial activity against *P. Gallinæceum* in chicks. None of the compounds tested showed any activity.

The versatility of sulphanilamides in combating many kinds of diseases induced chemists to test their usefulness as possible antimalarials also. The discovery by Diaz de Leon[1] that sulphanilamide possessed antimalarial activity gave the lead and subsequently enormous amount of work was done in the sulphonamide therapy of malarial infections when almost all the sulpha drugs were tested. As a result of these tests, sulphadiazine was established as the most outstanding antimalarial among the sulpha drugs, having action on the exoerythrocytic forms of bird malaria.[2, 3] In addition this drug possesses a causal prophylactic property in avian malaria. The sulpha drugs have shown activity against monkey malaria also. The antimalarial action of the sulpha drugs is due to their antibacterial property and there is ample evidence that sulphanilamides act on the malaria parasite by replacing *p*-aminobenzoic acid which is an important metabolite for the growth of malaria parasites.[4, 5] This mechanism of action of the sulpha drugs, being entirely different from that of other antimalarial drugs like quinine, atebrin and paludrine, will be of immense importance in that the sulpha drugs can come to the rescue in malaria when other potent antimalarials fail.

Metachloridine (2-metanilamido-5-chloro-pyrimidine), a pyrimidine sulphonamide derivative, has been claimed to be a suppressive antimalarial.[6]

As a sequel to the old methods of research on complicated heterocyclic systems for the synthesis of new and potent antimalarials, Curd and Rose started work on the chemically versatile pyrimidine ring. They first began preparing sulphur-free analogues of phenyl substituted pyrimidine type and by further variations in the series ultimately arrived at paludrine, which is a substituted biguanide derivative.[7] In this series of compounds the activity was attributed to the presence of a biguanide linkage having a conjugated double bond system of alternate carbon and nitrogen atoms and to some physico-chemical balance between the active groups on either side of the biguanide link.

Due to these reasons, it was thought worthwhile to explore further possibilities in the field of substituted biguanides as possible antimalarials in order to discover a better drug. In view of the interesting results obtained in the case of sulpha drugs as detailed previously, and due to the recognised potent nature of the $—SO_2NH—$ group, it was planned to synthesise substituted biguanides, where, in the $N^5$-nitrogen. the group $p$-$SO_2C_6H_4NH_2$ or the group $p$-$SO_2C_6H_4NO_2$ was attached and to study the antimalarial activity of the resulting compounds. Synthesis of such type of compounds was also prompted by the fact that compounds of the type

$$p—R—C_6H_4—SO_2.NH.C(=NH).NH.C(=NH).NHR'$$

where $R = NO_2$, $NH_2$, NHAc and $R' = H$, alkyl or aryl have been patented as chemotherapeutic agents.[8]

Accordingly, $p$-nitrobenzene sulphonyl chloride has been reacted with 4-Cl-, Br-, I-, 2 : 4-dichloro-, 2-Cl-, 3-Cl-, 4-$NO_2$-, 3-$NO_2$-, 4-$CH_3$-, 2-$CH_3$-, phenyl biguanides, $\alpha$ and $\beta$-naphthyl biguanides (or their hydrochlorides) and the resulting nitro products have been reduced to the corresponding amino compounds. These compounds have been tabulated below. Attempts were also made to synthesise $N^5$-$p$-Acetaminophenyl sulphonyl-$N^1$-aryl biguanides by condensing $p$-Acetaminobenzene sulphonyl chloride with aryl biguanides in suitable solvents and in the presence of catalysts. But no tangible results were obtained.

TABLE I. *Substituted Biguanides of the General Formula*

$$R–NH.C(=NH).NH.C(=NH).NHSO_2C_6H_4\,\phi$$

| No. | R | M.P. $\phi = NO_2$ °C. | M.P. $\phi = NH_2$ °C. |
|---|---|---|---|
| 1 | 4-$ClC_6H_4$- | .. | 220 | 178–79 |
| 2 | 4-$BrC_6H_4$- | .. | 212 | 198 |
| 3 | 4-$IC_6H_4$- | .. | 230 | 204 |
| 4 | 2 : 4-$Cl_2C_6H_3$- | .. | 191 | 175 |
| 5 | 2-$ClC_6H_4$- | .. | 222 | 180 |
| 6 | 3-$ClC_6H_4$- | .. | 194–96 | 170 |
| 7 | 4-$NO_2C_6H_4$- | .. | 172 | .. |
| 8 | 4-$NH_2C_6H_4$- | .. | .. | 160 |
| 9 | 3-$NO_2C_6H_4$- | .. | 161–62 | .. |
| 10 | 3-$NH_2C_6H_4$- | .. | .. | 154 |
| 11 | 4-$CH_3C_6H_4$- | .. | 217 | 192 |
| 12 | 2-$CH_3C_6H_4$- | .. | 208 | 188 |
| 13 | $\alpha$-$C_{10}H_7$- | .. | 167–69 | 135 |
| 14 | $\beta$-$C_{10}H_7$- | .. | 185–86 | 147 |

## Experimental

These compounds were prepared by condensing *p*-nitrobenzene sulphonyl chloride with the different biguanides in acetone-water medium, neutralising the hydrochloric acid evolved, with a solution of sodium hydroxide, added gradually during the reaction. The resulting nitro compound was filtered and after recrystallisation from dilute alcohol reduced to the amino compound with iron and hydrochloric acid. A typical experiment is detailed below.

*Preparation of $N^1$-p-chlorophenyl-$N^5$-(p-aminobenzene sulphonyl) biguanide* ($R = \text{p-}ClC_6H_4\text{-}$, $\phi\phi' = NH_2$).—*p*-Chlorophenyl biguanide (2·12 g, 0·01 M) was stirred into a mixture of water (12 c.c.) and acetone (15 c.c.). *p*-Nitrobenzene sulphonyl chloride (2·2 g., 0·01 M) was added gradually to the mixture. Thereafter sodium hydroxide (33%, 1·2 g.) was added drop by drop keeping the temperature at 20°–25° C. The resultant suspension was stirred for one hour at this temperature and filtered. The solid product was washed with water and recrystallised from hot aqueous alcohol. The yield of the nitro compound thus got was 2·5 g. and m.p. 220° C.

In order to prepare the amino compound, the nitro compound got above (2·31 g.) was heated under reflux for two hours with a mixture of ethyl alcohol (30 c.c.), water (10·5 c.c.), concentrated hydrochloric acid (d. 1·16, 0·6 c.c.) and iron filings (6 g.). The resulting suspension was made alkaline with ammonia and filtered hot. The filtrate was evaporated to remove alcohol, when the crude $N^1$-*p*-chlorophenyl-$N^5$-(*p*-aminobenzene sulphonyl) biguanide separated out. This was recrystallised from dilute alcohol (Yield: 1·2 g., m.p. 178–89°).

The other analogues were prepared in a similar manner. The different substituted biguanides used for the synthesis of the above compounds were prepared according to the general method of preparation of biguanides,[9] *viz.*, reacting the amines with dicyandiamide.

## Pharmacological Tests

The following typical compounds have been screened for antimalarial activities against *P. gallinaceum* in young chicks, not more than six weeks old.

None of these compounds showed any suppressive antimalarial activity.

The authors wish to record their thanks to Dr. K. P. Menon and Dr. G. R. Chandrasekhar for their help in the pharmacological examination of the compounds.

TABLE II

| No. | Compounds | Dosage in mgm./100 g. body wt. | Activity |
|---|---|---|---|
| 1 | 4-$ClC_6H_4NH.C(=NH).NH.C(=NH).NH.SO_2C_6H_4NH_2$ .. | 10 | — |
| 2 | 4-$BrC_6H_4NH.C(=NH).NH.C(=NH).NHSO_2C_6H_4NH_2$ .. | 10 | .. |
| 3 | 4-$IC_6H_4NH.C(=NH).NH.C(=NH).NHSO_2C_6H_4NH_2$ .. | 10 | .. |
| 4 | 2-$ClC_6H_4NH.C(=NH).NH.C(=NH).NHSO_2C_6H_4NH_2$ .. | 10 | .. |
| 5 | 3-$ClC_6H_4NH.C(=NH).NH.C(=NH).NHSO_2C_6H_4NH_2$ .. | 10 | .. |
| 6 | 4-$H_2NC_6H_4NH.C(=NH).NH.C(=NH).NHSO_2C_6H_4NH_2$ .. | 10 | .. |

The authors' thanks are due to Dr. B. H. Iyer for the keen interest he has taken throughout the course of this work.

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