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STUDIES IN ANTIMALARIALS

Part IX. N^1-Aryl-N^5-alkyl-biguanides*

By H. L. Bami and P. C. Guha

Following the discovery of Paludrine as a potent antimalarial with a new chemical approach to the problem (Curd and Rose, *J. Chem. Soc.*, 1946, 729; *cf.* Bami, Iyer and Guha (*a*) *J. Indian Inst. Sci.*, 1947, **29A**, 1), considerable potentiality has developed in the field of substituted biguanides as nucleii for further research. The cause of activity in the biguanide series of antimalarials has been attributed to the existence of tautomeric structures and many " switterion " modifications which are possible in these cases (Curd and Rose, *loc. cit.*). Considering that a biguanide link is essential for activity, the first attempt to improve upon the activity of paludrine has been to synthesise such compounds where the *p*-chlorophenyl group of paludrine has been replaced with 3- and 9-phenanthryl, 3-chloro-6-phenanthryl (May, *J. Org. Chem.*, 1947, **12**, 437, 443), and 6-methoxy-8-quinolyl (May, *et al.*, *J. Org. Chem.*, 1947, **12**, 869) groups. All these compounds were found to be inactive when tested against *P. gallinaceum* infection in chicks. Spink (*Ann. Trop. Med. and Parasitol.*, 1947, **41**, 36) has tried to explain the mode of action of paludrine according to Schonhofer's hypothesis (*Ztschr. f. Physiol. Chem.*, 1942. **274**, 1) as applied to plasmoquin and atebrin, and has suggested that the *p*-chlorophenyl group in this case has the parasiticidal properties, while the alkylbiguanide chain acts as a " conductophor " helping in the absorption, penetration and excretion of the drug. Work of May, *et al.* (*loc cit.*) as detailed above, was based upon similar reasoning but it is evident that substitution of potent parasiticidal groups either derived from phenanthryl type of antimalarials (May and Mosetting, *J. Org. Chem.*, 1946, **11**, 1, 105, 429, 627, 631, 636) or from plasmoquin, in place of chlorophenyl group does not result in active compounds. Consequently it is very doubtful if Schonhofer's theory can be adequately applied to explain the mode of action of biguanide type of antimalarials. Complete inactivity of methyl (in place of $CH(Me)_2$) analogue of paludrine also goes against Spink's explanation.

Taking into consideration that an aryl group (especially *p*-chlorophenyl group) is necessary at one end of the biguanide chain for antimalarial activity,

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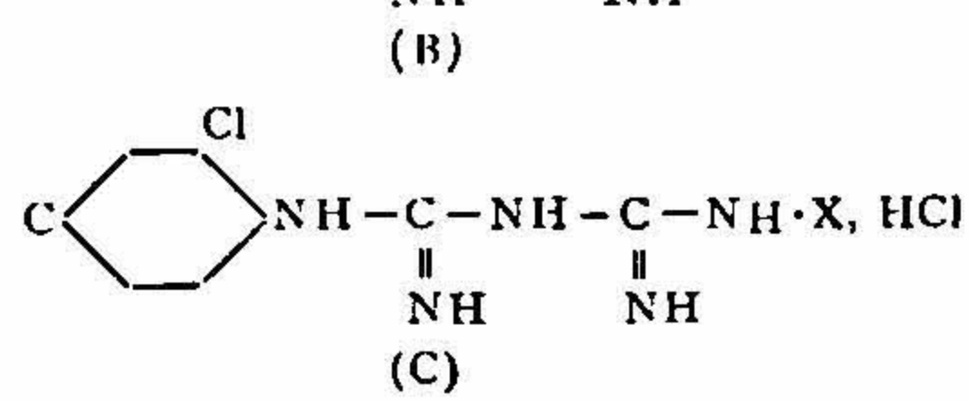
* Preliminary note published in *Current Science*, 1948, **17**, 272. Some *m.p.* have been revised later.

a number of biguanide derivatives have been prepared and tested where the alkyl group at the N^5-position of the N^1-aryl-biguanide has been replaced with 5- and- 8-quinolyl (Gupta. Iyer and Guha, *Current Science*, 1948, **17**, 53; Gupta and Guha, *ibid.*, 185), *p*-phenylarsonic acid (Roy, Iyer and Guha, (*Current Science*, 1948, **17**, 126), 2-thiazolyl [Bami and Guha, (*b*) *J. Indian Inst. Sci.*, 1949, **31A**, 1], *m*-phenyl-(5-chloro-2-pyrimidyl)-sulphonamide [Bami, Iyer and Guha, (*c*) *J. Indian Inst. Sci.*, 1948, **30 A**, 9; *cf.*, *Nature*, 1948, **162**, 146] and *p*-phenyl-(heterocyclic substituted or otherwise)-sulphonamide groups [Bami, Iyer and Guha, (*d*) *J. Indian Inst. Sci.*, 1947, **29 A**, 15; 1948, **30 A**, 1]. In these series, the last two types of compounds when tested against blood induced infection of *P. gallinaceum* in chicks [Bami, Iyer and Guha, (*e*) *Current Science*, 1947, **16**. 386] and *P. knowlesi* in monkeys (personal communication) showed encouraging suppressive antimalarial activity. Sulpha-biguanide derivatives [Bami *et al.*, (*d*) *loc cit.*] and metachloridine substituted arylbiguanides [Bami, *et al.*, (*c*) *loc cit.*] were however active only at relatively large dosage and were also toxic. In short none of the compounds tested so far came up to the standard of activity of paludrine.

As discussed already, attempts to discover an antimalarial better than paludrine in the biguanide series, have been directed towards addition of complex substituents in the biguanide chain, the results being not fruitful. It was thought worthwhile to study the effect of simpler substituents instead of complicating the structure. Consequently a number of analogues and isomers of paludrine itself have been synthesised and the effect of (i) chlorine atom in the different positions of the phenyl group [type A; (*a*)], (ii) other halogen atoms and cyano group at the para position of the phenyl ring (type B) and (iii) an extra chlorine atom in the *p*-chlorophenyl group [type A; (*b*)] have been studied.

It has been previously observed (Cure, *et al.*, *loc. cit.*) that some 2:4-dichlorophenyl substituted pyrimidine derivatives have shown encouraging activity which further encouraged the undertaking of the present study. The preliminary trials in our pharmacological laboratories suggested that the 2:4-dichloro analogue of paludrine was perhaps not very active but definitely toxic. In order to modify the properties of this compound suitably, a number of N^5-alkyl derivatives of type C have been synthesised. The alkylamines used for this study were mostly those not having the amino group at the end of their alkyl chain, and these amines could be called as higher homologues of isopropylamine (Bami, Iyer and Guha, *J. Indian Inst. Sci.*, 1947, **29 A**, 9). Use of simple alkyl groups like methyl and dimethyl- in this study was also due to previous considerations as reported by Curd

and Rose (*loc. cit.*). Replacement of chlorophenyl group by the naphthyl radical has also been effected [type A; (*c*)].

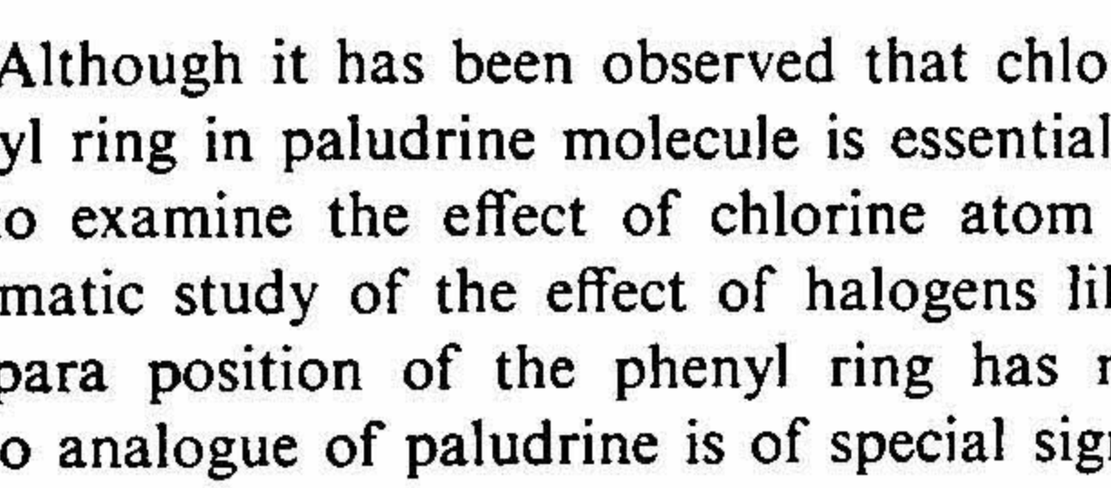


(A)

X = (*a*) *o*-chlorophenyl; *m*-chlorophenyl.

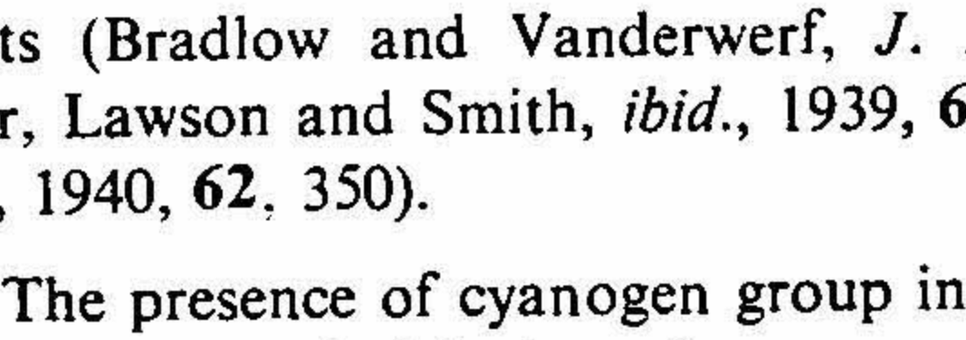
(*b*) 2 : 4 dichlorophenyl 3 : 4-dichlorophenyl

(*c*) α-naphthyl



(B)

X = Br, I, F and CN



(C)

X = alkyl groups.

Although it has been observed that chlorine in the para position of the phenyl ring in paludrine molecule is essential for activity, it will be interesting to examine the effect of chlorine atom occupying other positions. A systematic study of the effect of halogens like Bromo, Iodo and Fluoro at the para position of the phenyl ring has now been made. The study of fluoro analogue of paludrine is of special significance in view of the increasing interest and usefulness of the fluoro compounds as chemotherapeutic agents (Bradlow and Vanderwerf, *J. Amer. Chem. Soc.*, 1948, **70**, 654; Suter, Lawson and Smith, *ibid.*, 1939, **61**, 161; English, Mead and Nieman, *ibid.*, 1940, **62**, 350).

The presence of cyanogen group in place of halogen atom in pyrimidine types of antimalarials has given compounds of appreciable activity (Curd, *et al.*, *J. Chem. Soc.*, 1946, **351**, 362) and in the case of paludrine, study of a similar substituent may not be without significance.

The most suitable method for the synthesis of the compounds of type A, B and C has been found to be the (i) fusion of alkylamine hydrochloride with arylcyanoguanidine or (ii) reacting the amine and arylcyanoguanidine in alcoholic medium in presence of copper sulphate (Rathke, *Ber.*, 1879, **12**, 780; Hearth, *ibid.*, 1880, **13**, 1358; Rackmann, *Ann.*, 1910, **376**, 1701). The requisite arylcyanoguanidines were prepared by reacting the corresponding aryl-diazonium salt with dicyandiamide in alkali solution and subsequently removing the azo-nitrogens from the resulting aryl-azocyanoguanidines (Bami, *J. Indian Inst. Sci.*, 1948, **30 A**, 16).

The yields obtained by the fusion of aryl-cyanoguanidines with different alkylamine hydrochlorides were usually poor and could not be improved

under varying experimental conditions. The reasons for the poor yield have already been indicated [Bami, *et al.* (*a*) *loc cit.*]. In the case of cyano analogue of paludrine (type B; X = CN) the fusion method was, however, of particular utility because the hydrolysis of the cyano group could be avoided by this procedure.

The use of copper sulphate for the isolation of biguanides gave most satisfactory results and the rate of reaction could be judged by the purple-brown colour of the copper complex solution. The biguanides were always isolated as their hydrochloride salts and were usually sufficiently soluble in water. These salts were also soluble in alcohols, acetone, and dioxane. Free biguanide bases could be generated by treating the aqueous solution of the salt with strong sodium hydroxide solution, and were low melting, water insoluble solids which easily absorbed carbon dioxide from the atmosphere. All the biguanides chelated readily. The crystalline monohydrochloride salts of these biguanides broke down by prolonged boiling with hydrochloric acid, one of the breakdown products being the aryl-amine.

Compounds of type C and fluoro analogue of paludrine have been found to be too toxic though active when tested against avian malaria. A few of the compounds described in this paper have been mentioned in a patent (Indian Patent No. 36462, 1946) but they have been prepared by reacting an arylguanidine salt with alkylcyanamide, a method which has been previously used by us (Bami, Iyer and Guha, *loc. cit.*) for the preparation of paludrine.

Experimental

N^1-o-Chlorophenyl-N^5-isopropyl-biguanide hydrochloride (*type A; X = o-chlorophenyl*) (*I*).—*o*-Chlorophenylcyanoguanidine (2·7 g.), copper sulphate pentahydrate (1·56 g.) and isopropylamine (4 c.c.) were taken in a mixture of alcohol (15 c.c.) and water (10 c.c.) and refluxed for three hours. The excess of alcohol and isopropylamine was removed and the mixture was dissolved in hydrochloric acid (15 c.c.). Sodium sulphide hydrated (5 g.) dissolved in water (10 c.c.) was then added to the above solution and the entire mixture filtered. The filtrate was strongly alkalised and the base obtained was filtered and washed well with water. The biguanide base was dissolved in minimum hydrochloric acid (5%), treated with norite, filtered and concentrated when the product came out on chilling. The product was collected by filtration and recrystallised from dilute alcohol. White crystalline powder; m.p. 237°; yield 2·5 g. (Found: N, 23·72. $C_{11}H_{17}N_5Cl_2$ requires N, 24·13 per cent.).

N^1-m-Chlorophenyl-N^5-isopropylbiguanide hydrochloride (*type A: X = m chlorophenyl*) (*II*).—*m*-Chlorophenylcyanoguanidine (2·7 g.) and isopropyl-

amine (4 c.c.) were reacted together in the presence of copper sulphate and the product isolated and purified as under (I). White crystalline powder; m.p. 231°; yield 2·5 g. (Found: C, 45·1, H, 6·0, N, 24·23. $C_{11}H_{17}N_5Cl_2$ requires C, 45·5, H, 5·8, N, 24·13 per cent.).

N^1-2: 4-Dichlorophenyl-N^5-isopropylbiguanide hydrochloride (*type A*; *X* = 2: 4-*dichlorophenyl*) (*III*).—2: 4-Dichlorophenylcyanoguanidine (4 g.) and isopropylamine hydrochloride (2 g.) were heated together with occasional stirring at 140-50° for three hours. The mass was extracted with hot water (20 c.c.) twice and the aqueous extract treated with norite and filtered. The filtrate on concentration and cooling deposited the product which was collected and recrystallised from water. White crystalline salt; m.p. 215°; yield 1 g. (Found: N, 21·84. $C_{11}H_{16}N_5Cl_3$ requires N, 21·57 per cent.).

N^1-3: 4-Dichlorophenyl-N^5-isopropylbiguanide hydrochloride (*type A*; *X* = 3: 4-*dichlorophenyl*) (*IV*).—3: 4-Dichlorophenylcyanoguanidine (1·5 g.) and isopropylamine hydrochloride (1 g.) were heated to 160° and then maintained at 130–40° for two hours. The product was isolated and purified as under (III). White crystalline powder; m.p. 236°; yield 0·5 g. (Found: N, 21·53. $C_{11}H_{16}N_5Cl_3$ requires N, 21·57 per cent.).

N^1-β-Naphthyl-N^5-isopropylbiguanide hydrochloride (*type A*; *X* = β-*naphthyl*) (*V*).—β-Naphthylcyanoguanidine (0·5 g.) and isopropylamine hydrochloride (0·3 g.) were heated together at 170° for one hour. The product was isolated and purified as under (III). White crystalline powder; m.p. 229–30°; yield 0·3 g. (Found: N, 22·57. $C_{15}H_{20}N_5Cl$ requires N, 22·91 per cent.).

N^1-p-Fluorophenyl-N^5-isopropylbiguanide hydrochloride (*type B*; *X* = *F*) (*VI*).—*p*-Fluorophenylcyanoguanidine (1·5 g.) and isopropylamine hydrochloride (1·3 g.) were first melted together at 160° and then heated for one hour at 120–30°. The product was isolated and purified as under (III). White crystalline powder; m.p. 248°; yield 1·0 g. (Found: N, 26·08. $C_{11}H_{17}N_5ClF$ requires N, 25·68 per cent.).

N^1-p-Bromophenyl-N^5-isopropylbiguanide hydrochloride (*type B*; *X* = *Br*) (*VII*).—*p*-Bromophenylcyanoguanidine (12 g.), isopropylamine (15 c.c.) and copper sulphate pentahydrate (6·25 g.) were added to a mixture of alcohol (50 c.c.) and water (30 c.c.) and refluxed for three hours. The copper complex was dissolved in hydrochloric acid, treated with a solution of sodium sulphide (20 g. in 50 c.c. water) and the product isolated and purified as under (I). White crystalline powder; m.p. 245°; yield 6 g. (Found; N, 20·68. $C_{11}H_{17}N_5ClBr$ requires N, 20·92 per cent.).

N^1-p-Iodophenyl-N^5-isopropylbiguanide hydrochloride (*type B*; *X= I*) (*VIII*).—*p*-Iodophenylcyanoguanidine (2·8 g.) and isopropylamine hydrochloride (1·2 g.) were heated together for one hour at 180°. The product was isolated and purified as under (III). While crystalline powder; m.p. 237°; yield 1 g. (Found: N, 18·22. $C_{11}H_{17}N_5ClI$ requires N, 18·35 per cent.).

N^1-p-Cyanophenyl-N^5-isopropylbiguanide hydrochloride (*type B*; *X= CN*) (*IX*).—*p*-Cyanophenylcyanoguanidine (0·3 g.) and isopropylamine hydrochloride (0·5 g.) were heated together for one hour at 160°. The product was isolated and purified as under (III). White crystalline powder; m.p. 231–32°; yield 0·2 g. (Found: N, 29·75. $C_{12}H_{17}N_6Cl$ requires N, 29·94 per cent.).

N^1-2: 4-Dichlorophenyl-N^5-methylbiguanide hydrochloride (*type C*; *X= methyl*) (*X*).—2: 4-Dichlorophenylcyanoguanidine (4 g.) and methylamine hydrochloride (2 g.) were reacted together and the product isolated and purified as under (III). White crystalline solid; m.p. 215°; yield 2 g. (Found: C, 36·2, H, 4·5, N, 23·96. $C_9H_{13}N_5Cl_3$ requires C, 36·4, H, 4·3, N, 23·52 per cent.).

N^1-2: 4-Dichlorophenyl-N^5-dimethylbiguanide hydrochloride (*type C*; *X= dimethyl*) (*XI*).—2: 4-Dichlorophenylcyanoguanidine (2 g.) and dimethylamine hydrochloride (1 g.) were reacted together and the product isolated and purified as under (III). White powder; m.p. 231°; yield 1 g. (Found: N, 22·12. $C_{10}H_{15}N_5Cl_3$ requires N, 22·47 per cent.).

N^1-2: 4-Dichlorophenyl-N^5-2-butylbiguanide hydrochloride (*type C*; *X= 2-butyl*) (*XII*).—2: 4-Dichlorophenylcyanoguanidine (2 g.) and 2-butylamine hydrochloride (1·2 g.) were reacted together and the final product obtained as under (III). White crystalline powder; m.p. 240°; yield 1 g. (Found: N, 20·72. $C_{12}H_{18}N_5Cl_3$ requires N, 20·67 per cent.).

N^1-2: 4-Dichlorophenyl-N^5-3-pentylbiguanide hydrochloride (*type C*; *X= 3-pentyl*) (*XIII*).—2: 4-Dichlorophenylcyanoguanidine (2·2 g.) and 3-pentylamine hydrochloride (1·5 g.) were heated together for one hour at 180°. The product was isolated as under (III). White crystalline solid; m.p. 221–22°; yield 0·6 g. (Found: N, 20·07. $C_{13}H_{20}N_5Cl_3$ requires N, 19·81 per cent.).

N^1-2: 4-Dichlorophenyl-N^5-2-pentylbiguanide hydrochloride (*type C*; *X= 2-pentyl*) (*XIV*).—2: 4-Dichlorophenylcyanoguanidine (1·2 g.) and 2-pentylamine (2 c.c.) were reacted together for three hours in dilute alcohol in presence of copper sulphate (1·5 g.). The product was isolated and purified as under (I). White crystalline powder; m.p. 216–17°; yield 2 g. (Found: N, 20·02. $C_{13}H_{20}N_2Cl_3$ requires N, 19·81 per cent.).