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CONTENTS

STUDIES IN ANTIMALARIALS

Part X. N^1-Aryl-N^5-heterocyclic-biguanides

BY

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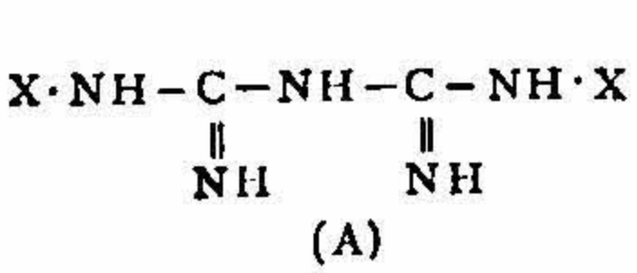
STUDIES IN ANTIMALARIALS

Part X. N^1-Aryl-N^5-heterocyclic-biguanides*

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

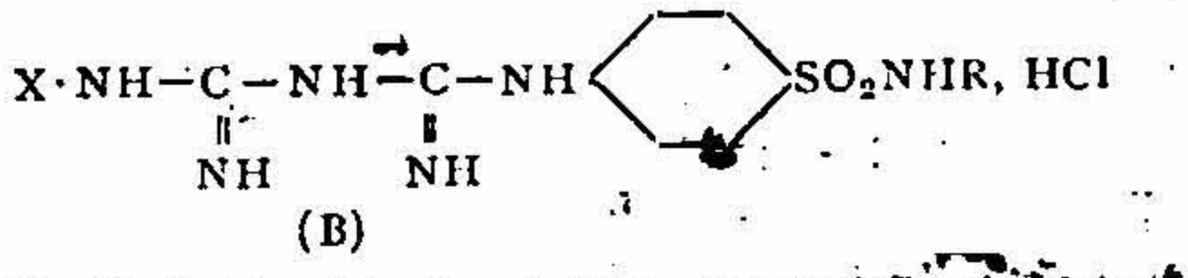
In order to study the effect of various substituents in the paludrine molecule as regards antimalarial activity, firstly quinolyl and phenanthryl groups were substituted in place of chlorophenyl group of paludrine but the resulting compounds proved to be inactive when tested against experimental malaria (May, *J. Org. Chem.*, 1947, **12**, 437, 443; May, *et al.*, *ibid.*, 869). The nucleii substituted in place of *p*-chloro-phenyl group were derived from plasmoquin and other phenanthryl derivatives of known antimalarial activity (May and Mosettig, *J. Org. Chem.*, 1946, **11**, 1, 105, 429, 627, 631, 636; Elderfield, *et al.*, *ibid.*, 111, 123, 136), the idea being that if in the case of paludrine the function of *p*-chlorophenyl group is to provide a parasiticidal group, then its replacement by other groups of confirmed parasiticidal property should give equally active or better drugs. The above failures discouraged the authors to take up further investigations on the above lines. Attempts were however made previously to convert 2-aminothiazole into 2-cyanoguanidino-thiazole by diazotising the amine and reacting it with dicyandiamide and denitrogenating the resulting triazene to give the required product. The product could not be obtained due to reasons already discussed (Bami, *J. Jndian Inst. Sci.*, 1948, **30 A**, 15; *cf.*, *Current Science*, 1948, **17**, 96).

It has been reported by Curd and Rose (*J. Chem. Soc.*, 1946, 729), that simple N^1-N^5-diaryl-biguanides of the type (A) did not possess any antimalarial activity and it was argued that this lack of activity may be due to the absence of any potential substituent in the N^5-aryl group. On this basis, a number of biguanide derivatives of the type (B), having potential substituents like *p*-sulphonamido group (substituted or otherwise) have been prepared (Bami, Iyer and Guha, *J. Indian Inst. Sci.*, 1947, **29 A**, 15; 1948, **30 A**, 1).



(A)

X = aryl group;



(B)

R = H, 2 thiazolyl, 2-pyrimidyl, 6 methyl-2-pyrimidyl and 4:6-dimethyl-2 pyrimidyl.

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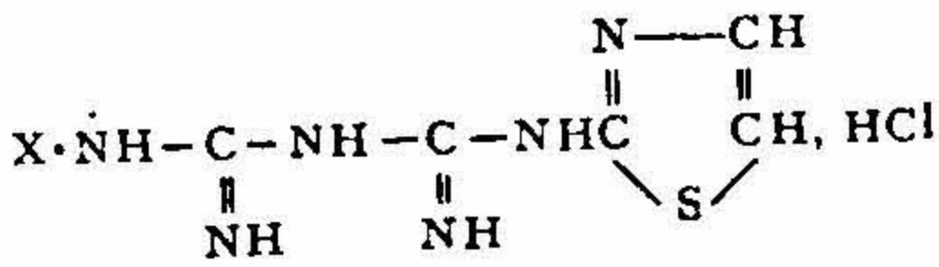
* A preliminary note of this work has been published in *Science & Culture*, 1949, **14**, 386.

Although simple sulphonamide substituted compounds of the type (B) were found to be inactive when tested against avian malaria (*P. gallinaceum* in chicks), the presence of heterocyclic rings in the sulphonamido part gave compounds possessing encouraging antimalarial activity (Bami, Iyer and Guha, *Current Science*, 1947, **16**, 386). In the beginning, due to potent antimalarial properties of sulphadiazine and the great physiological importance of pyrimidine ring systems, Curd and Rose (*J. Chem. Soc.*, 1946, 343) first prepared sulphonamide-free analogues of sulphadiazine of the type 2-aryl-amino-6-methyl-4-dialkylaminoalkylamino-pyrimidines and out of these a few showed encouraging activity. It was therefore thought worthwhile to prepare compounds of type (B) (heterocyclic substituted) without the grouping "C_6H_4-p-SO_2NH" and are represented by compounds of type C where the heterocyclic thiazolyl ring has been directly attached to the nitrogen in position 5 of the N^1-arylbiguanides. It will be interesting to compare the relative antimalarial activities of compounds of type C with those of sulphabiguanide derivatives (type B).

Although the effect of replacement of isopropyl group of paludrine by a number of different alkyl-, dialkyaminoalkyl-, aryl-, and substituted aryl groups have been studied (Bami and Guha, *J. Indian Inst. Sci.*, 1949, **31A**, 1), no detailed study of the effect of heterocyclic rings at this position has been made. Recently, in these laboratories, Gupta and Guha (*Current Science*, 1948, **17**, 53, 188) have prepared some N^1-aryl-N^5-quinolyl-biguanides with a similar object in view, but the pharmacological results are not yet available.



Type C

X = aryl group

For the synthesis of compounds of type C, a number of routes could be theoretically suggested but the most practicable and direct method which was successfully employed consisted in reacting the required arylcyanoguanidine with 2-aminothiazole-hydrochloride in suitable medium. Similar methods have also been previously employed by other workers (May, *et al.*, *loc. cit.*; Gupta and Guha, *loc. cit.*). The biguanide derivates were isolated as stable crystalline monohydrochlorides with high melting points and sparing solubility in alcohols, acetone, dioxane and ethyl-acetate. The yields were however rather poor. The free base could be isolated by treating the hydrochloride salt solution of the biguanide with dilute sodium hydroxide solution. The bases could be crystallised from dilute alcohol and gave picrates readily.

The present programme also included the introduction of other important heterocyclic rings in compounds of type C, but unfortunately the reaction did not proceed in the case of following amino heterocyclic rings which were specially synthesised for the purpose:

2-Amino-6-methoxy-benzothiazole, 2-amino-4-methyl-thiazole, 2-amino-6-methylpyrimidine, 2-amino-4-chloro-6-methylpyrimidine, 2-amino-4-hydroxy-6-methylpyrimidine and 5-amino-7-methoxy-2-chloro-acridine (atebrin base).

Attempts to react N^1-*p*-chlorophenylcyanoguanidine with 6-methoxy-2-amino-benzothiazole hydrochloride in alcohol, dioxane and amyl alcohol were unsuccessful. The fusion of the two reactants also failed to give the desired product while the use of copper sulphate to isolate the biguanide also did not meet with any success. Similar experiments were carried out with the remaining amino heterocyclics detailed above but in no case the desired product could be obtained by these methods. Cases of similar failures have been reported by May, *et al.* (*loc cit.*), where they have not been able to condense 7-chloro-4-aminoquinoline with isopropylcyanoguanidine by any of the above methods. They have attributed this failure of reaction to the selective nature of the amino group. Gupta and Guha (*loc. cit.*) have also not been able to react 2-amino-6-methoxy-benzothiazole and 5-amino-7-methoxy-2-chloroacridine with isopropyl-cyanamide to get the corresponding guanidine derivatives.

One of the compounds of type C (X = *p*-chloro-phenyl) was found to be moderately active though toxic when tested against avian malaria. The inertness of all these substituted amino-heterocyclics to react with aryl-cyano-guanidines seems to be due to the presence of substituent groupings.

Experimental

2-*Amino-thiazole* (*I*).—Thiourea (38 g.) and chloracetal (68 g.) prepared according to the method of Kluger (*Monatsh.*, 1905, **26**, 881) were taken in water (100 c.c.) and refluxed for twenty-four hours till the entire chloracetal had been used up. The solution was made strongly alkaline with sodium hydroxide solution (20%) and extracted with ether thrice. The total ether extract was dried over anhydrous magnesium sulphate and on the removal of ether the product came out as light coloured solid. Crude product was crystallised from alcohol. Light coloured crystalline solid; m.p. 90°; yield 30 g.

N^1-Phenyl-N^5-2-thiazolyl-biguanide hydrochloride (*type C*; *X = phenyl*) (*II*).—Phenylcyanoguanidine (4 g.) and 2-amino-thiazole (3·3 g.) were added to a mixture of alcohol (12 c.c.) and hydrochloric acid (3·3 c.c.) and refluxed for twelve hours. The solid which separated out was filtered, washed with

little alcohol and crystallised twice from dilute alcohol. Finally dried in air oven at 80–90° for one hour. White crystalline powder; m.p. 270° decomposition; yield 2 g. (Found: N, 28·72. $C_{11}H_{13}N_6ClS$ requires N, 28·33 per cent.).

N^1-p-Chlorophenyl-N^5-2-thiazolyl-biguanide hydrochloride (*type C*; *X = p-chlorophenyl*) (*III*).—*p*-Chlorophenylcyanoguanidine (9 g.) and 2-amino-thiazole (6 g.) were taken in a mixture of alcohol (25 c.c.) and hydrochloric acid (6 c.c.) and refluxed for twelve hours. The product which separated was filtered, washed with little alcohol, crystallised twice from dilute alcohol using a little norite and finally dried at 80–90° for one hour. White crystalline powder; m.p. 294° decomposition; yield 5 g. (Found: N, 25·52. $C_{11}H_{12}N_6Cl_2S$ requires N, 25·37 per cent.). (m.p. of the free base, 160°).

N^1-p-Bromophenyl-N^5-2-thiazolyl-biguanide hydrochloride (*type C*; *X = p-bromophenyl*) (*IV*).—*p*-Bromophenyl cyanoguanidine (3·6 g.) and 2-amino-thiazole (1·6 g.) were taken in alcohol (10 c.c.) and hydrochloric acid (1·6 c.c.) mixture and refluxed for eight hours. The product was isolated and purified as under (III). White crystalline powder; m.p. 183°; yield 2·3 g. (Found: N, 22·03. $C_{11}H_{12}N_6ClBrS$ requires N, 22·37 per cent.).

N^1-p-Iodophenyl-N^5-2-thiazolyl-biguanide hydrochloride (*type C*; *X = p-iodophenyl*) (*V*).—*p*-Iodophenylcyanoguanidine (5·7 g.) and 2-amino-thiazole (2 g.) were taken in a mixture of alcohol (10 c.c.) and hydrochloric acid (2 c.c.) and refluxed for twelve hours. The product was isolated as under (III) and crystallised from ethylacetate. White crystalline solid; m.p. 285° decomposition; yield 1·5 g. (Found: N, 19·56. $C_{11}H_{12}N_6ClIS$ requires N, 19·88 per cent.).

N^1-p-Tolyl-N^5-2-thiazolyl-biguanide hydrochloride (*type C*; *X = p-tolyl*) (*VI*).—*p*-Tolylcyanoguanidine (3·5 g.) and 2-amino-thiazole (2 g.) were reacted together and the product isolated and purified as under (V). White crystalline powder; m.p. 202°; yield 1·5 g. (Found: N, 27·10. $C_{12}H_{15}N_6ClS$ requires N, 26·94 per cent.).

N^1-2: 3-Dimethylphenyl-N^5-2-thiazolyl-biguanide hydrochloride (*type C*; *X = 2: 3-dimethylphenyl*) (*VII*).—2: 3-Dimethyl phenylcyanoguanidine (2·7 g.) and 2-amino-thiazole (1·7 g.) were reacted together and the product isolated and purified as described under (IV). White crystalline powder; m.p. 251°; yield 1 g. (Found: N, 25·56. $C_{13}H_{17}N_6ClS$ requires N, 25·88 per cent.).

N^1-p-Anisyl-N^5-2-thiazolyl-biguanide hydrochloride (*type C*; *X = p-anisyl*) (*VIII*).—*p*-Anisylcyanoguanidine (2 g.) and 2-aminothiazole (1·2 g.) were reacted together in alcoholic hydrochloric acid and the product obtained as

under (VI). White powder; m.p. 307° decomposition; yield 1 g. (Found: N, 25·43. $C_{12}H_{15}ON_6ClS$ requires N, 25·7 per cent.).

N^1-p-Nitrophenyl-N^5-2-thiazolyl-biguanide hydrochloride (*type C*; *X* = *p-nitrophenyl*) (*IX*).—*p*-Nitrophenylcyanoguanidine (2 g.) and 2-amino-thiazole (2 g.) were reacted together in alcoholic hydrochloric acid and the product obtained as under (V). Light yellow powder; m.p. 240° decomposition; yield 1 g. (Found: N, 28·69. $C_{11}H_{12}O_2N_7ClS$ requires N, 28·69 per cent.)

Preparation of Amino-Heterocyclics

Chloroacetone was prepared according to the method of Fritch, (*Ber.*, 1893, **26**. 997), as follows:—Marble chips (30 g.) were taken in a mixture of water (60 c.c.) and acetone (120 g.) and chlorine was passed through them at 60° till no more of the marble was left. The reaction mixture was allowed to stand overnight and the upper layer of the oil was separated, washed, dried and distilled. Colourless liquid; b.p. 112–18°/685 mm.; yield 100 g.

2-*Amino*-4-*methyl-thiazole hydrochloride* (*I*).—Chloroacetone (30 g.) and thiourea (30 g.) were refluxed together carefully for one hour and to the mixture some alcohol (50 c.c.) was added. The mixture was left overnight and the hydrochloride salt of 4-methyl-2-aminothiazole was collected and dried. m.p. 42°; yield 40 g.

2-*Amino*-6-*methoxy-benzothiazole* (*II*).—*p*-Methoxyphenylthiourea was converted into the required product by the use of bromine in chloroform according to the details given by Guha and Guha (personal communication).

5-*Amino*-2-*chloro*-7-*methoxy-acridine* (*III*).—2: 5-Dichloro-7-methoxy-acridine was prepared according to the method of Adien, *et al.*, (*J. Soc. Chem. Ind.*, 1941, **60**, 120) and converted into the required product as described by Guha and Guha (*J. Indian Inst. Sci.*, 1946, **28 A**, 70).

2-*Amino*-4-*hydroxy*-6-*methyl-pyrimidine* (*IV*).—Guanidine hydrochloride (10 g.), acetoacetic-ester (18 g.) and sodium carbonate (6 g.) were refluxed in absolute alcohol (38 c.c.) for twelve hours. The solid was filtered, washed well with water and dried. White powder; m.p. 270° decomposition; yield 30 g.

2-*Amino*-4-*chloro*-6-*methyl-pyrimidine* (*V*): *Method A*.—2-Amino-4-hydroxy-6-methyl-pyrimidine (IV) (30 g.) was treated with freshly distilled phosphorusoxychloride (150 c.c.) for eight hours. The clear solution was poured on ice and alkalised. The crude product was collected by filtration and crystallised from alcohol. Light coloured solid; m.p. 181°; yield 20 g.

Method B.—6-Methyl-uracil was prepared (Donleavy and Kise, *Org. Synthesis*, Vol. XVII, 63) and converted into 2:4-dichloro-6-methyl-pyrimidine by phosphorusoxychloride (Gabriel and Colman, *Ber.*, 1899, **32**, 1533) which was subsequently treated with alcoholic ammonia to give the required product. The yield was poor by this method.

2-*Amino*-6-*methyl-pyrimidine* (*VI*).—2-Amino-4-chloro-6-methyl-pyrimidine (V) was treated with zinc dust in hot water to give the corresponding chlorine-free pyrimidine derivative (Gabriel and Colman, *Ber.*, 1899, **32**, 2925).

Reactions between *p*-Chlorophenylcyanoguanidine and 6-Methoxy-2-amino-benzothiazole

[The following reactions were also tried in the case of heterocyclic amines (I, III, IV, V and VI) with similar results. Details are omitted].

(*a*) *p*-Chlorophenylcyanoguanidine (4 g.) and 6-methoxy-2-amino-benzothiazole hydrochloride (4·5 g.) were refluxed together in alcohol (15 c c.) for eighteen hours. No solid separated and the starting materials were almost quantitatively recovered on working up the product.

(*b*) Use of amyl alcohol also gave similar results as in the above case.

(*c*) *p*-Chlorophenylcyanoguanidine (4 g.) and 6-methoxy-2-amino-benzothiazole hydrochloride (4·5 g.) were fused together at 150° for four hours and the product worked up. The starting materials were recovered.

(*d*) *p*-Chlorophenylcyanoguanidine (4g.) and 6-methoxy-2-amino-benzothiazole (3·6 g.) were taken in a solution of copper sulphate (2·5 g.) in aqueous ethanol (50%; 30 c.c.) and refluxed for eight hours. The mixture was dissolved in hydrochloric acid and treated with sodium sulphide solution (5 g. in 10 c.c. water). The mixture was filtered and the filtrate alkalised. The alkali-insoluble product was filtered, washed and crystallised. This was found to be 6-methoxy-2-amino-benzothiazole which was quantitatively recovered. The alkali solution on acidification, gave the aryl-cyanoguanidine but most of it had been converted into *p*-chlorophenyl-guanylurea.

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