PRELIMINARY ANTIMALARIAL SCREENING TESTS OF SOME BIGUANIDE DERIVATIVES

A number of communications[1-3] have been published by us, on the synthesis of new potential antimalarials of the substituted biguanide type. The results of testing of some of these compounds against avian and simian malarias are now reported.

Avian Malaria Tests. Although the synthetic compounds could be tested in a number of ways in the light of recent developments in the field of antimalarial testing[4,5] but for the present work as a preliminary screening test, only the suppressive antimalarial activity of the compounds against the blood induced infection of *Plasmodium gallinaceum* in chicks, has been evaluated. Young cross breed country fowls, 8-10 weeks old, were infected intramuscularly with citrated blood freshly drawn from control birds showing peak infection. The size of the inoculum was so adjusted that the control group showed peak infection after 8-10 days invariably. Treatment group was orally fed with the requisite

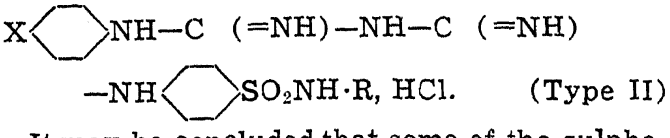
dose of the drug (in aqueous solution or suspension) twice daily for four days after 48 hours of infecting. After the treatment was over the blood smears were examined daily and the delay in reaching the peak infection in the case of drug treated group of birds in comparison to that of control was taken as criteria for the suppressive antimalarial activity. The antimalarial activities given below are with respect to paludrine which has given the maximum time lag between the peak infection of control and treated groups.

X.NH—C (=NH)—NH—C (=NH)—NH.R, HCl (Type I)

TABLE A. *Analogues and isomers of paludrine.*

No.	X	R	Dosage mmg./100 gm. body weight	Activity
1	*p*-Chlorophenyl	Isopropyl (Paludrine)	6	+++
2	do	do (acetate salt)	6	+++
3	*p*-Fluorophenyl[4]	do	20	+(toxic)
			4	−(toxic)
4	*m*-Chlorophenyl[4]	do	20	++
5	2 : 4-Dichlorophenyl[4]	do	40	−(toxic)
			20	−(toxic)
6	do	Methyl-propyl	4	−(toxic)

Metachloro analogue of paludrine (No. 4) has shown good activity while the fluoro analogue has been found to be inactive and toxic. The presence of an additional chlorine atom in the p-chlorophenyl ring of paludrine has also not led to active compounds (No. 5,6). In the case of toxic compounds, most of the treated birds died during or just after the treatment and on disection showed Hæmorrhage in the gizzard and congestion in the gullet indicating local iritation.



(Type II)

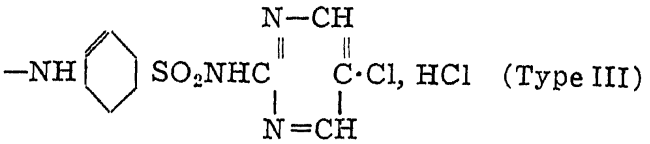
It may be concluded that some of the sulphabiguanide derivatives obtained from N'-pyrimidyl-sulphanilamides showed good suppressive antimalarial activity when tested at relatively large dosage. This suppressive activity is however not comparable to that of quinine or paludrine. Toxicity of compound No. 17 was determined in mice. Sulphabiguanides did not form metallic complexes

TABLE B. *Sulphabiguanides.*

No.	X	R	Dosage mmg./100 gm. b. wt.	Activity
7	Cl[1]	H	6	−
			12	−
8	CH_3O	H	6	−
			12	−
9	Cl	2-thiazolyl[1]	20	−
10	Br	do	40	−
11	H	2-pyrimidal	40	++
12	Cl	do	40	+
13	Br	do	20	−
14	CH_3O	do	20	++
15	NO_2	do	20	−
16	Cl	6-methyl-2-pyrimidyl[2]	40	++
17	Cl	6 : 4-dimethyl-2-pyrimidyl[2]	40	+(toxic)

(chelates) and activity in the case of these compounds shows that for antimalarial activity a suitably substituted biguanide group may be sufficient, apart from other considerations.

X.NH—C(=NH)—NH—C (=NH)[8]

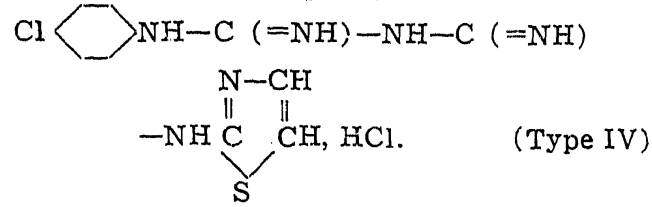


(Type III)

TABLE C. *Meta-chloridine substituted aryl biguanides.*

No.	X	Dosage mmg/100 gm. b. wt.	Activity
18	*p*-Chlorophenly.	40	++(toxic)
19	2 · 3-Diemthyl phenyl.	20	+

Although the above group of compounds showed suppressive antimalarial activity, compound No. 18 was found to be toxic at the above dosage. Compound No. 19 was however found to be non-toxic at this dosage when tested in mice, but was relatively less active Metachloridine substituted arylbiguanides resemble sulphabiguanides as regards their activity and chelating capacity.



(Type IV).

Compound (IV) (No. 20) when tested at a dosage of 40 mmg./100 gm.b. wt. was only found to be slightly active and excessively toxic. Replacement of isopropyl group by thiazolyl

ring in the paludrine molecule does not seem to result in active compounds.

Simian Malarir Tests.—Some of the compounds reported above were also tested against blood induced infection of *Plasmodium knowlesi* in Rhesus monkeys at the Malaria Institute of India for assessing their preliminary suppressive activity.

m-Chloro analogue (No. 4) and *p*-bromo analogue (Type I ; X = *p*-bromophenyl) of paludrine have shown encouraging suppressive activity. In the sulphabiguanide series, compound No. 7, 9, 11 and 17 have been found to be inactive while compound No. 16 as well as bromoanalogue of compound No. 7 (type II ; X = Br) have shown encouraging suppressive activity. Compound No. 18 and 20 have also failed to show any noteworthy activity.

These results are generally in agreement to those obtained in the case of avian malaria screening tests.

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