[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, INDIAN INSTITUTE OF SCIENCE]

Preparation of Some 1,5-Diaryl Biguanides

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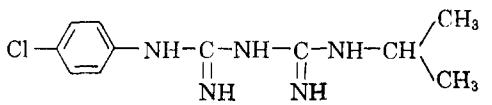
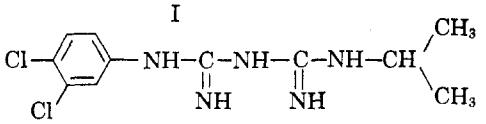
A series of 1,5-diaryl biguanides were prepared by treating arylcyanoguanidines with various aromatic amines in the presence of hydrochloric acid. Some of the symmetrical diarylbiguanides were made by treating dicyanimide with arylamines. A few of the compounds showed appreciable activity in experimental malaria.

Curd and Rose[1] first postulated that the toxicity of the quinoline and acridine antimalarials was mainly due to the fact that the ring systems involved were foreign to the body. From these and other considerations[2] they finally developed a new class of antimalarials of which paludrine (I) and more recently the dichloro analog (II) showed the greatest promise.[3,4] Compounds with the chlorophenyl group replaced by phenanthryl, quinolyl, etc., were inactive.[5] However, the isopropyl group could be replaced by others like quinolyl, phenylarsonic, sulfonamidophenyl, etc., without loss of activity.[6,7] It was found by Srinivasan[8] that biguanides that are inactive *in vivo* showed considerable activity in inhibiting the respiration of the malarial parasite *in vitro*. Diarylbiguanides with terminal groups which might help in absorption and resist detoxication were made to permit their study in experimental malaria.

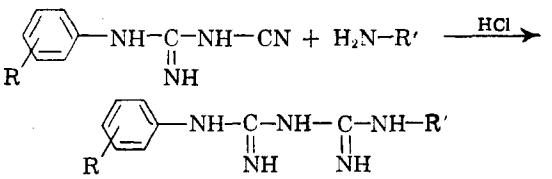


I

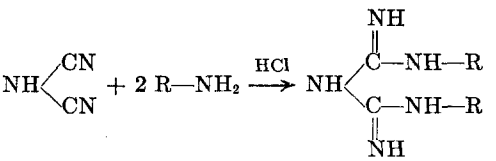


II

A convenient synthesis of such compounds consists in reacting arylcyanoguanidines with arylamines in the presence of hydrochloric acid.[3] *p*-Chloroaniline, 3,4-dichloroaniline, sulfanilic acid, metanilic acid, aniline, and diphenylamine were reacted with *p*-chlorophenylcyanoguanidine and phenylcyanoguanidine respectively to give the desired products as their hydrochlorides.



When dicyanimide is reacted with two moles of arylamines symmetrically substituted diarylbiguanides are obtained. Sulfanilic acid, metanilic acid, and diphenylamine were used to give the corresponding derivatives.



EXPERIMENTAL

Aryl cyanoguanidines were prepared according to well known procedures.[3] *1,5-diphenylbiguanide hydrochloride.* Aniline (2.4 g.), phenylcyanoguanidine (4 g.), concentrated hydrochloric acid (5 ml.), water (10 ml.), and alcohol (50 ml.) were heated on the water bath for 8 hr. On cooling, a crystalline mass separated, which was collected, decolorized, and recrystallized from water twice to give the pure product.

Molecular proportions of arylcyanoguanidines and different arylamines were reacted in this manner to give the various diarylbiguanides listed in the table.

Reaction of dicyanimide with amines. Calcium cyanamide (10 g.) was made to react with cyanogen bromide (10 g. of a 50% solution) in aqueous medium at room temperature for 12 hr. The reaction mixture was then warmed on the water bath and filtered hot. To the filtrate containing the dicyanimide was added sulfanilic acid (8 g.) and concentrated HCl (5 ml.) and the whole was refluxed for 6 hr. The hot solution was decolorized with Norit, filtered, and cooled to deposit crystals which were collected and recrystallized from water to give the pure hydrochloride of the product. Metanilic acid and diphenylamine were also reacted in this manner.

Pharmacological evaluation. Screening tests showed that compounds 3, 5, 8, 12, and 15 have appreciable activity against *P. gallinaceum* in chicks. Compounds 1, 3, and 12 showed 60–65% inhibition of the respiration of the malarial parasite *in vitro*, using the Warburg technique. Srinivasan obtained similar results with various other N^1, N^5-disubstituted biguanides which were inactive *in vivo*.

The formation of a dihydrotriazine like the active metabolite of paludrine or its dichloro analog is unlikely in the case of these diarylbiguanides. It is possible that the biguanide structure in itself has antimalarial activity; groups like arylsulfonic at the end of the biguanide chain probably

(1) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 343 (1946).
(2) A. R. D. Adams *et al.*, *Ann. Trop. Med. Parasitol.*, 39, 165 (1945).
(3) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 729 (1946).
(4) F. L. Rose, *Endeavour*, 18, 65 (1946).
(5) E. L. May *et al.*, *J. Org. Chem.*, 12, 437 (1947).
(6) H. L. Bami *et al.*, *J. Indian Inst. Sci.*, 29A, 15.
(7) H. L. Bami et al., *J. Indian Inst. Sci.*, 29A, 1.
(8) V. R. Srinivasan, Ph.D. thesis, University of Madras.

TABLE I

1,5-DIARYL BIGUANIDES

R—NH—C(=NH)—NH—C(=NH)—NH—R' HCl

No.	—R	—R'	M.P.[a]	Yield, %	Formula	% N Found	% N Calcd.
1	*p*-Chlorophenyl	*p*-Chlorophenyl	254	70	$C_{14}H_{14}Cl_3N_5$	19.62	19.55
2	3,4-Dichlorophenyl	*p*-Chlorophenyl	248	75	$C_{14}H_{13}Cl_4N_5$	17.68	17.82
3	*p*-Benzenesulfonic acid	*p*-Chlorophenyl	>300	75	$C_{14}H_{15}Cl_2N_5O_3S$	17.52	17.33
4	*p*-Benzenesulfonic acid	*p*-Chlorophenyl	>300	70	$C_{14}H_{15}Cl_2N_5O_3S$	17.18	17.33
5	*p*-Biphenyl	*p*-Chlorophenyl	262	65	$C_{20}H_{19}Cl_2N_5$	17.70	17.54
6	Phenyl	*p*-Chlorophenyl	242	65	$C_{14}H_{15}Cl_2N_5$	21.75	21.90
7	*p*-Biphenyl	Phenyl	180	65	$C_{20}H_{20}ClN_5$	19.01	19.17
8	*p*-Benzenesulfonic acid	Phenyl	>300	70	$C_{14}H_{16}ClN_5O_3S$	18.78	18.98
9	*m*-Benzenesulfonic acid	Phenyl	>300	65	$C_{14}H_{16}ClN_5O_3S$	18.87	18.98
10	Phenyl	Phenyl	220	70	$C_{14}H_{16}ClN_5$	24.37	24.22
11	3,4-Dichlorophenyl	Phenyl	213	65	$C_{14}H_{14}Cl_3N_5$	19.62	19.50
12	*p*-Benzenesulfonic acid	*p*-Benzenesulfonic acid	>300	35	$C_{14}H_{16}ClN_5O_6S_2$	15.80	15.50
13	*m*-Benzenesulfonic acid	*p*-Benzenesulfonic acid	>300	30	$C_{14}H_{16}ClN_5O_6S_2$	15.38	15.50
14	*p*-Biphenyl	*p*-Biphenyl	268	35	$C_{26}H_{24}ClN_5$	16.18	16.00
15	*p*-Biphenyl	*p*-Benzenesulfonic acid	>300	65	$C_{20}H_{20}ClN_5O_2S$	15.91	15.70

[a] All the compounds were crystallized from hot water as white crystals.

render it more resistant to detoxication by the host as well as facilitate absorption and penetration of the drug.

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Replacement of Halogen by Hydrogen in Nitro Aryl Halides: Some Applications in the Thiophene Series[1]

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The use of bromine as a blocking group during nitration of thiophene derivatives is described. The bromine in the bromonitrothiophenes is removed by treatment with hypophosphorous acid or with copper in acid medium.

The blocking groups commonly used to prevent aromatic substitution in a particular position (the sulfonic acid group which is removed by hydrolysis[3] and the nitro group which is removed by reduction to an amino group and replacement of the latter by hydrogen[4]) are *meta* directing. The methods recently described[5] for the replacement of halogen by hydrogen in nitro aryl halides permit the use of the *o,p*-directing halogens for the same purpose. This use of the halogens as removable blocking groups can be employed either for the determination of structure or for the synthesis of hitherto unavailable substituted aromatic compounds. These applications, which offer the most promise with heterocyclic aromatic compounds, are illustrated in the following paragraphs with examples from the thiophene series.

Thiophene on nitration furnishes almost exclusively the 2-nitro derivative which on further nitration yields, contrary to the usual statements,[6] principally 2,4-dinitrothiophene. The difficultly accessible 3-nitrothiophene furnishes on nitration exclusively 2,4-dinitrothiophene. On attempted further nitration, 2,4-dinitrothiophene is either unattacked or, if the conditions are sufficiently drastic, is destroyed. 2,5-Dinitrothiophene is not affected by attempts at further nitration.

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(2) Present address: Merck & Co., Rahway, N. J.

(3) *o*-Chlorophenol: Takagi and Kutani, *J. Pharm. Soc. Japan*, **517**, 260 (1925) [*Chem. Abstr.*, **20**, 2669 (1926)]. *o*-Bromophenol: R. C. Huston and M. M. Ballard, *Org. Syntheses*, **Coll. Vol. II**, 97 (1943).

(4) N. Kornblum, *Org. Reactions*, **II**, 262 (1944).

(5) A. H. Blatt and Norma Gross, *J. Org. Chem.*, **22**, 1046 (1957).

(6) A clarification of some inconsistencies in the chemistry of the mononitrothiophenes and the 2,4- and 2,5-dinitrothiophenes is given in the accompanying note, p. 1693.