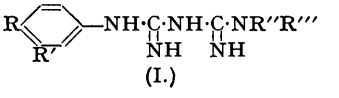
387. *Synthetic Antimalarials. Part XLVII.** N^1-3 : 4-*Dihalogenophenyl*-N^5-*alkyl- and* -N^5N^5-*dialkyl-diguanides.*

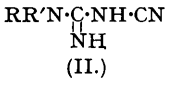
By A. F. Crowther, (the late) F. H. S. Curd, D. G. Davey, J. A. Hendry, W. Hepworth, and F. L. Rose.

Diguanides related to " Paludrine," but carrying various mono- and polyhalogenophenyl groups in place of *p*-chlorophenyl, have been made and examined for antimalarial activity. The 3 : 4-dihalogeno-derivatives are the most effective. *ortho*-Substitution always destroys antimalarial activity.

In previous papers in this series (Part X, *J.*, 1946, 729; Part XXVIII, *J.*, 1948, 1630) we have described the preparation of N^1-alkyl-N^5-aryl- and N^1N^1-dialkyl-N^5-aryl-diguanides, including " Paludrine " (Proguanil), which have high antimalarial activity. During an extension of the search for still more active compounds the six isomeric N^1-dichlorophenyl-N^5-*iso*propyldiguanides were prepared and examined for their action against *P. gallinaceum* in chicks. The four isomers containing *ortho*-chlorine atoms were inactive. The 3 : 5-dichloro-compound was roughly comparable with Proguanil (I; R = Cl, R′ = R″ = H, R‴ = Pr^i) in activity and the 3 : 4-dichloro-compound had an activity completely unprecedented in this series (see Table I). Its suppressive activity (roughly 5—10 times that of Proguanil on a dosage basis) stimulated the search amongst similar compounds. An exhaustive study was made of the nine possible combinations of (I; R = Cl, Br, or I; R′ = Cl, Br, or I; R″ = Pr^i; R‴ = H) and similarly



(I.)



(II.)

with (I; R″ = Et, R‴ = H), (I; R″ = Pr^n, R‴ = H), (I; R″ = Me, R‴ = Pr^n), (I; R″ = Me, R‴ = Pr^i). In addition the series (I; R = R′ = Cl) was extended to include the terminal groupings methyl, *n*-butyl, *sec.*-butyl, *iso*butyl, dimethyl, and diethyl. The biological results are set out in Tables II—VI.

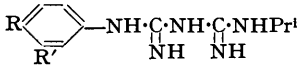
For any given aryl grouping the compound with a terminal *iso*propyl group was invariably the most active. Terminal ethyl, *n*-propyl, and methyl-*iso*propyl groups conferred a somewhat lower activity, whilst the methyl-*n*-propyl group was even less effective.

All the 3 : 4-dihalogeno-compounds examined have shown markedly higher activities than the corresponding members of the *p*-halogeno-series and, as will be seen from study of Table II, the choice made of the particular halogen atom had little influence on the therapeutic effect. It is of interest that (I; R = R′ = Cl, R″ = Me, R‴ = H) had some slight antimalarial activity whereas (I; R = Cl, R′ = R″ = H, R‴ = Me) was inactive at the highest possible dose (Part X, *loc. cit.*).

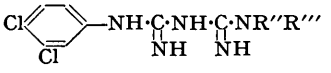
* Part XLVI, *J.*, 1951, 1038.

TABLE I. $Cl_2C_6H_3\cdot NH\cdot C(=NH)\cdot NH\cdot C(=NH)\cdot NHPr^i$

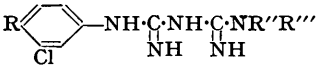
Ref. no.	Position of Cl relative to diguanide chain.	Dose, mg./kg.	Activity.	Ref. no.	Position of Cl relative to diguanide chain.	Dose, mg./kg.	Activity.
5942	2 : 3	40	—	5911	2 : 6	20	—
5559	2 : 4	40	—	5943	3 : 4	1	+++
5740	2 : 5	40	—	5912	3 : 5	6·5	+++

TABLE II. 

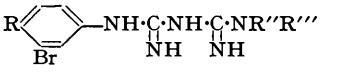
Ref. no.	R.	R′.	Dose, mg./kg.	Activity.	Ref. no.	R.	R′.	Dose, mg./kg.	Activity.
6173	Br	Cl	0·7	+++	6422	Cl	I	0·8	+++
6174	I	Cl	0·8	+++	6428	Br	I	0·9	+++
6366	Cl	Br	0·7	+++	6423	I	I	1·4	+++
6282	Br	Br	0·4	+++	7767	MeO	Cl	40	++
6326	I	Br	0·9	+++					

TABLE III. 

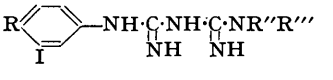
Ref. no.	R″.	R‴.	Dose, mg./kg.	Activity.	Ref. no.	R″.	R‴.	Dose, mg./kg.	Activity.
7395	Me	H	40	++	7396	Bu^i	H	40	++
7392	Et	H	2·5	+++	7408	Me	Me	40	+
7390	Pr^n	H	2·6	+++	7391	Me	Pr^i	2·7	++
7411	Bu^n	H	13·5	+++	7410	Et	Et	6·8	+++
7409	*sec.*-Bu	H	6·8	+++					

TABLE IV. 

Ref. no.	R.	R″.	R‴.	Dose, mg./kg.	Activity.	Ref. no.	R.	R″.	R‴.	Dose, mg./kg.	Activity.
6483	Br	Et	H	1·8	+++	6502	I	Et	H	4·0	+++
6485	Br	Pr^n	H	7·4	+++	6486	I	Pr^n	H	10·0	+++
6586	Br	Me	Pr^n	15·3	+++	6675	I	Me	Pr^n	34·4	+++
6484	Br	Me	Pr^i	5·0	+++	6487	I	Me	Pr^i	3·9	+++

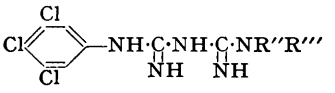
TABLE V. 

Ref. no.	R.	R″.	R‴.	Dose, mg./kg.	Activity.	Ref. no.	R.	R″.	R‴.	Dose, mg./kg.	Activity.
6716	Cl	Et	H	3·5	+++	7013	Br	Me	Pr^n	17·8	+++
6914	Cl	Pr^n	H	7·2	+++	6831	Br	Me	Pr^i	8·6	+++
6857	Cl	Me	Pr^n	15·2	+++	6858	I	Et	H	4·5	+++
6717	Cl	Me	Pr^i	7·6	+++	6859	I	Pr^n	H	3·7	+++
7012	Br	Et	H	3·2	+++	7035	I	Me	Pr^n	18·9	++
6815	Br	Pr^n	H	0·8	+++	7079	I	Me	Pr^i	3·8	+++

TABLE VI. 

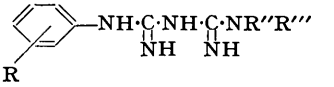
Ref. no.	R.	R″.	R‴.	Dose, mg./kg.	Activity.	Ref. no.	R.	R″.	R‴.	Dose, mg./kg.	Activity.
6600	Cl	Et	H	8·0	+++	6623	Br	Me	Pr^n	37·6	++
6602	Cl	Pr^n	H	16·6	+++	6624	Br	Me	Pr^i	9·4	+++
6603	Cl	Me	Pr^n	34·4	++	7892	I	Et	H	20·0	+++
6601	Cl	Me	Pr^i	8·6	+++	7263	I	Pr^n	H	5·0	+++
6622	Br	Et	H	8·9	+++	7159	I	Me	Pr^n	21·0	—
7264	Br	Pr^n	H	4·6	+++	6625	I	Me	Pr^i	6·5	+++

TABLE VII.



Ref. no.	R″.	R‴.	Dose, mg./kg.	Activity.	Ref. no.	R″.	R‴.	Dose mg./kg.	Activity.
7163	Et	H	27·6	+++	6063	Pr^i	H	5·0	+++
6912	Pr^n	H	7·2	++	6911	Me	Pr^i	10·0	+++

TABLE VIII.



Ref. no.	R.	R″.	R‴.	Dose, mg./kg.	Activity.	Ref. no.	R.	R″.	R‴.	Dose, mg./kg.	Activity.
6755	*m*-Cl	Et	H	22·1	++	6352	*m*-I	Pr^i	H	30·4	+++
6574	*m*-Cl	Pr^n	H	92·8	++	6509	*p*-I	Et	H	7·2	+++
6756	*m*-Br	Et	H	51·2	+++	6573	*p*-I	Pr^n	H	10·0	+++
6575	*m*-Br	Pr^n	H	107·0	++	6572	*p*-I	Bu^n	H	63·2	+++
6246	*m*-Br	Pr^i	H	10·0	+++	6867	*p*-I	Bu^i	H	40·0	+
6774	*m*-I	Et	H	58·7	++	6605	*p*-I	Me	Pr^n	15·8	+++
6950	*m*-I	Pr^n	H	30·4	++						

Several N^1-3 : 4 : 5-trichlorophenyl-N^5-alkyl- and -N^5N^5-dialkyl-diguanides were also prepared and examined. High activity, of the same order as that of the *p*-chloro-series, was encountered (Table VII).

The monohalogenoaryldiguanide series has also been extended (Table VIII), in order to give a more complete picture of the activity of this type of compound. There was little difference in activity between corresponding members of the selected group (I; R = R″ = H, R′ = halogen, R‴ = alkyl), and the *p*-iodo-compounds were roughly equal in chemotherapeutic effectiveness to the corresponding members of the *p*-chloro-series (Part X, *loc. cit.*).

The activity in a causal prophylaxis test was found to parallel the therapeutic activity in all cases.

The diguanides described herein were all prepared by one or other or both of the methods described in Part XXVIII (*loc. cit.*). In the first of these an aryldicyandiamide (II; R = aryl, R′ = H) was condensed with an alkyl- or dialkyl-amine hydrochloride in nitrobenzene at about 135°. The other method was the converse of this. An arylamine hydrochloride was condensed with an alkyl- or dialkyl-dicyandiamide (II; R = alkyl, R′ = H or alkyl), usually in 2-ethoxyethanol. Both the aryl- and the alkyl-dicyandiamides were prepared from sodium dicyanamide and the appropriate amine hydrochloride (Part XXVIII, *loc. cit.*).

EXPERIMENTAL.

4-Bromo-3-chloroaniline.—4-Bromo-3-chloroacetanilide (20 g.; Wheeler and Valentine, *Amer. Chem. J.*, **1899**, **22**, 270) was boiled under reflux with 5N-hydrochloric acid (50 c.c.) for 3 hours. The solution was cooled, and the crystals which separated were filtered off, washed with a little water, and dried (14·6 g.). Crystallisation from 2N-hydrochloric acid gave *4-bromo-3-chloroaniline hydrochloride* as colourless plates, m. p. 227° (Found: N, 6·1. C_6H_5NClBr,HCl requires N, 5·8%).

3-Bromo-4-chloroaniline.—(*a*) *m*-Bromoacetanilide (15·5 g.) was dissolved in glacial acetic acid (60 c.c.) and chlorine (5·4 g.) was passed into the solution. The mixture was kept at room temperature for 30 minutes and the solid was then filtered off, washed with acetic acid, drained thoroughly, and crystallised from aqueous ethanol, giving 4-chloro-3-bromoacetanilide (3·2 g.), m. p. 127—128° (Chattaway and Orton, *J.*, **1901**, **79**, 466, gave m. p. 130°). Dilution of the acetic acid liquors with water (400 c.c.) gave probably 5-bromo-2-chloroacetanilide, colourless needles (from aqueous ethanol), m. p. 138—140° (Chattaway and Orton, *loc. cit.*, gave m. p. 141°). The 3-bromo-4-chloroacetanilide (7·2 g.) was hydrolysed by boiling it with 5N-hydrochloric acid (16 c.c.) for 30 minutes. The mixture was cooled, and the crystals were filtered off, washed with 2N-hydrochloric acid, and dried, giving colourless needles (6·0 g.) (from ethanol) of *3-bromo-4-chloroaniline hydrochloride*, m. p. 243—244° (Found: N, 6·2. C_6H_5NClBr,HCl requires N, 5·8%). Conversion into the base gave colourless plates [from light petroleum (b. p. 60—80°)], m. p. 81·5—82° (Found: N, 6·95. Calc. for C_6H_5NClBr: N, 6·8%). Chattaway and Orton (*loc. cit.*) gave m. p. 78°.

(*b*) 2-Bromo-1-chloro-4-nitrobenzene (65 g.) (Körner and Contardi, *R. Accad. Lincei*, **1913**, [v], **22**, I, 825; *Chem. Abs.*, **1914**, **8**, 74) [from 2-bromo-4-nitroaniline (Körner and Contardi, *R. Accad. Lincei*, **1914**, [v], **23**, I, 285; *Zentr.*, **1914**, **85**, II, 470)] was suspended in ethanol (450 c.c.) and added slowly to a solution of stannous chloride (190 g.) in 10N-hydrochloric acid (400 c.c.) at 20—30°. The mixture was then stirred at 60° for 24 hours and steam-distilled to remove the ethanol, and the residue made strongly alkaline with 10N-sodium hydroxide and again steam-distilled. 3-Bromo-4-chloroaniline solidified in the receiver, was filtered off, and dried (41 g.); it had m. p. 74—78°.

3-*Chloro*-4-*iodoaniline*.—The method of Dains, Vaughan, and Janney (*J. Amer. Chem. Soc.*, 1918, **40**, 934) in which *m*-chloroaniline is iodinated was used. It was found convenient to use benzene instead of ether as the solvent.

3 : 4-*Dibromoaniline*.—(*a*) 1 : 2-Dibromo-4-nitrobenzene was prepared by dissolving 2-bromo-4-nitroaniline (65 g.) in a mixture of acetic acid (375 c.c.) and sulphuric acid (225 c.c.). The solution was diluted with water (225 c.c.), then cooled to 0°, and a solution of sodium nitrite (22 g.) in water (225 c.c.) was added slowly with stirring and cooling. The solution was set aside for 1 hour and then added dropwise with stirring and cooling to a solution of cuprous bromide [from copper sulphate crystals (75 g.)] in hydrobromic acid (126 c.c.; 48%). The mixture was then warmed to 40° and then kept at room temperature for 16 hours. Water (5 l.) was added and, after 3 hours, the solid was filtered off, washed with water, and dried (85 g.; m. p. 54—57°). Riese (*Annalen*, 1872, **164**, 179) gave m. p. 58°.

The nitro-compound was reduced in the same manner as 2-bromo-1-chloro-4-nitrobenzene (see above). The first runnings of the final steam-distillation appeared to contain *m*-bromoaniline, but the remainder of the distillate gave 3 : 4-dibromoaniline, colourless prisms (from aqueous ethanol), m. p. 77—79°. Körner (*Gazzetta*, 1874, **4**, 370) gave m. p. 80·4°.

(*b*) 3 : 4-Dibromoacetanilide (Körner, *Gazzetta*, 1895, **25**, I, 96) was hydrolysed by boiling 5N-hydrochloric acid and gave colourless needles (from 2N-hydrochloric acid) of 3 : 4-dibromoaniline hydrochloride, m. p. 226° (Found : N, 4·95. Calc. for $C_6H_5NBr_2,HCl$: N, 4·9%). (Körner, *loc. cit.*, gave m. p. 220—230°). Treatment with 2N-sodium hydroxide gave the base, m. p. 80—81°.

3-*Bromo*-4-*iodoaniline*.—An attempt to prepare this amine by the reduction of 2-bromo-1-iodo-4-nitrobenzene (Körner, *ibid.*, 1874, **4**, 385) with stannous chloride gave only *m*-bromoaniline. It was therefore made by the method of Dains, Vaughan, and Janney (*loc. cit.*).

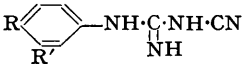
4-*Chloro*-3-*iodoaniline*.—(*a*) 1-Chloro-2-iodo-4-nitrobenzene (10·6 g.; Körner and Contardi, *R. Accad. Lincei*, 1913, [v], **22**, I, 825; *Chem. Abs.*, 1914, **8**, 74; from 2-chloro-5-nitroaniline), stannous chloride (25·4 g.), 10N-hydrochloric acid (50 c.c.), and ethanol (20 c.c.) were stirred together at 60° for 24 hours. 10N-Sodium hydroxide was added in excess and the mixture was steam-distilled. The pale yellow oil, which distilled, rapidly crystallised, was filtered off, washed with water, dried, and gave colourless plates of 4-*chloro*-3-*iodoaniline*, m. p. 70° (Found : N, 6·05. C_6H_5NClI requires N, 5·5%). The *hydrochloride* formed colourless needles from 2N-hydrochloric acid, m. p. 241° (Found : C, 24·95; H, 2·65; N, 5·2. C_6H_5NClI,HCl requires C, 24·8; H, 2·1; N, 4·8%).

(*b*) Iodine monochloride (81·25 g.) in glacial acetic acid (300 c.c.) was added to a stirred solution of *p*-nitroaniline (69 g.) in glacial acetic acid (400 c.c.) at 20—25° during 15 minutes. The mixture was kept at room temperature for 16 hours, filtered from a small amount of solid, and poured into water (6 l.). The pale yellow crystals of 2-iodo-4-nitroaniline were filtered off, washed with water, and dried at 60° (109 g.; m. p. 105—106°) (Willgerodt and Arnold, *Ber.*, 1901, **34**, 3344, described a slightly more elaborate procedure and gave m. p. 105°).

The 2-iodo-4-nitroaniline (26·4 g.), dissolved in glacial acetic acid (125 c.c.) and sulphuric acid (75 c.c.), was added to ice (75 g.). The mixture was stirred at 0° whilst a solution of sodium nitrite (7·25 g.) in water (75 c.c.) was slowly added, and then added dropwise to a stirred solution of cuprous chloride (12 g.) in 10N-hydrochloric acid (25 c.c.) at 0°. Reaction was completed by stirring for 1 hour at 0—10° and then on the steam-bath until all the nitrogen had been evolved. The solution was poured into water (1 l.), and the solid filtered off, washed with water, and dried. The 1-chloro-2-iodo-4-nitrobenzene, purified slightly by dissolution in ethanol and reprecipitation by water (24·3 g.), had m. p. 68° (Körner and Contardi, *loc. cit.*, gave m. p. 78°).

This crude nitro-compound was shaken in methanol (100 c.c.) with Raney nickel and hydrogen at room temperature and pressure. When reaction was complete, the mixture was filtered and 10N-hydrochloric acid (100 c.c.) added to the filtrate. Almost colourless needles of 4-chloro-3-iodoaniline hydrochloride separated and were filtered off, washed with ethanol, and dried (17·5 g.); they had m. p. 236° (Found : Cl′, 12·1. Calc. for C_6H_5NClI,HCl : Cl′, 12·2%).

TABLE IX.



				Found, %.			Required, %.			
R.	R′.	M. p.	Formula.	C.	H.	N.	C.	H.	N.	Remarks.*
H	Br	233—234°	$C_8H_7N_4Br$	40·15	2·85	—	40·2	2·9	—	Feathery needles.†
H	I	236—237	$C_8H_7N_4I$	33·6	2·65	19·1	33·6	2·45	19·6	Needles.
Cl	Cl	237—238	$C_8H_6N_4Cl_2$	42·35	2·9	24·45	41·9	2·6	24·5	—
Br	Cl	234	$C_8H_6N_4ClBr$	35·1	2·05	—	35·1	2·2	—	†
I	Cl	241	$C_8H_6N_4ClI$	29·9	1·8	17·1	29·95	1·9	17·5	†
Cl	Br	234	$C_8H_6N_4ClBr$	35·05	2·25	20·4	35·1	2·2	20·5	Flat needles.
Br	Br	244—245	$C_8H_6N_4Br_2$	30·55	2·0	18·0	30·2	1·9	17·6	Needles.
I	Br	251—252	$C_8H_6N_4BrI$	27·2	1·65	15·2	26·3	1·6	15·3	Needles.
Cl	I	227—228	$C_8H_6N_4ClI$	29·75	2·1	17·3	29·95	1·9	17·5	Buff-coloured plates.

* Crystd. from EtOH unless marked †.

† Purified by dissolution in sodium hydroxide solution and reprecipitation by dilute hydrochloric acid.

TABLE X.

Ref. no.	Method of prep.	M. p.	Formula.	Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.	Remarks.
Compounds of Table I.												
5942	b	245—246°	$C_{11}H_{15}N_5Cl_2,HCl$	40·55	4·75	21·1	—	40·7	4·9	21·6	—	
5559	b	249	$C_{11}H_{15}N_5Cl_2,HCl$	41·05	5·1	21·65	—	40·7	4·9	21·6	—	Prepd. in water.
5740	b	234—235	$C_{11}H_{15}N_5Cl_2,HCl$	41·05	5·1	21·6	—	40·7	4·9	21·6	—	Prepd. in aqueous dioxan.
5911	b	245—246	$C_{11}H_{15}N_5Cl_2,HCl$	40·95	5·15	21·65	—	40·7	4·9	21·6	—	
5943	a and b *	246	$C_{11}H_{15}N_5Cl_2,HCl$	41·0	5·05	21·1	—	40·7	4·9	21·6	—	
5912	b	239—240	$C_{11}H_{15}N_5Cl_2,HCl$	40·65	4·95	21·6	—	40·7	4·9	21·6	—	
Compounds of Table II.												
6173	b	237	$C_{11}H_{15}N_5ClBr,HCl$	35·45	4·15	18·95	—	35·3	4·3	19·0	—	Rods.
6174	a and b	220—222	$C_{11}H_{15}N_5ClI,HCl$	Identical with material described in Part XLVIII.								
6366	b	239	$C_{11}H_{15}N_5ClBr,HCl$	35·4	4·25	18·95	—	35·3	4·3	19·0	—	Plates.
6282	b	240	$C_{11}H_{15}N_5Br_2,HCl$	32·05	3·8	16·95	—	31·9	3·9	16·9	—	Prisms.
6326	b	236	$C_{11}H_{15}N_5BrI,HCl$	28·3	3·65	15·1	—	28·7	3·5	15·2	—	Plates.
6422	b	238	$C_{11}H_{15}N_5ClI,HCl$	32·0	3·85	16·85	—	31·7	3·9	16·8	—	Plates.
6428	b	239	$C_{11}H_{15}N_5BrI,HCl$	28·95	3·1	15·05	—	28·7	3·5	15·2	—	Plates.
6423	b	237	$C_{11}H_{15}N_5I_2,HCl$	26·3	3·4	13·65	—	26·0	3·2	13·8	—	Plates.
7767	b	233—234	$C_{12}H_{18}ON_5Cl,HCl$	44·95	5·9	21·7	—	45·0	5·9	21·9	—	Plates.
Compounds of Table III.												
7395	a	233	$C_9H_{11}N_5Cl_2,HCl$	36·75	4·1	23·9	—	36·4	4·0	23·6	—	Plates.
7392	b	216	$C_{10}H_{13}N_5Cl_2,HCl$	37·9	4·35	23·0	—	38·65	4·5	22·5	—	Curved rods.
7390	b	237—238	$C_{11}H_{15}N_5Cl_2,HCl$	40·8	4·45	21·25	—	40·7	4·9	21·6	—	Plates.
7411	b	197	$C_{12}H_{17}N_5Cl_2,HCl$	42·8	5·1	20·35	—	42·55	5·3	20·7	—	Rods.
7409	b	250	$C_{12}H_{17}N_5Cl_2,HCl$	42·25	5·6	21·2	—	42·55	5·3	20·7	—	Needles.
7396	b	221	$C_{12}H_{17}N_5Cl_2,HCl$	42·55	5·95	21·15	—	42·55	5·3	20·7	—	Prisms.
7408	a and b	271	$C_{10}H_{13}N_5Cl_2,HCl$	38·9	4·1	22·8	—	38·65	4·5	22·5	—	Needles.
7391	b	251—252	$C_{12}H_{17}N_5Cl_2,HCl$	42·75	5·3	20·45	—	42·55	5·3	20·7	—	Fine needles.
7410	a and b	231	$C_{12}H_{17}N_5Cl_2,HCl$	42·45	5·45	20·5	—	42·55	5·3	20·7	—	Flat rods.
Compounds of Table IV.												
6483	b	217	$C_{10}H_{13}N_5ClBr,HCl$	34·25	4·4	20·1	—	33·8	3·9	19·7	—	Plates.
6485	b	217	$C_{11}H_{15}N_5ClBr,HCl$	36·15	4·6	19·0	—	35·3	4·3	19·0	—	Fine needles.
6586	b	234	$C_{12}H_{17}N_5ClBr,HCl$	38·0	5·0	18·3	—	37·6	4·7	18·3	—	Needles.
6484	b	244	$C_{12}H_{17}N_5ClBr,HCl$	37·75	5·0	18·3	—	37·6	4·7	18·3	—	Needles.
6502	b †	226—227	$C_{10}H_{13}N_5ClI,HCl$	29·9	3·25	17·35	—	29·85	3·5	17·4	—	Minute rods.
6486	b †	225	$C_{11}H_{15}N_5ClI,HCl$	31·75	3·95	16·75	—	31·7	3·9	16·8	—	Small needles.
6675	b †	229—230	$C_{12}H_{17}N_5ClI,HCl$	33·85	4·25	15·8	—	33·6	4·2	16·3	—	Needles.
6487	b †	231	$C_{12}H_{17}N_5ClI,HCl$	33·6	4·25	16·0	—	33·6	4·2	16·3	—	Needles.

Compounds of Table V.												
6716	b	215—216	$C_{10}H_{13}N_5ClBr,HCl$	33·9	3·7	20·05	—	33·8	3·9	19·7	—	Plates.
6914	b	197—198	$C_{11}H_{15}N_5ClBr,HCl$	35·8	4·5	18·75	—	35·3	4·3	19·0	—	Small needles.
6857	b	232	$C_{12}H_{17}N_5ClBr,HCl$	37·5	4·65	18·15	—	37·6	4·7	18·3	—	Needles.
6717	b	240—241	$C_{12}H_{17}N_5ClBr,HCl$	37·55	4·85	19·05	—	37·6	4·7	18·3	—	Needles.
7012	b	213—214	$C_{10}H_{13}N_5Br_2,HCl$	30·4	3·6	16·6	—	30·0	3·5	17·5	—	
6815	b	218	$C_{11}H_{15}N_5Br_2,HCl$	32·2	3·7	16·5	—	31·9	3·9	16·9	—	Needles.
7013	b	234—235	$C_{12}H_{17}N_5Br_2,HCl$	33·8	4·35	17·1	—	33·7	4·2	16·4	—	Needles.
6831	b	234—235	$C_{12}H_{17}N_5Br_2,HCl$	33·95	3·9	16·3	—	33·7	4·2	16·4	—	Thick needles.
6858	b	220—221	$C_{10}H_{13}N_5BrI,HCl$	26·75	2·9	14·9	—	26·9	3·1	15·7	—	Minute needles.
6859	b	227—228	$C_{11}H_{15}N_5BrI,HCl$	28·8	3·4	14·6	—	28·7	3·5	15·2	—	Rods.
7035	b	228—229	$C_{12}H_{17}N_5BrI,HCl$	30·2	3·7	14·15	—	30·35	3·8	14·75	—	Rods.
7079	b	232—233	$C_{12}H_{17}N_5BrI,HCl$	30·7	3·9	15·0	—	30·35	3·8	14·75	—	Needles.
Compounds of Table VI.												
6600	b	197—198	$C_{10}H_{13}N_5ClI,HCl$	29·7	3·35	16·85	8·45	29·85	3·5	17·4	8·8	Prisms.
6602	b	198—199	$C_{11}H_{15}N_5ClI,HCl$	31·6	3·25	16·8	—	31·7	3·9	16·8	—	Minute needles.
6603	b	205—206	$C_{12}H_{17}N_5ClI,HCl$	33·2	3·8	16·2	8·15	33·6	4·2	16·3	8·5	Rods.
6601	b	239—240	$C_{12}H_{17}N_5ClI,HCl$	32·9	4·4	16·5	8·3	33·6	4·2	16·3	8·5	Prisms.
6622	b	200—201	$C_{10}H_{13}N_5BrI,HCl$	26·2	3·3	15·6	7·8	26·9	3·1	15·7	7·9	Needles.
7264	b	232—233	$C_{11}H_{15}N_5BrI,HCl$	29·45	3·65	14·9	7·7	28·7	3·5	15·2	7·7	Needles.
6623	b	208—209	$C_{12}H_{17}N_5BrI,HCl$	30·4	3·8	14·65	7·3	30·35	3·8	14·75	7·5	Needles.
6624	b	241—242	$C_{12}H_{17}N_5BrI,HCl$	30·45	3·7	14·5	7·7	30·35	3·8	14·75	7·5	Prisms.
7892	b	212—213	$C_{10}H_{13}N_5I_2,HCl$	24·05	3·2	14·05	—	24·3	2·8	14·2	—	
7263	b	226—227	$C_{11}H_{15}N_5I_2,HCl$	26·3	3·2	13·5	7·0	26·0	3·2	13·8	7·0	Plates.
7159	b	221	$C_{12}H_{17}N_5I_2,HCl$	28·3	3·6	13·2	6·75	27·6	3·5	13·4	6·8	Rods.
6625	b	235	$C_{12}H_{17}N_5I_2,HCl$	28·05	3·1	13·55	6·75	27·6	3·5	13·4	6·8	Needles.
Compounds of Table VII.												
7163	b	239—240	$C_{10}H_{12}N_5Cl_3,HCl$	34·85	3·9	19·8 20·2	—	34·8	3·8	20·3	—	Needles.
6912	b	228—229	$C_{11}H_{14}N_5Cl_3,HCl$	36·15	4·15	19·3	—	36·8	4·2	19·5	—	Minute rods.
6063	b	254—255	$C_{11}H_{14}N_5Cl_3,HCl$	36·85	4·3	19·3	—	36·8	4·2	19·5	—	
6911	b	234—235	$C_{12}H_{16}N_5Cl_3,HCl$	38·65	4·8	18·5	—	38·6	4·6	18·8	—	Needles.
Compounds of Table VIII.												
6755	b	210—211°	$C_{10}H_{14}N_5Cl,HCl$	43·7	5·35	25·1	—	43·5	5·4	25·35	—	Fine needles.
6574	b	194—195	$C_{11}H_{16}N_5Cl,HCl$	45·65	5·65	24·6	12·3	45·5	5·8	24·15	12·2	Rods.
6756	b	216—217	$C_{10}H_{14}N_5Br,HCl$	37·7	4·65	21·5	—	37·4	4·7	21·8	—	Platelets.
6575	b	194—195	$C_{11}H_{16}N_5Br,HCl$	39·2	5·25	20·7	10·5	39·5	5·1	20·9	10·6	Minute prisms.
6246	a	218	$C_{11}H_{16}N_5Br,HCl$	39·6	5·8	20·4	—	39·5	5·1	20·9	—	Microcrystals.
6774	b	226—227	$C_{10}H_{14}N_5I,HCl$	32·9	4·0	19·0	—	32·65	4·1	19·0	—	Rods.
6950	a	208—209	$C_{11}H_{16}N_5I,HCl$	34·75	4·6	18·45	—	34·6	4·45	18·35	—	Minute prisms.
6352	b	246	$C_{11}H_{16}N_5I,HCl$	35·3	4·5	18·2	—	34·6	4·45	18·35	—	Elongated prisms.
6509	b	239—240	$C_{10}H_{14}N_5I,HCl$	32·6	4·05	18·9	—	32·65	4·1	19·0	—	Needles.
6573	b ‡	222—224	$C_{11}H_{16}N_5I,HCl$	34·3	4·35	—	9·3	34·6	4·45	—	9·3	Needles from EtOH–EtOAc.
6572	b	207	$C_{12}H_{18}N_5I,HCl$	36·2	4·5	17·7	—	36·4	4·8	17·7	—	Prisms from EtOH–EtOAc.
6867	b	231	$C_{12}H_{18}N_5I,HCl$	36·2	5·05	17·3	—	36·4	4·8	17·7	—	Plates.
6605	b ‡	238	$C_{12}H_{18}N_5I,HCl$	36·7	5·0	18·05	—	36·4	4·8	17·7	—	Needles.

* Experiment performed by Mr. S. Birtwell. † Compounds prepared by Dr. G. J. Stacey. ‡ Prepared in water.

4-Bromo-3-iodoaniline.—Ice (75 g.) was added to a cold solution of 2-iodo-4-nitroaniline (26·4 g.) in acetic acid (125 c.c.) and sulphuric acid (75 c.c.). Sodium nitrite (7·25 g.) in water (75 c.c.) was added at 0° during 30 minutes. The mixture was stirred at 0° for 1 hour and then added to a stirred solution of cuprous bromide [from copper sulphate pentahydrate (25 g.)] in hydrobromic acid (42 c.c.; 50%) at −5° to 0° during 1 hour. The mixture was stirred for a further hour at 0—10° then at 80° until all the nitrogen was evolved, cooled to 40°, and poured into ice-cold water (1 l.). The pale brown granular solid was filtered off, washed with water, and dried (32·4 g.). Crystallisation from methanol afforded buff-coloured prisms of 1-bromo-2-iodo-4-nitrobenzene, m. p. 96—99°. Wheeler and Valentine (*loc. cit.*) gave m. p. 95—96°.

The nitro-compound was reduced either by stannous chloride in hydrochloric acid, or catalytically with Raney nickel and hydrogen as for the previous amine, giving 4-bromo-3-iodoaniline as colourless plates [from light petroleum (b. p. 60—80°)], m. p. 77·5°. It gave the hydrochloride, m. p. 222°, and an acetyl derivative, colourless prisms (from aqueous ethanol), m. p. 137—139°. Wheeler and Valentine, *loc. cit.*, gave m. p. 77°, 210°, and 138—139° respectively.

3 : 4-*Di-iodoaniline.*—The base was prepared according to the method of Brenans (*Bull. Soc. chim.*, 1903, **29**, 604) and gave the *hydrochloride*, colourless needles, m. p. 199°, from ethanol–ethyl acetate (Found : N, 4·1, 4·05. $C_6H_5NI_2$,HCl requires N, 3·7%).

*Methyl-*n*-propyldicyandiamide* (II; R = Me, R′ = Pr^n).—Methyl-*n*-propylamine hydrochloride (43·5 g.), sodium dicyanamide (35 g.), and butanol (100 c.c.) were stirred together under reflux for 3 hours. The mixture was cooled and filtered and the filtrate evaporated under reduced pressure. The residual syrup did not crystallise and was used in this state for the preparation of diguanide derivatives.

sec.-*Butyldicyandiamide* (II; R = *sec.*-Bu, R′ = H).—*sec.*-Butylamine hydrochloride (11 g.), sodium dicyanamide (9 g.), and butanol (75 c.c.) were stirred together under reflux for 3 hours. The cooled suspension was filtered and the filtrate evaporated to small bulk. Crystals separated. These were filtered off, washed with butanol, and dried (2·0 g.). Crystallisation from butanol gave colourless plates of N^1N^5-*di*-sec.-*butyldiguanide hydrochloride*, m. p. 264° (Found : C, 48·9; H, 10·35; N, 28·15. $C_{10}H_{23}N_5$,HCl requires C, 48·1; H, 9·7; N, 28·1%). The butanol liquors were evaporated to dryness leaving crude *sec.*-butyldicyandiamide as an uncrystallisable syrup, which was used as such for the preparation of a diguanide derivative.

Aryldicyandiamides (II; R = aryl, R′ = H).—Table IX records *dicyandiamides* prepared from sodium dicyanamide and the appropriate arylamine hydrochloride (Part XXVIII, *loc. cit.*).

N^1-*Aryl*-N^5-*alkyl- and* -N^5N^5-*dialkyl-diguanide Hydrochlorides.*—The diguanides were prepared by one or other or both of the two methods of Part XXVIII (*loc. cit.*), *viz.*, (*a*) from the appropriate aryldicyandiamide and alkyl- or dialkyl-amine hdrochloride heated together in nitrobenzene and (*b*) from the appropriate arylamine hydrochloride and alkyl- or *NN*-dialkyl-dicyandiamide heated together in 2-ethoxyethanol (except where otherwise stated). All the diguanide hydrochlorides were colourless crystalline solids and were recrystallised from water except where otherwise stated. The *compounds* prepared are recorded in Table X.

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