CHEMOTHERAPY OF MALARIA

Part VII. Phenylene-Diguanidine Derivatives

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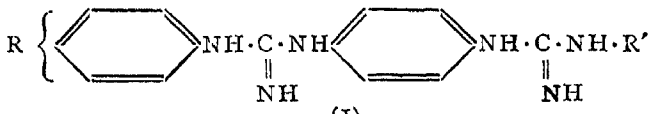
In view of the fact that some guanidine derivatives show distinct antimalarial activity[1] and that paludrine is also a biguanide, it was thought worthwhile to prepare and test compounds of general formula (I), with two guanidine groups separated by a benzene ring. Compounds of this type in which one of the guanidine residue is replaced by amidine residues have been prepared



(I)

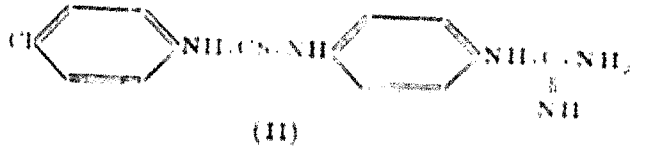
where R = H, *o*.Cl; *m*.Cl; *p*.Cl; *m*.Br; *p*.Br; *o*.Me; *m*.Me; *p*.Me; *o*.MeO; *p*.MeO.
R′ = H; isoPropyl–; *n*.Butyl.

by the English workers and found to be devoid of activity.[2] Since this work was started, compounds of type (I) have been prepared by Safer and Kushner[3] and some of these have been reported to possess trypanocidal activity.

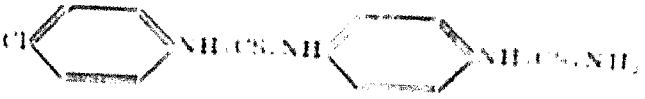
Attempts were first made to work out a general method for the synthesis of a compound (I, R = Cl; R′ = H), so that this could be used to synthesise series of the type (I). *p*-Aminophenylguanidine did not react with either *p*-chlorophenylcyanamide or S-methyl-*p*-chlorophenylisothioureas hydroiodide. This is not unexpected because the free amino group in *p*-aminophenylguanidine has been found[4] not to react with S-methyl-isothiourea sulphate to furnish the diguanidine derivative. The same negative results were obtained by using *p*-aminophenylthiourea in place of *p*-aminophenylguanidine. On the other hand, *p*-aminophenylguanidine and *p*-aminophenylthiourea condensed with *p*-chlorophenylisothiocyanate to furnish respectively-4 (4′-chlorophenylthioureido) phenyl guanidine (II) and 4 (4′ chlorophenylthioureido) phenyl phenylthiourea (III).

S-Methyl-*p*-chlorophenylisothiourea hydriodide reacted with *p*-phenylenediamine to furnish 4 (4′-chlorophenylguanidino) aniline (IV) which could also be prepared by the action of *p*-chloro phenylcyanamide on acetphenylenediamine and hydrolysing the resulting acetaminoguanidine derivative.[5] The

guanidine derivative (IV) obtained did not react with S-methylisothiourea sulphate to furnish the diguanidine but on the other hand with thiocyanic acid yielded 4-(4'-chlorophenylguanidino) phenyl thiourea (V). The best method of converting these thiourea and dithiourea derivative into guanidines proved to be to treat the S-methyl derivatives with ammonia. Treatment of the dithiourea derivatives with alcoholic ammonia and mercuric oxide furnished the corresponding diurea derivative instead of the diguanidine.



(II)



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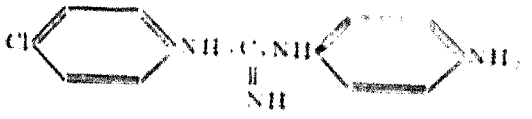
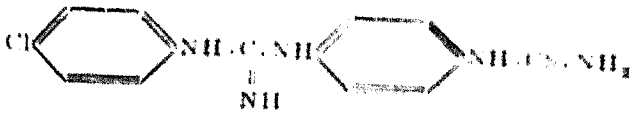


(IV)



(V)

In view of the above observations, the following general method was adopted to prepare a series of diguanidinophenyl derivatives of formula (I). The thiourea derivatives (VI, wherein R' H, isoPr, *n*.Bu) were prepared (Table I) by the methods described in the experimental part. These thioureas were in turn condensed with a number of isothiocyanates to furnish the dithioureas of formula (VII), which are listed in Table II. These dithioureas reacted with two molecular equivalents of methyliodide to yield the di-S-methyl derivatives (Table III) which by the prolonged action of ammonia furnished the guanidine derivatives of formula (I). The compounds obtained are presented in Table IV.

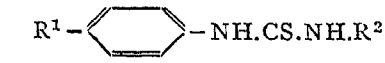
(VI)

(VII)

Eleven compounds (Nos. 63, 66, 68, 70, 71, 72, 75, 76, 78, 79 and 82) were tested for their antimalarial action on *Plasmodium berghi* in mice and were found to be devoid of activity.

TABLE I

Phenylthioureas



Serial No.	R^1	R^2	Molecular Formula	M.P./°C.	Nitrogen % Req.	Found
1	Acetamino-	H-	$C_9H_{11}N_3OS$	211–12	20·09	20·07
2	Acetamino-	*iso*-Propyl-	$C_{12}H_{17}N_3OS$	212–	16·73	16·71
3	Acetamino-	*n*-Butyl	$C_{13}H_{19}N_3OS$	185–86	15·09	15·23
4	Acetamino-	Di-ethyl-	$C_{13}H_{19}N_3OS$	213–14	15·85	16·10
5	Acetamino-	*p*-Chlorophenyl-	$C_{15}H_{14}N_3OSCl$	202–	13·01	13·14
6	Nitro-	*iso*-Propyl-	$C_{10}H_{13}N_3O_2S$	197–98	17·80	17·50
7	Amino-	H-[1]	$C_7H_9N_3S$	201–02	25·14	25·00
8	Amino-	*iso*-Propyl-[2]	$C_{10}H_{15}N_3S$	147–48	20·08	20·36
9	Amino-	*n*-Butyl-[3]	$C_{11}H_{17}N_3S$	123–24	18·83	19·01
10	Amino-	*p*-Chlorophenyl-	$C_{13}H_{12}N_3SCl$	241–43	15·19	14·91

1. Hydrochloride, m.p. 278-80° ; Picrate, m.p. 190–92°.
2. Hydrochloride, m.p. 231° (dec.); Picrate, m.p. 129–31°.
3. Hydrochloride, m.p. 238° ; Picraté, m.p. 166°.

EXPERIMENTAL

Isothiocyanates.—These were prepared according to the standard method by the action of carbon disulphide on the amines in ammonium or sodium hydroxide solution, the ammonium or the sodium salt of the dithioformic acid formed in the reaction dissolved in water, treated with a solution of copper sulphate and steam distilled or extracted with a solvent. Thus were prepared: isopropyl-, *n*-butyl-, phenyl-, *p*-chlorophenyl-, *m*-chlorophenyl- *o*-chlorophenyl-, *m*-bromophenyl-, *p*-bromophenyl-, *o*-tolyl-, *m*-tolyl-, *p*-tolyl- *o*-methoxyphenyl-, *p*-methoxyphenyl-isothiocyanates. *p*-Acetaminophenyl-isothiocyanate had m.p. 198–99° (Found: N, 14·58. $C_9H_{11}N_2OS$ requires N, 14·56%).

Phenylthioureas.—The various derivatives listed in Table I were prepared by the action of different isothiocyanates on the appropriate amines in an inert solvent. 2:4-dinitroaniline and *p*-acetaminophenylisothiocyanate did not react to furnish the thiourea derivative.

N-p-Nitrophenyl-N'-isopropylthiourea (*No.* 6).—A mixture of *p*-nitroaniline (13·9 g.) and isopropylisothiocyanate (12·1 g.) was heated in an oil-bath at 130° for 30 minutes and then at 150° for 30 minutes. The reaction mixture was cooled and diluted with ether, where by the thiourea derivative crystallised out in needles (yield, 15 g.). It was recrystallised from alcohol.

TABLE II

N^1-aryl-N^2-(p-alkylthiocarbamido)-phenylthioureas

R^1-NH CS NH-⟨ ⟩-NH CS NH R^2

Serial No.	R^1	R^2	Molecular Formula	M.P.*/ C.	Nitrogen % Req.	Found
11	H-	*iso*-Propyl-	$C_{11}H_{16}N_4S_2$	200 01	20·89	20·79
12	Phenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2$	189 90	16·32	16·50
13	Phenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2$	195 96; 214 17	15·65	15·51
14	*p*-Chlorophenyl-	H-	$C_{14}H_{13}N_4S_2Cl$	237 39;	16·64	16·49
15	*p*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Cl$	190 91; 214 17	14·83	14·48
16	*p*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Cl$	219 21	14·26	14·00
17	*o*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Cl$	197 98, above 290	14·83	15·25
18	*o*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Cl$	192 93; 211 13	14·26	14·21
19	*m*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Cl$	187 88; 205 06	14·83	15·09
20	*m*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Cl$	181 83; 215 17	14·26	13·88
21	*p*-Bromophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Br$-	214 18	13·27	13·36
22	*p*-Bromophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Br$-	219 20	12·81	12·88
23	*m*-Bromophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Br$	171 72; 197 98	13·27	13·29
24	*m*-Bromophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Br$	179 80; 215 19	12·81	12·45
25	*p*-Tolyl-	*iso*-Propyl-	$C_{18}H_{21}N_4S_2$	168 70	15·68	16·01
26	*p*-Tolyl-	*n*-Butyl-	$C_{19}H_{23}N_4S_2$	195 96; 215 17	15·04	15·17
27	*m*-Tolyl-	*iso*-Propyl	$C_{18}H_{21}N_4S_2$	172 73; 209 12	15·68	15·50
28	*m*-Tolyl-	*n*-B-Pyl-	$C_{19}H_{23}N_4S_2$	176 77; 215 18	15·04	14·85
29	*o*-Tolyl-	*iso*-Propyl-	$C_{18}H_{21}N_4S_2$	190 91	15·68	15·47
30	*o*-Tolyl-	*n*-Butyl-	$C_{19}H_{23}N_4S_2$	186 87; 214 16	15·04	14·78
31	*p*-Anisyl-	*iso*-Propyl-	$C_{18}H_{21}N_4S_2O$	174 75; 220 21	14·90	14·75
32	*p*-Anisyl-	*n*-Butyl-	$C_{19}H_{23}N_4S_2O$	215 18	14·42	14·59
33	*o*-Anisyl-	*iso*-Propyl-	$C_{18}H_{21}N_4S_2O$	188 90	14·90	14·92
34	*o*-Anisyl-	*n*-Butyl-	$C_{19}H_{23}N_4S_2O$	181 82; 214 18	14·42	14·43
35	*iso*-Propyl-	*iso*-Propyl-	$C_{14}N_{22}N_4S_2$	220 21	18·06	17·87

* Most of the compounds from this series first melt, resolidify and melt again.

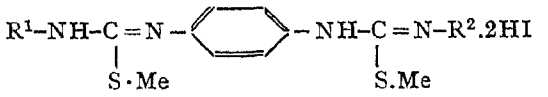
N-p-Acetaminophenyl-N'-isopropylthiourea (*No.* 2). To a boiling solution of *p*-acetaminophenylisothiocyanate (19·2 g.) in acetone (130 c.c.) was added isopropylamine (10 c.c.) and the mixture refluxed for one hour. The crystalline solid that had separated was collected, washed (yield, 23·7 g.) and crystallised from alcohol.

The same compound was obtained by the action of isopropyl isothiocyanate (10·1 g.) on *p*-aminoacetanilide (15·0 g.) in acetone (130 c.c.); Yield, 22 g.

N-p-Aminophenyl-N'-isopropylthiourea (*No.* 8). This was prepared (i) by the hydrolysis of the abovementioned acetaminothiourea derivative in alco-

TABLE III

Dimethyl derivatives of N^1-aryl-N^2-alkylthiocarbamidophenylthioureas



Serial No.	R^1	R^2	Molecular Formula	M.P./°C.	Nitrogen % Req.	Found
36	H-	*iso*-Propyl	$C_{13}H_{22}N_4S_2I_2$	..	..	..
37	Phenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2$	189–90	..	..
38	Phenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2$	185–86	..	..
39	*p*-Chlorophenyl-	H-	$C_{16}H_{19}N_4S_2I_2Cl$	193–94	8·99	8·51
40	*p*-Chlorophenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2Cl$	180–82	8·45	7·88
41	*p*-Chlorophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Cl$	175–76	..	..
42	*o*-Chlorophenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2Cl$	179–80	..	..
43	*o*-Chlorophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Cl$	175–76	..	..
44	*m*-Chlorophenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2Cl$	174–76	..	..
45	*m*-Chlorophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Cl$	173–74	..	..
46	*p*-Bromophenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2Br$	176–77	7·92	7·89
47	*p*-Bromophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Br$	180–82	..	..
48	*m*-Bromophenyl-	*iso*-Propyl	$C_{19}H_{25}N_4S_2I_2Br$	179–80	7·92	7·93
49	*m*-Bromophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Br$	176–77	..	..
50	*p*-Tolyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2$	187–88	..	..
51	*p*-Tolyl-	*n*-Butyl-	$C_{21}H_{29}N_4S_2I_2$	183–85	..	..
52	*o*-Tolyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2$	193–95	..	..
53	*o*-Tolyl-	*n*-Butyl-	$C_{21}H_{29}N_4S_2I_2$	174–75	..	..
54	*m*-Tolyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2$	190–92	..	..
55	*m*-Tolyl-	*n*-Butyl-	$C_{21}H_{29}N_4S_2I_2$	172–74	..	
56	*p*-Anisyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2O$	186–87	..	
57	*p*-Anisyl-	*n* Bu yl-	$C_{21}H_{29}N_4S_2I_2O$	188–89	..	..
58	*o*-Anisyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2O$	186–89	..	..
59	*o*-Anisyl-	*n*-Butyl-	$C_{21}H_{29}N_4S_2I_2O$	175–77	..	..
60	*iso*-Propyl-	*iso*-Propyl	$C_{16}H_{28}N_4S_2I_2$	221–22	..	..

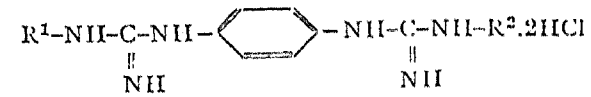
holic hydrochloric acid and (ii) by the catalytic hydrogenation of the corresponding nitroderivative described above with Raney nickel and hydrogen at room temperature at 45 lb.

4 (4′-*Substituted phenylthioureidio*) *phenylthioureas* (*formula VII*).—These compounds were prepared by the action of the isothiocyanates on *p*-aminophenylthioureas in acetone or benzene solution. The dithioureas were thrown out. The compounds obtained are listed in Table II.

N-p-Chlorophenyl-N′-p-isopropylthiocarbamidophenylthiourea (*No.* 15).—*p*-Chlorophenylisothiocyanate (9·3 g.) was added to a clear solution of *p*-aminophenylisopropylthioureas (10·45 g.) dissolved in acetone (100 c.c.). On shaking the flask for about 5 minutes, a bulky precipitate was thrown out.

TABLE IV

N^1-Aryl-N^2-(p-alkylguanido) phenyl-guanidines dihydrochlorides



Serial No.	R^1	R^2	Molecular Formula	M.P./°C.	Nitrogen % Req.	Found	M.P./°C. of Picrate
61	H-	*iso*-Propyl-	$C_{11}H_{20}N_6Cl_2$	208–09	27·36	27·54	212–14
62	Phenyl-	*iso*-Propyl-	$C_{17}H_{24}N_6Cl_2$	265–66	21·93	20·89	210–13
63	Phenyl-	*n*-Butyl-	$C_{18}H_{26}N_6Cl_2$	254–55	21·14	20·94	212–13
64	*p*-Chlorophenyl-	H-	$C_{14}H_{17}N_6Cl_3$	272–73	22·37	22·13	273–74
65	*p*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{23}N_6Cl_3$	280–82	20·11	20·32	165–67
66	*p*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{25}N_6Cl_3$	235–36	19·46	19·06	217–18
67	*o*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{23}N_6Cl_3$	279–80	20·11	19·86	130–32
68	*o*-Chlorophenyl-	*n*-Butyl	$C_{18}H_{25}N_6Cl_3$	253	19·46	19·64	120–21
69	*m*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{23}N_6Cl_3$	289–90	20·11	20·23	190–92
70	*m*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{25}N_6Cl_3$	229–30	19·46	19·39	240–45
71	*p*-Bromophenyl-	*iso*-Propyl-	$C_{17}H_{23}N_6Cl_2Br$	265–66	18·18	18·20	..
72	*p*-Bromophenyl-	*n*-Butyl-	$C_{18}H_{25}N_6Cl_2Br$	245–46	17·64	17·32	219–20
73	*m*-Bromophenyl-	*iso*-Propyl-	$C_{13}H_{23}N_6Cl_2Br$	273–74	18·18	18·63	151–52
74	*m*-Bromophenyl-	*n*-Butyl-	$C_{18}H_{25}N_6Cl_2Br$	217–18	17·64	17·83	210–12
75	*p*-Tolyl-	*iso*-Propyl-	$C_{18}H_{26}N_6Cl_2$	260–61	21·14	21·08	118–19
76	*p*-Tolyl-	*n*-Butyl-	$C_{19}H_{28}N_6Cl_2$	255–56	20·48	19·82	209–10
77	*o*-Tolyl-	*iso*-Propyl-	$C_{18}H_{26}N_6Cl_2$	287	21·14	20·60	217–19
78	*m*-Tolyl-	*iso*-Propyl	$C_{18}H_{26}N_6Cl_2$	256–57	21·14	20·80	195–97
79	*m*-Tolyl–	*n*-Butyl-	$C_{19}H_{28}N_6Cl_2$	230–31	20·48	20·80	223–24
80	*o*-Anisyl-	*iso*-Propyl-	$C_{18}H_{26}N_6Cl_2O$	259–60	20·32	19·94	165–66
81	*p*-Anisyl-	*iso*-Propyl-	$C_{18}H_{26}N_6Cl_2O$	243–44	20·32	20·04	197–98
82	*p*-Anisyl-	*n*-Butyl-	$C_{19}H_{28}N_6Cl_2O$	241–42	19·67	19·47	183–84
83	*iso*-Propyl-	*iso*-Propyl-	$C_{14}H_{26}N_6Cl_2$	292–93	24·00	23·76	..

The mixture was refluxed for about 20 minutes, the contents cooled in an ice bath, the solid collected, washed with more cold acetone and dried (yield, 17·5 g.). On crystallisation from alcohol, it had m.p. 214–17°.

The same compound was prepared by the action of N-(*p*-chlorophenyl)-N′-*p*-amino-phenylthiourea on isoprophyl isothiocyanate in acetone.

The Di-S-methyl derivatives of the dithiourea derivatives

These were prepared by allowing two molecular equivalents of methyl iodide to react in alcoholic solution with the dithiourea derivatives of formula (VII) listed in Table II. The mixture was shaken and gently refluxed for about 10 minutes and then cooled. The solution was diluted with ether, whereby an oil separated which solidified. The solid was collected.

The majority of the compounds prepared were susceptible to action by light and turned dark. Only a few numbers could be crystallised from alcohol. On heating with higher boiling solvents or even in contact with cold alkalies, these di-S-methyl derivatives suffered decomposition. The compounds prepared are listed in Table III.

Preparation of the diguanidine derivatives of formula (I)

The abovementioned hydriodides of the S-methylisothioureas were dissolved in alcohol, and ammonia gas passed into the boiling solution. After about 20 hours, the reaction mixture was filtered, and concentrated to a small bulk. The free guanidines were liberated by the addition of 20% alkali; the oil that separated was collected, dissolved in ether, dried and mixed with alcoholic hydrochloric acid whereby the hydrochloride separated out as an oil or gum which after separation and trituration with acetone solidified. They were crystallised from acetone and alcohol mixture.

The diguanidines prepared are listed in Table IV.

Action of mercuric oxide and alcoholic ammonia on the dithiourea derivatives.—N-*p*-Chlorophenyl-N′-(*iso*propylthiocarbamido) phenylthiourea (3·79 g.), mercuric oxide (4·7 g.) and alcoholic ammonia (75 c.c. of 18%) were refluxed on the steam-bath for 2 hours. The black mercuric sulphide that was formed was separated and the filtrate after treating with a little charcoal was concentrated to a small bulk. On dilution, a solid was thrown out (1·1 g.). On crystallisation it had m.p. 97–98° (Found: N, 16·30). The analytical figure agrees with that for the diurea compound ($C_{17}H_{19}N_4O_2Cl$) which requires N, 16·15%.

Similarly the action of mercuric oxide and alcoholic ammonia on N-*m*-chlorophenyl-N′-(*p*-isopropylthiocarbamido) phenylthiourea furnished the corresponding diurea derivative, m.p. 115–17° (Found: N, 16·20; $C_{17}H_{19}N_4O_2Cl$ requires N, 16·15%).

N-p-Thiocarbaminophenyl-N′-isopropylthiourea.—*p*-Amino phenyl-isopropylthiourea (10·45 g.) was dissolved in water (120 c.c.) containing con. HCl (4·2 c.c.) and to this was added ammonium thiocyanate (4·2 g.) dissolved in water (15 c.c.). The reaction mixture was concentrated to about a third of its original volume and then cooled in ice-bath. The solid that was thrown out was collected (yield, 9·6 g.) and on crystallisation from alcohol, it had m.p. 200°.

N-p-Aminophenyl-N′-p-chlorophenylguanidine hydriodide (IV).—A mixture of *p*-phenylenediamine (10·8 g.) and S-methyl-*p*-chlorophenylisothiourea

hydriodide (32·8 g.) in alcohol (200 c.c.) was refluxed on the steam-bath for 12 hours, the methylmercaptan that evolved being absorbed in an alkali trap. The solvent was removed from the reaction mixture and the residue stirred with ether whereby the guanidine derivative separated (yield, 24 g.). Crystallised from alcohol, it separated in needles and had m.p. 203° (Found: N, 14·27; $C_{13}H_{14}N_4ClI$ requires N, 14·41%). The picrate had m.p. 206°. The acetyl derivative had m.p. 248° (Found: N, 12·90; $C_{15}H_{17}N_4ClI$ requires N, 13·00%).

N-p-Chlorophenyl-N'-p-guanidinophenylthiourea hydriodide (*II*).—A mixture of *p*-aminophenylguanidine hydriodide (11·2 g.), *p*-chlorophenylisothiocyanate (6·67 g.) and acetone (80 c.c.) was refluxed for one hour. The reaction mixture was treated with a little charcoal and filtered. On cooling, the hydriodide of the guanylthiourea separated in fine needles (yield, 5 g.). The mother liquor on dilution with ether furnished 2·3 g. more of the compound. On crystallisation from alcohol, it had m.p. 193–94° (Found: N, 15·28; $C_{14}H_{14}N_5SClI$ requires N, 15·64%).

The S-methylisothiourea hydriodide of the above compound was prepared by the action of methyliodide in acetone solution. On crystallisation from acetone, it had m.p. 185–86° (Found: N, 11·34; $C_{15}H_{16}N_5SClI_2$ requires N, 11·55%).

N-p-Chlorophenyl-N'-p-thiocarbamidophenylguanidine (*I*).—To *p*-chlorophenyl-*p*-aminophenylguanidine hydriodide (3·33 g.) dissolved in alcohol (250 c.c.) was added ammonium thiocyanate (0·84 g.) dissolved in water (5 c.c.) and the reaction mixture refluxed for 2 hours on the steam-bath, concentrated to a third of its volume, made slightly alkaline to litmus by addition of 10% sodium hydroxide solution. The reaction product was thrown out as an oil which on keeping solidified (yield, 2·7 g.). This was used as such without purification for the next stage.

The S-methylisothiourea derivative was obtained as an oil and this was also used as such for conversion into the diguanidine derivative.

Summary

Phenylenediguanidine derivatives of formula (I) have been synthesised to assess their antimalarial activity. The method consists in condensing phenylthiourea derivatives of formula (VI) with a series of isothiocyanates, to obtain the dithiourea derivatives (VII), the di-S-methyl derivatives of which reacted with ammonia to furnish the diguanidine derivatives (I). The other methods tried to prepare diguanidine derivatives are also described. Eleven

of the derivatives of formula (I) showed no antimalarial activity when tested against *P. berghi* infections in mice.

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