334. *Synthetic Antimalarials. Part XXX. Some* N^1-*Aryl*-N^4 : N^5-*Dialkyldiguanides and Observations on the Conversion of Guanylthioureas into Diguanides.*

By S. Birtwell, F. H. S. Curd, J. A. Hendry, and F. L. Rose.

A series of N^1-*p*-chlorophenyl-N^4 : N^5-dialkyldiguanides (III; R and R′ = alkyl) has been synthesised, using two general methods, in order to determine the effect on antimalarial activity of introducing an alkyl group on N^4 of the N^1-*p*-chlorophenyl-N^5-alkyldiguanides described in Part X (*J.*, 1946, 729). The first method involves the reaction of *N*-cyano-*S*-methyl-*N*′-alkyl*iso*thioureas with alkylamines to give N^1 : N^2-dialkyldicyandiamides which are then condensed with *p*-chloroaniline. In the second method the alkylamine is caused to react, in presence of a desulphurising agent, with *N*-*p*-chlorophenylguanyl-*N*′-alkylthioureas obtained from *p*-chlorophenylguanidine and alkyl *iso*thiocyanates: the use of ammonia in place of the alkylamine gives the parent diguanide type (III; R = alkyl, R′ = H).

The observation that *N*-arylguanyl- and *N*-alkylguanyl-thioureas with amines and desulphurising agents such as mercuric oxide give the corresponding dicyandiamides, diguanides being formed in reasonable yield only under conditions normally required for the reaction of the latter with amines, suggests that the conversion of *N*-arylguanyl-*N*′-alkylthioureas into diguanides may proceed analogously through the intermediate production of carbodi-imides (X).

The *S*-alkyl derivatives of the several types of guanylthioureas referred to above also yield diguanides under certain conditions, the intervention of a desulphurising agent being then unnecessary.

In connection with the study being made in these laboratories of the effect of changes of chemical constitution on antimalarial activity among derivatives of diguanide, a number of N^1-*p*-chloro-

phenyl-N^4 : N^5-dialkyldiguanides (III; R and R′ = alkyl) has been made. It is the purpose of the present paper to record the synthetic methods that have been used. Compounds of type (III) can be considered as derived from the earlier pyrimidine type (II) (*J.*, 1946, 370, 720) in the same way that the N^1-aryl-N^2 : N^5-dialkyldiguanides (IV; R′ and R″ = alkyl), described in Part XXIX (this vol., p. 1636) were evolved from the original pyrimidine type (I). Fission of the pyrimidine ring of the type (II) along the line *a* leaves a skeleton (V) which is incorporated in the diguanides of type (III; R and R′ = alkyl).

A very convenient method for the preparation of diguanides of type (III) was found to be the condensation of *p*-chloroaniline with N^1 : N^2-dialkyldicyandiamides (VII; R and R′ = alkyl). This type of disubstituted dicyandiamide, hitherto unknown, has been synthesised by condensing *N*-cyano-*S*-methyl-*N*′-alkyl*iso*thioureas (VI; R = alkyl) with alkylamines. The synthesis is analogous to that initially described and used in Part XXVIII (this vol., p. 1630) for the preparation of N^1-monoalkyldicyandiamides in which the same intermediates were brought into reaction with ammonia. The reaction was first explored with *N*-cyano-*S*-methyl-*N*′-*iso*propyl*iso*-thiourea (VI; R = Pr$^\beta$) and *iso*propylamine. When these were heated together in alcoholic solution at 120° for 6 hours the product was shown to be N^1 : N^2-*di*iso*propyldicyandiamide* (VII; R = R′ = Pr$^\beta$) since it reacted with *p*-chloroaniline hydrochloride in boiling aqueous 2-ethoxyethanol solution to give N^1-p-*chlorophenyl*-N^4 : N^5-*di*iso*propyldiguanide* (III; R = R′ = Pr$^\beta$) *hydrochloride* identical with the product made by an alternative method described below.

Because of the equivalence of N^1 and N^2 in the dicyandiamide molecule it is obviously possible to proceed in two ways when utilising this method for the preparation of N^1 : N^2-dialkyl-dicyandiamides in which the alkyl groups are different. This is illustrated by the preparation of N^1-*ethyl*-N^2-iso*propyldicyandiamide*, not only by the action of ethylamine on *N*-cyano-*S*-methyl-*N*′-*iso*propyl*iso*thiourea (VI; R = Pr$^\beta$), but also from *iso*propylamine and *N*-cyano-*S*-methyl-*N*′-ethyl*iso*thiourea (VI; R = Et).

Parallel with the work described in Part XXIX (*loc. cit.*) on the condensation of aryl *iso*thiocyanates with mono- and di-alkylguanidines, we explored the reaction of alkyl *iso*thiocyanates with *p*-chlorophenylguanidine. *iso*Propyl *iso*thiocyanate, which was first investigated, reacted when merely heated with *p*-chlorophenylguanidine on the steam-bath. Analysis of the product indicated that it was the desired N-p-*chlorophenylguanyl*-N′-iso*propyl-thiourea* (VIII; R = Cl, R′ = Pr$^\beta$), but additional proof was provided by its conversion with alcoholic ammonia and lead monoxide at room temperature into N^1-*p*-chlorophenyl-N^5-*iso*-propyldiguanide (III; R = Pr$^\beta$, R′ = H) (Part X, *J.*, 1946, 729). The foregoing *N*-*p*-chlorophenylguanyl-*N*′-*iso*propylthiourea reacted analogously with *iso*propylamine, instead of ammonia, and a desulphurising agent to give N^1-*p*-chlorophenyl-N^4 : N^5-di*iso*propyldiguanide (III; R = R′ = Pr$^\beta$). Similarly, methyl *iso*thiocyanate reacted with *p*-chlorophenylguanidine to give (VIII; R = Cl, R′ = Me) from which N^1-*p*-chlorophenyl-N^4 : N^5-dimethyldiguanide (III; R = R′ = Me) (isolated as its *hydrochloride*) was obtained by the action of methylamine and mercuric oxide, and the identity of the product with that obtained by condensation of N^1 : N^2-*dimethyldicyandiamide* (VII; R = R′ = Me) with *p*-chloroaniline established.

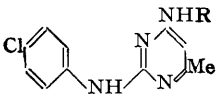
For the preparation of N^1-*p*-chlorophenyl-N^4-methyl-N^5-*iso*propyldiguanide, N-p-*chloro-phenylguanyl*-N′-*methylthiourea* was condensed with *iso*propylamine in presence of mercuric oxide, although it was theoretically possible to proceed from *N*-*p*-chlorophenylguanyl-*N*′-*iso*-propylthiourea and methylamine. This is due to the equivalence of N^4 and N^5 in the diguanide molecule and the fact that the alkyl groups involved are different.

By the above methods a series of N^1-*p*-chlorophenyl-N^4 : N^5-dialkyldiguanides were prepared for antimalarial test, the results of which will be published elsewhere. The dystherapeutic effect of a N^4-alkyl group was such that it did not appear worth while to prepare any N^1-aryl-N^4-alkyl-N^5-dialkyldiguanides, and the condensation of guanylthioureas of type (VIII) with dialkylamines was not therefore explored.

The *N*-*p*-chlorophenylguanyl-*N*′-alkylthioureas of type (VIII; R = Cl, R′ = alkyl) were tested for antimalarial activity by Dr. D. G. Davey using *P. gallinaceum* in chicks; all were inactive.

The conversion of *N*-*p*-chlorophenylguanyl-*N*′-*iso*propylthiourea (VIII; R = Cl, R′ = Pr$^\beta$) into N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide, referred to above, was also attempted *via* the corresponding *S*-methyl derivative (IX; R = Cl, R′ = Pr$^\beta$, R″ = SMe). This compound was obtained by the action of methyl iodide in methanol solution on (VIII; R = Cl, R′ = Pr$^\beta$) and also by condensation of *N*-cyano-*S*-methyl-*N*′-*iso*propyl*iso*thiourea with *p*-chloroaniline hydrochloride, although in poor yield. The latter type of reaction is reminiscent of the work

of Slotta, Tschesche, and Dressler (*Ber.*, 1930, **63**, 208), who condensed the sodium salt of *N*-cyano-*N'*-phenylthiourea with aniline hydrochloride in alcohol solution to obtain *N*-phenyl-*N'*phenylguanylthiourea.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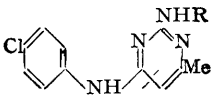
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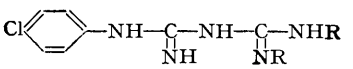
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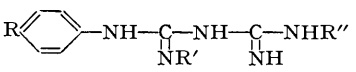
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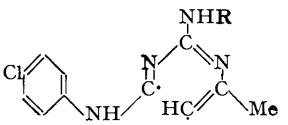
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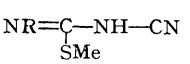
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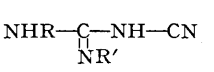
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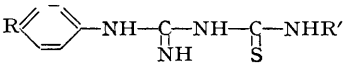
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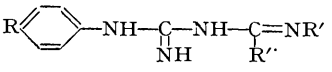
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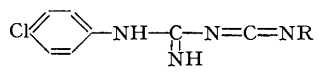
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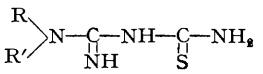
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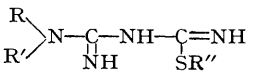
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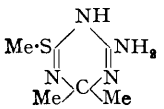
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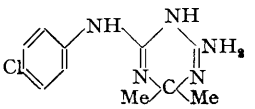
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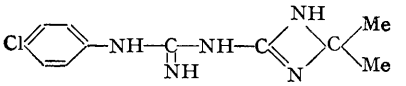
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Although Slotta and Tschesche (*Ber.*, 1929, **62**, 1390) had described the reaction of *N*-guanyl-*N'*-methyl-*S*-ethyl*iso*thiourea hydrobromide with methylamine and dimethylamine respectively to give N^1 : N^2-dimethyldiguanide and N^1 : N^1 : N^2-trimethyldiguanide, when (IX; R = Cl, R' = Pr$^\beta$, R'' = SMe) was heated with saturated alcoholic ammonia for 6 hours at 100° no formation of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide could be detected and analysis of the product (and of its *hydrochloride* and *acetate*) proved it to be N-p-*chlorophenylguanyl*-O-*ethyl*-N'-iso*propyl*iso*urea* (IX; R = Cl, R' = Pr$^\beta$, R'' = OEt). On repeating the reaction at a slightly higher temperature (120°) the same production of (IX; R = Cl, R' = Pr$^\beta$, R'' = OEt) was observed in one experiment, but in another some diguanide (III; R = Pr$^\beta$, R' = H) formation was demonstrated. The formation of *N*-*p*-chlorophenylguanyl-*O*-ethyl-*N'*-*iso*propyl*iso*urea when (IX; R = Cl, R' = Pr$^\beta$, R'' = SMe) is heated with alcoholic ammonia is most easily accounted for by the initial loss of methylthiol from the *N*-*p*-chlorophenylguanyl-*S*-methyl-*N'*-*iso*propyl*iso*thiourea followed by the addition of solvent, instead of ammonia, to the resulting carbodi-imide (X; R = Pr$^\beta$), and, in conformity with this (IX; R = Cl, R' = Pr$^\beta$, R'' = SMe), reacted normally with *iso*propylamine in the absence of a solvent to give N^1-*p*-chlorophenyl-N^4 : N^5-di*iso*propyldiguanide (III; R = R' = Pr$^\beta$).

These results suggest that the conversion of guanylthioureas of type (VIII; R = Cl, R' = alkyl) into diguanides of type (III; R = alkyl, R' = H or alkyl) by the action of ammonia or an alkylamine in presence of a desulphurising agent also proceeds *via* a carbodi-imide (X; R = alkyl), and other investigations, described below, which we have carried out on the conversion of guanylthioureas into diguanides tend to support this view. [By the action of mercuric oxide on *N*-phenyl-*N'*-(*NN'*-diphenylguanyl)thiourea Rathke and Oppenheim *Ber.*, 1890, **23**, 1669) isolated a substance which was considered to be a carbodi-imide.]

By analogy with the conversion (see above) of *N*-*p*-chlorophenylguanyl-*N'*-*iso*propylthiourea (VIII; R = Cl, R' = Pr$^\beta$) into the diguanide (III; R = R' = Pr$^\beta$) by reaction with methanolic *iso*propylamine and mercuric oxide at room temperature, it was thought that (VIII; R = Cl, R' = H) treated similarly might yield N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (IV; R = Cl, R' = H, R'' = Pr$^\beta$). Actually it was found that the main reaction was the conversion of p-*chlorophenylguanylthiourea* into *p*-chlorophenyldicyandiamide. Some unchanged (VIII; R = Cl, R' = H) was also isolated, and in addition a small more highly basic fraction was separated in which it was possible to detect some N^1 : N^5-disubstituted diguanide by shaking

with ammoniacal copper sulphate and benzene, when a pink colour developed in the benzene owing to formation of a benzene-soluble copper complex of the diguanide (cf., Gage and Rose, *Ann. Trop. Med. Parasit.*, 1946, **40**, 333). Following this, isolation of a very small amount of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (IV; R = Cl, R′ = H, R″ = Pr$^\beta$) as its acetate was achieved. Many similar experiments (not detailed) were performed, with ammonia, methylamine, dimethylamine, or methyl*iso*propylamine in place of *iso*propylamine, and with different desulphurising agents such as mercuric chloride and copper sulphate; the temperature was also varied from 10° to 65°. In every case *p*-chlorophenyldicyandiamide was the main product, and the yield of diguanide, though variable, was never more than 5%, and often considerably less. The formation of these small amounts of diguanides by direct interaction of (VIII; R = Cl, R′ = H) with the alkylamines, although not definitely excluded, appeared unlikely since it was separately demonstrated that a small yield of diguanide resulted from the interaction of *p*-chlorophenyldicyandiamide with methanolic *iso*propylamine under similar conditions, either with or without mercuric oxide. Furthermore, it was subsequently shown that higher yields of diguanides were obtained from arylguanylthioureas by reaction with alkylamine hydrochlorides and a desulphurising agent under conditions previously found suitable (Part XXVIII, *loc. cit.*) for the reaction of aryldicyandiamides with alkylamines. Thus *p*-chlorophenylguanylthiourea and *iso*propylamine hydrochloride reacted in nitrobenzene at 130—135° in presence of mercuric oxide to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide, and *p*-iodophenylguanylthiourea (VIII; R = I, R′ = H) was similarly converted into N^1-*p*-iodophenyl-N^5-*iso*propyldiguanide (IV; R = I, R′ = H, R″ = Pr$^\beta$).

The desulphurisation of *p*-chlorophenylguanylthiourea to give *p*-chlorophenyldicyandiamide was also effected by means of mercuric oxide in boiling methanol solution without any *iso*propylamine, although the reaction was less facile than in the presence of the amine. This conversion is undoubtedly analogous to that of *N*-(*N*-phenyl-*N*′-*p*-tolylguanyl)thiourea into N^1-phenyl-N^2-*p*-tolyldicyandiamide (Fromm and Weller, *Annalen*, 1908, **361**, 306) and of *N*-(*NN*′-di-*p*-methoxyphenylguanyl)thiourea into N^1 : N^2-di-*p*-methoxyphenyldicyandiamide (Fromm, *ibid.*, 1912, **394**, 258) by the action of lead monoxide under alkaline conditions. Even earlier, Rathke (*Ber.*, 1878, **11**, 962) had demonstrated the conversion of guanylthiourea itself into dicyandiamide by the action of silver nitrate.

Our failure to obtain N^1-*p*-methoxyphenyl-N^5-*iso*propyldiguanide by interaction of iso*propylguanylthiourea* (XI; R = Pr$^\beta$, R′ = H) with *p*-anisidine in methanol solution at 50—60° in presence of mercuric oxide can probably likewise be attributed to the ready desulphurisation of the guanylthiourea to give *iso*propyldicyandiamide (VII; R = Pr$^\beta$, R′ = H) and the unsuitability of the conditions to effect condensation of the dicyandiamide with the *p*-anisidine. In support of this it was demonstrated that treatment of (XI; R = Pr$^\beta$, R′ = H) with mercuric oxide in alcoholic solution at 55—60° in presence of trimethylamine gave rise to *iso*propyldicyandiamide together with a second substance having the empirical formula $C_5H_{10}N_4S$ which was assumed to be one, or possibly a mixture, of the various possible oxidation products of (XI; R = Pr$^\beta$, R′ = H) (a thiadiazole or dihydro-1 : 2 : 4-triazole-thione). Successful conditions which were later discovered for the condensation of *iso*propylguanylthiourea and *p*-bromoaniline hydrochloride in presence of mercuric oxide to give N^1-*p*-bromophenyl-N^5-*iso*propyldiguanide (IV; R = Br, R′ = H, R″ = Pr$^\beta$) resembled those employed for the condensation of alkyldicyandiamides with arylamines (Part XXVIII).

For comparison, and in view of the work of Slotta and Tschesche (*Ber.*, 1929, **62**, 1398), who prepared a number of substituted alkyldiguanides and alkylene bisdiguanides by the reaction of guanyl-*S*-ethyl*iso*thiourea hydrobromide with alkylamines and alkylenediamines, it was decided to explore the reaction of arylguanyl-*S*-alkyl*iso*thioureas of type (IX; R′ = H, R″ = S·Alkyl) with alkylamines and of alkylguanyl-*S*-alkyl*iso*thioureas of type (XII; R = R″ = alkyl, R′ = H or alkyl) with arylamines. Accordingly the condensation of p-*chlorophenylguanyl*-S-*methyl*iso*thiourea hydriodide* (as IX; R = Cl, R′ = H, R″ = SMe) with various alkylamines was investigated. Using methanol as the solvent and carrying out the reaction in the cold with a reaction time of 4—7 days, the yields of diguanide were very variable—20% with *iso*propylamine and 90% with dimethylamine—and this is probably attributable to the facility of the desired reaction (elimination of methylthiol between the two reactants) compared with that of *p*-chlorophenyldicyandiamide formation. This substance was the main product of many of the reactions tried, and its formation appeared to be favoured by the presence of material quantities of water (illustrated by the reactions using methylamine).

The effect of water was again observed in a number of reactions carried out at higher temperatures with a view to promoting condensation of the amine with the *p*-chlorophenyldi-

cyandiamide formed. *N*-*p*-Chlorophenylguanyl-*S*-methyl*iso*thiourea hydriodide and *iso*propylamine under anhydrous conditions in nitrobenzene at 130—135° gave little or no diguanide, whereas at the same temperature in presence of water they gave a 70% yield of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide.

Attention was then directed to the condensation of salts of *N*-alkylguanyl-*S*-alkyl*iso*thioureas (XII; R = R″ = alkyl, R′ = H or alkyl) with arylamines, and it was found that such reactions were successfully effected under conditions favouring the condensation of alkyldicyandiamides with arylamines. This can, however, only be regarded as presumptive evidence, and not positive proof, that the reactions proceeded *via* the alkyldicyandiamides formed by loss of alkylthiol from the *N*-alkylguanyl-*S*-alkyl*iso*thioureas. The reactions of this type included condensation of the *hydriodide* of N-iso*propylguanyl*-S-*methyl*isothiourea (XII; R = Pr^{β}, R′ = H R″ = Me) with *p*-chloroaniline in boiling aqueous solution to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide, of N-(N-*methyl*-N-iso*propylguanyl*)-S-*methyl*isothiourea (XII; R = Pr^{β}, R′ = R″ = Me) *hydriodide* with *p*-chloroaniline to give N^1-*p*-chlorophenyl-N^5-methyl-N^5-*iso*propyldiguanide, and of *N*-*n*-butylguanyl-*S*-methyl*iso*thiourea (XII; R = Bu^{α}, R′ = H, R″ = Me) as its hydriodide with *p*-bromoaniline to give N^1-*p*-bromophenyl-N^5-*n*-butyldiguanide (IV; R = Br, R′ = H, R″ = Bu^{α}).

The above investigations utilising aryl- and alkyl-guanylthioureas were preceded by a considerable amount of work on the synthesis of such compounds. Under conditions similar to those used for the preparation of diguanides from cyanamides and guanidines (forthcoming publication), dimethylcyanamide could not be induced to react with thiourea to give *NN*-dimethylguanylthiourea. Instead, dimethylthiourea and dimethylguanidine (identified as it spicrate) were formed, presumably by the addition of the thermal decomposition products of thiourea to the dimethylcyanamide.

The method of preparation of guanylthiourea described in U.S.P. 2,364,594, which involves the reaction of dicyandiamide with carbon disulphide and potassium hydroxide to give dipotassium ω-cyanoguanidinodithiocarbonate followed by ring closure of this with acetic acid and hydrolysis of the resulting 4 : 6-diamino-2-mercapto-1 : 3 : 5-thiadiazine with a strong acid, was confirmed, but the application of this method to aryl- and alkyl-dicyandiamides failed at the first stage. Both *p*-chlorophenyldicyandiamide and *iso*propyldicyandiamide afforded only tars on treatment with carbon disulphide and potassium hydroxide, but the method was not exhaustively investigated because it was found that the addition of hydrogen sulphide to a dicyandiamide provided a very convenient method for the preparation of the required aryl- and alkyl-guanylthioureas.

Bamberger (*Ber.*, 1883, **16**, 1460) and Slotta and Tschesche (*ibid.*, 1929, **62**, 1398) used this route for the preparation of the parent guanylthiourea. Their method was modified slightly, and the dicyandiamides were heated with a methanol solution of hydrogen sulphide (at least two equivalents) at 70—80° for at least 48 hours. Initially a catalytic amount of sodium was added (cf. Kinder, *Annalen*, 1923, **431**, 187; the addition of hydrogen sulphide to nitriles), but in later preparations this was omitted with no lowering of the yield. By this method *p*-chlorophenylguanylthiourea and *p*-iodophenylguanylthiourea were made, besides the monoalkyl compounds, *iso*propyl (XI; R = Pr^{β}, R′ = H) and n-*butylguanylthiourea* (XI; R = Bu^{α}, R′ = H), and the dialkyl derivatives NN-*diethyl*- (XI; R = R′ = Et) and N-*methyl*-N-iso*propyl-guanylthiourea* (XI; R = Me, R′ = Pr^{β}). In the case of *p*-chlorophenylguanylthiourea a small amount of p-*chlorophenyldithiobiuret* was isolated, identical with that made by condensing *p*-chloroaniline with "xynthane hydride" (perthiocyanic acid) (cf. Glutz, *Annalen*, 1870, **154**, 44; Tursini, *Ber.*, 1884, **17**, 584; Fromm *et al.*, *Annalen*, 1893, **275**, 20; 1906, **348**, 161; *Ber.*, 1895, **28**, 1096; Underwood and Dains, *J. Amer. Chem. Soc.*, 1935, **57**, 1768), and by interaction of *p*-chlorophenyl *iso*thiocyanate with *S*-methyl*iso*thiourea followed by thiohydrolysis of the product (method of Johnson *et al.*, *Amer. Chem. J.*, 1903, **30**, 167; Olin and Dains, *J. Amer. Chem. Soc.*, 1930, **52**, 3326; Underwood and Dains, *Kansas Univ. Sci. Bull.*, 1936, **24**, 5). It may be significant that the sodium catalyst was used in this preparation, although U.S.P. 2,371,112 describes the preparation of dithiobiuret itself by heating dicyandiamide with hydrogen sulphide under pressure in presence of an inert solvent.

Besides *p*-chlorophenylguanyl-*S*-methyl*iso*thiourea, mentioned above, a number of homologous compounds (IX; R = Cl, R′ = H, R″ = SEt, SPr^{β}, $S{\cdot}CH_2Ph$) were prepared in order to permit their examination for antimalarial activity. This was thought to be of interest on account of their formal analogy to the diguanides of type (III; R = alkyl, R′ = H) and because they likewise afford benzene-soluble copper complexes. However, none of the compounds exhibited any activity against *P. gallinaceum* in chicks.

The guanylthioureas, both alkyl and aryl, were *S*-alkylated by treatment with alkyl halides. The alkylguanylthioureas (XI; R = alkyl, R′ = H or alkyl) reacted with methyl iodide in the cold, and the arylguanylthioureas (VIII; R′ = H) after 2—6 hours at 60—65°. The reaction between *p*-chlorophenylguanylthiourea and *iso*propyl bromide to give (IX; R = Cl, R′ = H, R″ = SPr$^{\beta}$) required 24 hours at 70—80° for completion. An attempt was also made to prepare this type of compound by the reaction of cyanamides with *S*-alkyl*iso*thioureas. It was thought that this might be more successful than with the parent thiourea, since the *S*-alkyl compounds are stronger bases, and in this respect resemble guanidines. Owing to the instability of the *S*-alkyl*iso*thioureas, however, the use of very mild conditions was indicated, and the condensation of dimethylcyanamide and of methyl*iso*propylcyanamide with *S*-methyl*iso*thiourea was attempted in acetone. No guanyl-*S*-alkyl*iso*thioureas were obtained: instead, both reactions gave a 20—30% yield of a substance which gave the correct analysis for 2-*amino*-4-*methylthio*-6-*dimethyldihydro*-1 : 3 : 5-*triazine* (XIII) which could have been formed by reaction of 2 mols. of *S*-methyl*iso*thiourea with the acetone used as solvent. This was later substantiated experimentally. The supposed constitution of (XIII) was further supported by the fact that it reacted with *p*-chloroaniline to give a product identical with that obtained by the reaction of *p*-chlorophenyldiguanide and acetone which, from its properties, would appear to be 2-*amino*-4-p-*chloroanilino*-6-*dimethyldihydro*-1 : 3 : 5-*triazine* (XIV). It does not form a copper complex, and this is regarded as evidence for the condensation of the acetone across N^2 and N^4, since N^1-aryl-N^2 : N^5-dialkyl- and N^1-aryl-N^4 : N^5-dialkyl-diguanides retain this property as does 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine (Part IV, *J.*, 1946, 362), and this fact appears to exclude the alternative structure (XV). The simple elimination of water between the acetone and one of the terminal amino-groups appears to be excluded not only by the non-formation of a copper-complex but also by the inactivity of the substance as an antimalarial, and our inability to effect its reduction to N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide.

Experimental.

N^1 : N^2-*Diiso*propyldicyandiamide (VII; R = R′ = Pr$^{\beta}$).—*N*-Cyano-*S*-methyl-*N′-iso*propyl*iso*thiourea (4 g.) (Part XXVIII, *loc. cit.*), *iso*propylamine (15 c.c.), and alcohol (45 c.c.) were heated in a sealed tube at 120° for 6 hours. The contents of the tube were then evaporated to half their original volume and set aside to crystallise. The material which separated was collected and recrystallised from alcohol giving the *product* as colourless leaflets, m. p. 194° (Found: C, 57·2; H, 9·4; N, 32·6. $C_8H_{16}N_4$ requires C, 57·15; H, 9·5; N, 33·3%).

N^1-*Ethyl*-N^2-iso*propyldicyandiamide* (VII; R = Et, R′ = Pr$^{\beta}$).—(*a*) *N*-Cyano-*S*-methyl-*N′-iso*propyl*iso*thiourea (4 g.), ethylamine (20 c.c. of 33%), and alcohol (40 c.c.) were heated at 120° for 6 hours in a closed vessel. The mixture was then evaporated to dryness and the residue crystallised from light petroleum (b. p. 80—100°)–*n*-propanol to give N^1-*ethyl*-N^2-iso*propyldicyandiamide* as colourless leaflets, m. p. 132—133° (Found: C, 54·6; H, 9·3; N, 36·0. $C_7H_{14}N_4$ requires C, 54·55; H, 9·1; N, 36·4%).

(*b*) *N*-Cyano-*S*-methyl-*N′*-ethyl*iso*thiourea (4 g.), *iso*propylamine (15 c.c.), and alcohol (25 c.c.) were heated for 6 hours at 120° and worked up as described under (*a*) to give the same compound, m. p. and mixed m. p. 133°.

N^1 : N^2-*Dimethyldicyandiamide* (VII; R = R′ = Me).—Prepared similarly from *N*-cyano-*N′S*-dimethyl*iso*thiourea and methylamine, this *compound* crystallised from *n*-propanol as colourless leaflets, m. p. 174—175° (Found: C, 42·9; H, 7·0; N, 49·6. $C_4H_8N_4$ requires C, 42·9; H, 7·1; N, 50·0%).

N^1-*Methyl*-N^2-*ethyldicyandiamide* (VII; R = Me, R′ = Et).—Prepared from *N*-cyano-*N′S*-dimethyl*iso*thiourea and ethylamine, this *compound* crystallised from water as colourless prisms, m. p. 98—99° (Found: C, 47·5; H, 7·9; N, 44·7. $C_5H_{10}N_4$ requires C, 47·6; H, 7·9; N, 44·4%).

N^1-*Methyl*-N^2-n-*butyldicyandiamide* (VII; R = Me, R′ = Bu$^{\alpha}$).—Prepared from *N*-cyano-*N′S*-dimethyl*iso*thiourea and *n*-butylamine, this *compound* formed small colourless prisms, m. p. 91—92° (Found: C, 54·6; H, 9·0; N, 36·5. $C_7H_{14}N_4$ requires C, 54·55; H, 9·1; N, 36·4%).

N^1-n-*Propyl*-N^2-iso*propyldicyandiamide* (VII; R = Pr$^{\alpha}$, R′ = Pr$^{\beta}$).—Prepared from *N*-cyano-*S*-methyl-*N′-iso*propyl*iso*thiourea and *n*-propylamine, this *compound* crystallised from light petroleum (b. p. 80—100°)–*iso*propanol as colourless prisms, m. p. 131° (Found: C, 57·1; H, 9·7; N, 32·9. $C_8H_{16}N_4$ requires C, 57·15; H, 9·5; N, 33·3%).

N^1-iso*Propyl*-N^2-n-*butyldicyandiamide* (VII; R = Pr$^{\beta}$, R′ = Bu$^{\alpha}$).—Prepared from *N*-cyano-*S*-methyl-*N′-iso*propyl*iso*thiourea and *n*-butylamine, this *compound* separated from *iso*propanol–light petroleum as colourless prisms, m. p. 104—105° (Found: C, 59·7; H, 9·8; N, 30·5. $C_9H_{18}N_4$ requires C, 59·3; H, 9·9; N, 30·8%).

N^1-iso*Propyl*-N^2-cyclo*hexyldicyandiamide* (VII; R = Pr$^{\beta}$, R′ = C_6H_{11} *cyclo*).—Prepared from *N*-cyano-*S*-methyl-*N′-iso*propyl*iso*thiourea and *cyclo*hexylamine, this *compound* formed colourless prisms from alcohol, m. p. 192° (Found: C, 63·3; H, 9·4; N, 26·6. $C_{11}H_{20}N_4$ requires C, 63·5; H, 9·6; N, 26·9%).

N-p-*Chlorophenylguanyl*-N′-iso*propylthiourea* (VIII; R = Cl, R′ = Pr$^{\beta}$).—*p*-Chlorophenylguanidine (17 g.) (for convenient method of preparation see Part XXV, this vol., p. 586) and *iso*propyl *iso*thiocyanate (12 g.) were heated on the steam-bath for 1½ hours, a homogeneous mixture being quickly obtained. The excess of *iso*propyl *iso*thiocyanate was removed by steam distillation, and 2N-hydrochloric acid (55 c.c.) added to the hot residue. The resulting solid was filtered off when cold, dried, and extracted

thoroughly with ethyl acetate in the cold. The insoluble material crystallised from dilute hydrochloric acid to give N-p-*chlorophenylguanyl*-N′-iso*propylthiourea hydrochloride* (yield, 20·6 g.) as colourless prisms, m. p. 178° (Found : C, 43·0; H, 5·0; N, 18·2; Cl, 22·6; S, 10·7. $C_{11}H_{15}N_4ClS$,HCl requires C, 43·0; H, 5·2; N, 18·2; Cl, 23·1; S, 10·4%) (5168). The *base* was obtained by treating a solution of the hydrochloride in hot water with sodium hydroxide solution, boiling for a few minutes, and cooling. After drying, it crystallised from benzene–light petroleum (b. p. 80—100°) as colourless prisms, m. p. 100—101° (Found : C, 49·1; H, 5·2; N, 20·8. $C_{11}H_{15}N_4ClS$ requires C, 48·8; H, 5·5; N, 20·7%).

Conversion of N-p-*Chlorophenylguanyl*-N′-iso*propylthiourea into* N¹-p-*Chlorophenyl*-N⁵-iso*propyldiguanide*.—The above hydrochloride (2 g.), lead monoxide (4 g.), and saturated alcoholic ammonia (20 c.c.) were stirred vigorously overnight. The mixture was then filtered and the residue washed with alcohol. The solvent was removed from the filtrate by evaporation, and the residue dissolved in acetone. After filtration to remove a little insoluble material, acetic acid was added so as just to destroy the alkalinity to brilliant-yellow. After ½ hour the resulting precipitate was filtered off, washed with acetone, and dried to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate (yield, 0·5 g.), m. p. 185°, undepressed in admixture with authentic material (see Part X, *J.*, 1946, 729) (Found : C, 49·5; H, 5·9; N, 22·3. Calc. for $C_{11}H_{16}N_5Cl,CH_3{\cdot}CO_2H$: C, 49·7; H, 6·4; N, 22·3%).

N-p-*Chlorophenylguanyl*-N′-*methylthiourea* (VIII; R = Cl, R′ = Me).—Similarly prepared from methyl *iso*thiocyanate and *p*-chlorophenylguanidine, the *base* crystallised from alcohol in small colourless needles, m. p. 118° (Found : C, 44·4; H, 4·5; N, 23·2. $C_9H_{11}N_4ClS$ requires C, 44·5; H, 4·5; N, 23·1%), and the *hydrochloride* (5308) separated from dilute hydrochloric acid as colourless needles, m. p. 177—178° (Found : C, 37·8; H, 4·5; N, 19·3; Cl, 24·7; S, 11·4. $C_9H_{11}N_4ClS$,HCl,0·5H_2O requires C, 37·5; H, 4·5; N, 19·4; Cl, 24·6; S, 11·1%).

N-p-*Chlorophenylguanyl*-N′-*ethylthiourea* (VIII; R = Cl, R′ = Et).—The *hydrochloride* (5381), prepared from ethyl *iso*thiocyanate and *p*-chlorophenylguanidine, crystallised from water as long colourless prisms, m. p. 177° (Found : C, 41·1; H, 4·6; N, 19·2. $C_{10}H_{13}N_4ClS$,HCl requires C, 41·0; H, 4·8; N, 19·1%). The *base* crystallised from *iso*propanol in small colourless prisms, m. p. 97—98° (Found : C, 46·8; H, 5·2; N, 21·7. $C_{10}H_{13}N_4ClS$ requires C, 46·8; H, 5·1; N, 21·8%).

N-p-*Chlorophenylguanyl*-N′-n-*propylthiourea* (VIII; R = Cl, R′ = Pr^{α}).—The *hydrochloride*, prepared from *p*-chlorophenylguanidine and *n*-propyl *iso*thiocyanate, crystallised from dilute hydrochloric acid and then from acetone as long colourless needles, m. p. 171° (Found : C, 43·1; H, 5·2; N, 17·7; S, 10·0. $C_{11}H_{15}N_4ClS$,HCl requires C, 43·0; H, 5·2; N, 18·2; S, 10·4%) (5288). The *base*, liberated from a hot aqueous solution of the hydrochloride with sodium hydroxide, crystallised from alcohol as colourless prisms, m. p. 116° (Found : C, 48·9; H, 5·5; N, 20·4. $C_{11}H_{15}N_4ClS$ requires C, 48·8; H, 5·5; N, 20·7%).

N-p-*Chlorophenylguanyl*-N′-n-*butylthiourea* (VIII; R = Cl, R′ = Bu^{α}).—The *hydrochloride*, prepared from *n*-butyl *iso*thiocyanate and *p*-chlorophenylguanidine, crystallised from dilute hydrochloric acid as colourless prisms, m. p. 172° (Found : C, 45·5; H, 6·0; N, 17·5; S, 10·1. $C_{12}H_{17}N_4ClS$,HCl requires C, 44·9; H, 5·6; N, 17·45; S, 10·0%) (5289). A solution of the hydrochloride in hot water was made alkaline with ammonia and the liberated base extracted with benzene. Evaporation of the dried (K_2CO_3) benzene solution left an oil which solidified on trituration with light petroleum (b. p. 80—100°). Crystallisation of this solid from *iso*propanol gave N-p-*chlorophenylguanyl* N′-n-*butylthiourea* as colourless prisms, m. p. 97—98° (Found : C, 50·6; H, 6·0; N, 19·6. $C_{12}H_{17}N_4ClS$ requires C, 50·6; H, 6·0; N, 19·7%).

N¹-p-*Chlorophenyl*-N⁴ : N⁵-*di*iso*propyldiguanide* (III; R = R′ = Pr^{β}).—(*a*) *N-p*-Chlorophenylguanyl-*N′-iso*propylthiourea (5·4 g.), *iso*propylamine (5 g.), methanol (15 c.c.), and mercuric oxide (8·6 g.) were stirred at room temperature for 16 hours. The mixture was then filtered and the inorganic residue washed well with methanol. The filtrate and washings were evaporated to dryness. The solid residue was dissolved in ethyl acetate (50 c.c.), and the alkalinity of the solution to brilliant-yellow removed by addition of alcoholic hydrogen chloride. The precipitated *hydrochloride* was collected, dried, and crystallised from alcohol; it formed colourless prisms, m. p. 254° (Found : C, 50·9; H, 7·1; N, 21·2; Cl, 20·9; Cl′, 10·4. $C_{14}H_{22}N_5Cl$,HCl requires C, 50·6; H, 6·9; N, 21·1; Cl, 21·4; Cl′, 10·7%) (5301). The *base*, obtained by the addition of sodium hydroxide to a hot aqueous solution of the hydrochloride, crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 136° (Found : C, 57·1; H, 7·3; N, 23·6; Cl, 12·3. $C_{14}H_{22}N_5Cl$ requires C, 56·9; H, 7·4; N, 23·7; Cl, 12·0%).

(*b*) N^1 : N^2-Di*iso*propyldicyandiamide (0·2 g.), *p*-chloroaniline hydrochloride (0·3 g.), water (5 c.c.), and 2-ethoxyethanol (1 c.c.) were heated at the boil for 3 hours. The product which separated on cooling was filtered off and dissolved in excess of hydrochloric acid. The filtered solution was treated with ammonia to reduce the acidity until it was just acid to Congo-red. On standing, the hydrochloride separated and was purified by crystallisation from water to give the same product as in (*a*), m. p. and mixed m. p. 254°.

N¹-p-*Chlorophenyl*-N⁴ : N⁵-*dimethyldiguanide* (III; R = R′ = Me).—(*a*) A mixture of *N-p*-chlorophenylguanyl-*N′*-methylthiourea (5 g.), methylamine hydrochloride (6·75 g.), sodium methoxide (5·4 g.), methanol (30 c.c.), and mercuric oxide (8·6 g.) was stirred for 18 hours. It was then filtered and the solution evaporated to dryness. The residue was dissolved in a mixture of equal parts of water and hydrochloric acid and the solution treated with sodium hydroxide until it remained only faintly acid to Congo-red. The precipitated *hydrochloride* (3 g.) crystallised from water as colourless prisms, m. p. 249—250° (Found : C, 43·8; H, 5·2; N, 25·2. $C_{10}H_{14}N_5Cl$,HCl requires C, 43·5; H, 5·4; N, 25·4%) (6093).

(*b*) N^1 : N^2-Dimethyldicyandiamide (2 g.), *p*-chloroaniline hydrochloride (3 g.), and water (20 c.c.) were refluxed for 1½ hours. The product which separated on cooling was collected, washed with a little 2-ethoxyethanol, and crystallised from water to give N^1-*p*-chlorophenyl-N^4 : N^5-dimethyldiguanide hydrochloride, m. p. and mixed m. p. 250° (Found : C, 43·8; H, 5·4; N, 25·3%).

N¹-p-*Chlorophenyl*-N⁴-*methyl*-N⁵-*ethyldiguanide* (III; R = Me, R′ = Et).—N^1-Methyl-N^2-ethyldicyandiamide (3 g.) and *p*-chloroaniline hydrochloride (4 g.) were boiled with water (20 c.c.) for 1½ hours. After cooling, the product which had separated was filtered off, dried, and triturated with ethyl acetate

It then crystallised from water to give the *hydrochloride* (6094) as colourless prisms, m. p. 215° (Found : C, 45·6; H, 5·8; N, 24·2. $C_{11}H_{16}N_5Cl$,HCl requires C, 45·5; H, 5·9; N, 24·1%).

N¹-p-*Chlorophenyl*-N⁴-*methyl*-N⁵-iso*propyldiguanide* (III; R = Me, R′ = Pr$^{\beta}$).—*N*-*p*-Chlorophenylguanyl-*N*′-methylthiourea hydrochloride (5·6 g.), methanol (15 c.c.), and sodium methoxide (1·08 g.) were stirred for 10 minutes. *iso*Propylamine (5 g.) and mercuric oxide (8·6 g.) were then added and the stirring continued for 18 hours. The mixture was then filtered and the inorganic residue washed with methanol. The filtrate and washings were evaporated to dryness and the residue dissolved in 2N-hydrochloric acid. The resulting solution, after filtration, was treated with sodium hydroxide so as just to destroy the Congo-red acidity. The precipitated *hydrochloride* crystallised from water as small colourless prisms, m. p. 205—206° (Found : C, 47·4; H, 6·3; N, 22·7. $C_{12}H_{18}N_5Cl$,HCl requires C, 47·4; H, 6·25; N, 23·0%) (5328).

N¹-p-*Chlorophenyl*-N⁴-*methyl*-N⁵-n-*propyldiguanide* (III; R = Me, R′ = Pr$^{\alpha}$).—*N*-*p*-Chlorophenylguanyl-*N*′-*n*-propylthiourea (5·4 g.), methylamine hydrochloride (6·75 g.), sodium methoxide (5·4 g.), methanol (15 c.c.), and mercuric oxide (8·6 g.) were stirred for 16 hours and the mixture then worked up as described above. The *hydrochloride* (5322) crystallised from water as colourless prisms, m. p. 164° (Found : C, 47·2; H, 5·9; N, 22·7. $C_{12}H_{18}N_5Cl$,HCl requires C, 47·4; H, 6·25; N, 23·0%).

N¹-p-*Chlorophenyl*-N⁴-*methyl*-N⁵-n-*butyldiguanide* (III; R = Me, R′ = Bu$^{\alpha}$).—(*a*) *N*¹-Methyl-*N*³-*n*-butyldicyandiamide (2 g.), *p*-chloroaniline hydrochloride (3·2 g.), and water (20 c.c.) were boiled under reflux for 1½ hours. The *hydrochloride* which separated on cooling was purified by crystallisation from water; it formed small colourless prisms, m. p. 175—176° (Found : C, 49·3; H, 6·6; N, 21·9. $C_{13}H_{20}N_5Cl$,HCl requires C, 49·1; H, 6·6; N, 22·0%) (5321).

(*b*) Obtained from *N*-*p*-chlorophenylguanyl-*N*′-*n*-butylthiourea and methylamine as described above for the corresponding *n*-propyl compound, the hydrochloride had m. p. and mixed m. p. 175—176° (Found : C, 48·8; H, 6·4; N, 22·3%).

N¹-p-*Chlorophenyl*-N⁴-*ethyl*-N⁵-iso*propyldiguanide* (III; R = Et; R′ = Pr$^{\beta}$).—Prepared from *N*¹-ethyl-*N*²-*iso*propyldicyandiamide and *p*-chloroaniline, the *hydrochloride* crystallised from water as colourless needles, m. p. 234—235° (Found : C, 49·0; H, 6·6; N, 21·8. $C_{13}H_{20}N_5Cl$,HCl requires C, 49·1; H, 6·6; N, 22·0%) (5569).

N¹-p-*Chlorophenyl*-N⁴-n-*propyl*-N⁵-iso*propyldiguanide* (III; R = Pr$^{\alpha}$, R′ = Pr$^{\beta}$).—Prepared from *N*¹-*n*-propyl-*N*²-*iso*propyldicyandiamide and *p*-chloroaniline hydrochloride in boiling aqueous 2-ethoxyethanol solution, the *hydrochloride* formed colourless needles, m. p. 235—236° (Found : C, 50·9; H, 7·1; N, 21·3. $C_{14}H_{22}N_5Cl$,HCl requires C, 50·6; H, 6·9; N, 21·1%).

N¹-p-*Chlorophenyl*-N⁵-cyclo*hexyl*-N⁴-iso*propyldiguanide* (III; R = Pr$^{\beta}$, R′ = C_6H_{11} *cyclo*).—Prepared from *N*¹-*cyclo*hexyl-*N*²-*iso*propyldicyandiamide and *p*-chloroaniline hydrochloride, the *hydrochloride* crystallised from 2-ethoxyethanol as small colourless prisms, m. p. 238—239° (Found : C, 54·7; H, 7·3; N, 18·6. $C_{17}H_{26}N_5Cl$,HCl requires C, 54·8; H, 7·3; N, 18·8%) (5592).

N¹-p-*Chlorophenyl*-N⁴-n-*propyl*-N⁵-n-*butyldiguanide* (III; R = Pr$^{\alpha}$, R′ = Bu$^{\alpha}$).—Prepared from *N*-*p*-chlorophenylguanyl-*N*′-*n*-propylthiourea and *n*-butylamine, the *hydrochloride* crystallised from water as small colourless needles, m. p. 163—164° (Found : C, 52·0; H, 7·0; N, 20·2. $C_{15}H_{24}N_5Cl$,HCl requires C, 52·1; H, 7·2; N, 20·2%) (5386).

N¹-p-*Ethoxyphenyl*-N⁴-iso*propyl*-N⁵-n-*butyldiguanide*.—Prepared from *N*¹-*iso*propyl-*N*³-*n*-butyldicyandiamide and *p*-phenetidine hydrochloride, the *hydrochloride* crystallised from water as colourless prisms, m. p. 199° (Found : C, 57·6; H, 8·4; N, 19·9. $C_{17}H_{29}ON_5$,HCl requires C, 57·4; H, 8·4; N, 19·7%) (5570).

N¹-(6-*Methoxy*-8-*quinolyl*)-N⁴-n-*propyl*-N⁵-iso*propyldiguanide*.—*N*¹-*n*-Propyl-*N*³-*iso*propyldicyandiamide (3 g.), 8-amino-6-methoxyquinoline hydrochloride (4·5 g.), and 2-ethoxyethanol (15 c.c.) were boiled under reflux for 3 hours. The *hydrochloride* which separated on cooling and adding ethyl acetate was purified by crystallisation from water; it formed pale yellow prisms, m. p. 254° (Found : C, 56·8; H, 7·1; N, 22·0. $C_{18}H_{26}ON_6$,HCl requires C, 57·1; H, 7·1; N, 22·2%) (5752).

N-p-*Chlorophenylguanyl*-S-*methyl*-N′-iso*propyl*iso*thiourea* (IX; R = Cl, R′ = Pr$^{\beta}$, R″ = SMe).—(*a*) *N*-*p*-Chlorophenylguanyl-*N*′-*iso*propylthiourea (8·6 g.), methyl iodide (8 g.), and methanol (40 c.c.) were refluxed for 2 hours and the solution then evaporated to dryness under reduced pressure. The residue was warmed with water to *ca.* 50° and made alkaline to brilliant-yellow with ammonia. The resulting solid was collected, washed with water, and crystallised from dilute alcohol, giving colourless prisms (9·2 g.), m. p. 92° (Found : C, 50·9; H, 5·9. $C_{12}H_{17}N_4ClS$ requires C, 50·6; H, 6·0%). A solution of the *base* in warm dilute hydrochloric acid deposited the *hydrochloride* on cooling; recrystallised from dilute hydrochloric acid it formed colourless prisms, m. p. 201—202° (Found : C, 44·8; H, 5·5; N, 17·6. $C_{12}H_{17}N_4ClS$,HCl requires C, 44·9; H, 5·6; N, 17·45%) (5593).

(*b*) *p*-Chloroaniline (1·27 g.) was dissolved in water (30 c.c.) by the addition of hydrochloric acid to give a solution just acid to Congo-red. This was added to *N*-cyano-*S*-methyl-*N*′-*iso*propyliso*thiourea* (1·57 g.), and a solution of copper sulphate (1 g.) in the minimum quantity of water was added, followed by dioxan (10 c.c.). The mixture was refluxed for 1 hour, cooled, and filtered. The filtrate was extracted with chloroform and then treated with sodium chloride. The precipitated solid was collected and crystallised from water, giving the same hydrochloride (0·3 g.), m. p. 200° (Found : C, 44·5; H, 5·6; N, 17·8; S, 9·7. $C_{12}H_{17}N_4ClS$,HCl requires S, 10·0%).

Reaction of N-p-*Chlorophenylguanyl*-S-*methyl*-N′-iso*propyl*iso*thiourea with Alcoholic Ammonia*.—(*a*) The preceding compound (2 g.) and saturated alcoholic ammonia (50 c.c.) were heated for 6 hours at 120° in a sealed tube. The contents of the tube were evaporated to dryness and the residue stirred with 2N-hydrochloric acid. The resulting solid was filtered off. The filtrate when tested for the presence of diguanide by the method of Gage and Rose (*loc. cit.*) gave a negative result. Crystallisation of the solid from very dilute hydrochloric acid gave N-p-*chlorophenylguanyl*-O-*ethyl*-N′-iso*propyl*iso*urea hydrochloride*, m. p. 175° (Found : C, 49·4; H, 6·5; N, 17·8. $C_{13}H_{19}ON_4Cl$,HCl requires C, 48·9; H, 6·3; N, 17·6%). The hydrochloride when warmed with dilute sodium hydroxide for a few minutes gave an oil which was extracted with benzene, and the extract dried (Na_2SO_4) and evaporated. Crystallisation of the residue from light petroleum (b. p. 80—100°) gave the *base* (IX; R = Cl, R′ = Pr$^{\beta}$, R″ = OEt) as colourless

needles, m. p. 100—101° (Found : C, 54·9; H, 6·7; N, 19·6. $C_{13}H_{19}ON_4Cl$ requires C, 55·2; H, 6·7; N, 19·8%). The *acetate*, prepared from the base in acetone solution with acetic acid, had m. p. 149° (Found : C, 52·4; H, 6·7; N, 16·8. $C_{13}H_{19}ON_4Cl,CH_3{\cdot}CO_2H$ requires C, 52·6; H, 6·7; N, 16·4%).

(*b*) *N*-*p*-Chlorophenylguanyl-*S*-methyl-*N*′-*iso*propyl*iso*thiourea (2 g.) and alcoholic ammonia (40 c.c.) were heated in a sealed tube for 6 hours at 120°. The contents of the tube were evaporated to dryness to leave an oil which was treated with 2N-hydrochloric acid. Part dissolved, leaving a residue of the hydrochloride of *N*-*p*-chlorophenylguanyl-*O*-ethyl-*N*′-*iso*propyl*iso*urea which was removed by filtration. The filtrate was made faintly alkaline to brilliant-yellow with ammonia, and N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride, m. p. and mixed, m. p. 244°, was precipitated.

Reaction of N-p-*Chlorophenylguanyl*-S-*methyl*-N′-iso*propyl*isothiourea *with* iso*Propylamine*.—(IX; R = Cl, R′ = Pr$^\beta$, R″ = SMe) (1 g.) and *iso*propylamine (10 c.c.) were heated for 6 hours at 120° in a closed vessel. Evaporation of the contents left an oil which was extracted with 2N-hydrochloric acid. The extract was filtered and treated with ammonia so as just to destroy the Congo-red acidity. On standing, a precipitate developed (0·7 g.) which was collected and proved to be N^1-*p*-chlorophenyl-N^4 : N^5-di*iso*propyldiguanide hydrochloride. Crystallised from water it formed colourless prisms, m. p. and mixed m. p. 254°.

Condensation of Dimethylcyanamide and Thiourea.—Dimethylcyanamide (7·0 g.) was added to a suspension of thiourea (7·6 g.) in boiling butanol (20 c.c.) and the mixture boiled for 1 hour. On cooling, the resulting solution deposited crystals which were filtered off, washed with butanol, and dried (2·3 g., m. p. 160—162°). Concentration of the mother liquors gave a further crop (2 g.) of the same material of rather lower m. p. The two crops were combined and crystallised from methanol to give *NN*-dimethylthiourea as colourless prisms, m. p. 163—164°, undepressed by an authentic specimen (Found : S, 31·0. Calc. for $C_3H_8N_2S$: S, 30·8%). Wallach (*Ber.*, 1899, **32**, 1873) gives m. p. 158—159°. The final butanol mother liquors were evaporated to dryness under reduced pressure, leaving a brown viscous oil which when treated with methanolic picric acid afforded dimethylguanidine picrate, m. p. 226—228° undepressed in admixture with an authentic specimen (Clarke and Phillips, *J. Amer. Chem. Soc.*, 1923, **45**, 1755).

Guanylthiourea.—Pellets of potassium hydroxide (168 g.) and carbon disulphide (100 c.c.) were added to a well-stirred suspension of dicyandiamide (126 g.) in acetone (1 l.) cooled to − 10° to − 5°. The temperature was then allowed gradually to rise to 15°, and the resulting suspension stirred at 15—25° for a further 3½ hours. The yellow product was filtered off, washed with acetone, and dried (288 g.).

This dipotassium ω-cyanoguanidinodithiocarbonate (118 g.) was dissolved in water (4 l.), and acetic acid added with good stirring until the solution was neutral to litmus. The precipitated 4 : 6-diamino-2-thio-1 : 3 : 5-thiadiazine was filtered off, washed with water, and dried (43 g.); m. p. > 300°.

4 : 6-Diamino-2-thio-1 : 3 : 5-thiadiazine (40 g.), water (500 c.c.), and orthophosphoric acid (37·5 c.c.) were boiled under reflux for 4 hours. The charcoaled and filtered solution was allowed to cool overnight, and guanylthiourea phosphate crystallised; it was collected, washed with water, and dried (yield, 27·5 g.). A further small crop (4 g.) was obtained by evaporation of the mother liquors to small bulk. To a solution of this phosphate (50 g.) in water (500 c.c.) kept at 90° a solution of hydrated barium hydroxide (80 g.) in water (100 c.c.) was added until the solution was faintly alkaline to phenolphthalein. After cooling, the barium phosphate was filtered off and the filtrate evaporated under reduced pressure to small bulk. The *base*, which crystallised, was collected, dried, and crystallised from methanol; it formed colourless prisms, m. p. 175—176° (decomp.) (Found : N, 47·2. $C_2H_6N_4S$ requires N, 47·45%).

p-*Chlorophenylguanylthiourea* (VIII; R = Cl, R′ = H).—*p*-Chlorophenyldicyandiamide (78 g.) and a methanolic solution of hydrogen sulphide (800 c.c., saturated at 0°), containing dissolved sodium (1·6 g.), were heated in a closed vessel at 70—80° for 50 hours. The resulting mixture was filtered and poured into a mixture of water (1600 c.c.) and hydrochloric acid (80 c.c.). The small amount of material precipitated was filtered off, washed, and crystallised from alcohol–water, and consisted of p-*chlorophenyldithiobiuret* (4 g.), m. p. 163—165° (decomp.) undepressed by an authentic sample (see below) (Found : Cl, 14·4; S, 26·6. $C_8H_8N_3ClS_2$ requires Cl, 14·5; S, 26·1%). The acid filtrate from this material was evaporated under reduced pressure to 500 c.c. and cooled. The p-*chlorophenylguanylthiourea hydrochloride* [colourless plates from dilute hydrochloric acid, m. p. 190—191° (decomp.) (Found : Cl, 26·4; S, 12·1. $C_8H_9N_4ClS,HCl$ requires Cl, 26·8; S, 12·1%)], which separated was filtered off, dissolved in hot water (1 l.), and the solution poured into water (100 c.c.) and ammonia (30 c.c., *d* 0·88) to give the *base* as a tar which gradually solidified. It was collected, washed well with water, and crystallised from methanol–water, giving colourless prisms (66 g.), m. p. 166—167° (Found : C, 42·2; H, 4·0; N, 24·5; Cl, 15·6; S, 14·4. $C_8H_9N_4ClS$ requires C, 42·0; H, 3·9; N, 24·5; Cl, 15·5; S, 14·0%).

N-p-*Chlorophenylguanyl*-S-*methyl*iso*thiourea* (IX; R = Cl, R′ = H, R″ = SMe).—*p*-Chlorophenylguanylthiourea (92 g.), methanol (50 c.c.), and methyl iodide (10 c.c.) were boiled under reflux for 4 hours and the solution then evaporated to dryness under reduced pressure. Trituration of the oily residue with ethyl acetate gave N-p-*chlorophenylguanyl*-S-*methyl*iso*thiourea hydriodide* which crystallised from acetone–benzene as colourless prisms (10·7 g.), m. p. 167° (Found : C, 29·5; H, 3·1; S, 8·7. $C_9H_{11}N_4ClS,HI$ requires C, 29·15; H, 3·2; S, 8·6%).

N-p-*Chlorophenylguanyl*-S-*ethyl*iso*thiourea* (IX; R = Cl, R′ = H, R″ = SEt).—Prepared similarly from *p*-chlorophenylguanylthiourea and ethyl iodide, the *hydriodide* crystallised from acetone–benzene as colourless plates, m. p. 179—180° (Found : C, 31·3; H, 3·6; N, 14·5; S, 8·7. $C_{10}H_{13}N_4ClS,HI$ requires C, 31·2; H, 3·6; N, 14·6; S, 8·3%).

N-p-*Chlorophenylguanyl*-S-iso*propyl*iso*thiourea* (IX; R = Cl, R′ = H, R″ = SPr$^\beta$).—A suspension of *p*-chlorophenylguanylthiourea (4·6 g.) in dry alcohol (25 c.c.) was boiled under reflux with *iso*propyl bromide (5 c.c.) for 24 hours. A clear solution was gradually obtained from which crystalline material separated towards the end of the reaction. After cooling, the resulting N-p-*chlorophenylguanyl*-S-iso*propyl*iso*thiourea hydrobromide* was filtered off and crystallised from water containing a little hydrobromic acid; it formed colourless prisms, m. p. 223° (decomp.) (Found : C, 37·9; H, 4·6; S, 9·4; Br′, 22·9. $C_{11}H_{15}N_4SCl,HBr$ requires C, 37·6; H, 4·6; S, 9·1; Br′, 22·8%).

N-p-*Chlorophenylguanyl*-S-*benzyl*iso*thiourea* (IX; R = Cl, R′ = H, R″ = S·CH_2Ph) —*p*-Chlorophenylguanylthiourea (22·8 g.), methanol (150 c.c.), and benzyl chloride (11·5 c.c.) were boiled under

reflux for 2 hours. The crystalline *hydrochloride* which separated on cooling was collected, and the mother liquors evaporated to give a second crop; crystallised from methanol it formed colourless plates, m. p. 226—227° (decomp.) (Found: C, 51·0; H, 4·6; S, 9·4. $C_{15}H_{15}N_4ClS,HCl$ requires C, 50·7; H, 4·5; S, 9·0%).

p-*Chlorophenyldithiobiuret* (Experiments by Dr. N. Barton).—(*a*) Sodium (6·9 g.) was dissolved in alcohol (150 c.c.). To this solution, cooled in ice, finely ground *S*-methyl*iso*thiourea sulphate (44 g.) was added with stirring. After ½ hour a solution of *p*-chlorophenyl *iso*thiocyanate (51 g.) in alcohol (100 c.c.) was added. The mixture was allowed to regain room temperature and stirred for 2 hours. During this time a solid separated which was isolated by dilution with water (600 c.c.) and filtration, washed with water, and dried. Crystallisation from benzene gave 1-p-*chlorophenyl*-4-S-*methyl*iso*dithiobiuret* (63 g.), m. p. 135—137° (Found: C, 42·1; H, 3·9; N, 16·4; S, 24·6. $C_9H_{10}N_3ClS_2$ requires C, 41·6; H, 3·9; N, 16·2; S, 24·7%).

Sodium (9·2 g.) was dissolved in alcohol (400 c.c.), and hydrogen sulphide passed in for 2 hours. 1-*p*-Chlorophenyl-4-*S*-methyl*iso*dithiobiuret (52 g.) was added and the solution refluxed for 1 hour. After filtering and cooling, the solution was acidified with acetic acid and diluted with water to a total volume of 1 l. The solid which separated was filtered off, washed with water, and crystallised from dilute alcohol to give *p*-chlorophenyldithiobiuret, m. p. 164° (decomp., varies with rate of heating) (Found: S, 26·1. Calc. for $C_8H_8N_3ClS_2$: S, 26·1%) (yield, 65%). Repeated recrystallisation of *p*-chlorophenyldithiobiuret frequently leads to decomposition and is to be avoided. The substance is soluble in cold dilute sodium hydroxide, in ammonia, and in dilute sodium carbonate solution on warming.

(*b*) *p*-Chloroaniline (19 g.) and perthiocyanic acid (15 g.) (Chattaway and Stevens, *J.*, 1897, **71**, 607) were ground together and then stirred and heated by means of a boiling water-bath. After about ½ hour the fluid melt solidified. After a further ½ hour's heating the melt was ground and refluxed with carbon disulphide for ½ hour. The undissolved solid was collected, washed with a little carbon disulphide, and dried. It was then dissolved in 2N-sodium hydroxide at 40—50°, the solution filtered to remove insoluble matter, and the filtrate acidified with 2N-hydrochloric acid. The precipitated solid was filtered off, washed with water until acid-free, and crystallised from dilute alcohol to give *p*-chlorophenyldithiobiuret (11·3 g.), m. p. 163—165° (decomp.) undepressed by material made by method (*a*).

p-*Iodophenylguanylthiourea* (VIII; R = I, R′ = H).—*p*-Iodophenyldicyandiamide (42·9 g.) (Part XXVIII, *loc. cit.*) was heated in a pressure bottle with a solution of hydrogen sulphide (10 g.) in methanol (300 c.c.) at 70—80° for 48 hours. After cooling, the mixture was made strongly acid to Congo-red with hydrochloric acid. The crystalline material which separated on standing was collected and crystallised from methanol to give p-*iodophenylguanylthiourea hydrochloride* as colourless plates, m. p. 196—197° (decomp.) (Found: C, 26·6; H, 2·8; N, 15·8; S, 9·2. $C_8H_9N_4IS,HCl$ requires C, 26·9; H, 2·8; N, 15·7; S, 9·0%).

iso*Propylguanylthiourea* (XI; R = Pr$^\beta$, R′ = H).—N^1-*iso*Propyldicyandiamide (12·6 g.) (Part XXVIII) and a saturated (at 0°) solution of hydrogen sulphide in methanol were heated in a pressure bottle at 70—80° for 48 hours. The resulting solution was evaporated to dryness under reduced pressure, leaving an oil which crystallised on stirring with water and standing, and was almost pure iso*propylguanylthiourea* (9 g.). Crystallised from water it formed colourless prisms, m. p. 115—116° (Found: C, 37·8; H, 7·3; N, 35·1; S, 20·4. $C_5H_{12}N_4S$ requires C, 37·5; H, 7·5; N, 35·0; S, 20·0%). Addition of oxalic acid to the liquors from the above base precipitated the oxalate which afforded a further quantity of the base (2·5 g.) on decomposition with alcoholic ammonia.

N-iso*Propylguanyl*-S-*methyl*iso*thiourea* (XII; R = Pr$^\beta$, R′ = H, R″ = Me).—When methyl iodide (3·5 g.) and a solution of *iso*propylguanylthiourea (4·0 g.) in acetone (20 c.c.) were mixed, reaction occurred with evolution of heat. After 1 hour the filtered mixture was evaporated to small bulk and allowed to crystallise. The *hydriodide* (5·65 g.) was filtered off and crystallised from acetone–benzene as colourless plates, m. p. 156—157° (Found: C, 24·2; H, 5·0; S, 10·6. $C_6H_{14}N_4S,HI$ requires C, 23·8; H, 5·0; S, 10·6%).

N-*Butylguanylthiourea* (XI; R = Bu$^\alpha$, R′ = H), prepared from N^1-*n*-butyldicyandiamide and hydrogen sulphide as described above for the *iso*propyl compound, crystallised from water as colourless prisms, m. p. 144—145° (Found: C, 41·2; H, 7·8; N, 32·3; S, 18·7. $C_6H_{14}N_4S$ requires C, 41·4; H, 8·0; N, 32·2; S, 18·4%). When treated with methyl iodide in acetone solution as in the preparation of *S*-methyl-*N*-*iso*propylguanyl*iso*thiourea it was converted into *N*-*n*-butylguanyl-*S*-methyl*iso*thiourea hydriodide which failed to crystallise.

NN-*Diethylguanylthiourea* (XI; R = R′ = Et), prepared from N^1 : N^1-diethyldicyandiamide and hydrogen sulphide, separated from water as colourless prisms, m. p. 118—120° (Found: C, 41·5; H, 7·9; N, 32·0; S, 18·6. $C_6H_{14}N_4S$ requires C, 41·4; H, 8·0; N, 32·2; S, 18·4%).

N-(NN-*Diethylguanyl*)-S-*methyl*iso*thiourea hydriodide* (as XII; R = R′ = Et, R″ = Me), prepared from the preceding compound and methyl iodide, crystallised from acetone–benzene as colourless plates, m. p. 133—134° (Found: C, 26·9; H, 5·4; S, 10·2. $C_7H_{16}N_4S,HI$ requires C, 26·6; H, 5·4; S, 10·1%).

N-*Methyl*-N-iso*propylguanylthiourea* (XI; R = Me, R′ = Pr$^\beta$), prepared from N^1-methyl-N^1-*iso*propyldicyandiamide, crystallised from water as colourless prisms, m. p. 139—140° (Found: C, 41·3; H, 7·8; N, 32·3; S, 18·2. $C_6H_{14}N_4S$ requires C, 41·4; H, 8·0; N, 32·2; S, 18·4%).

N-(N-*Methyl*-N-iso*propylguanyl*)-S-*methyl*iso*thiourea* (XII; R = R″ = Me, R′ = Pr$^\beta$), prepared from (XI; R = Me, R′ = Pr$^\beta$) and methyl iodide, separated from acetone–benzene as colourless rectangular plates, m. p. 183—185° (Found: C, 26·8; H, 5·3; S, 10·5. $C_{17}H_{16}N_4S,HI$ requires C, 26·6; H, 5·4; S, 10·1%).

Attempted Reaction of Methyl iso*Propylcyanamide with* S-*Methyl*iso*thiourea in Acetone.*—Sodium (2·3 g.) was dissolved in acetone (100 c.c.), the solution cooled, and *S*-methyl*iso*thiourea sulphate (14 g.) and methyl*iso*propylcyanamide (9·8 g.) added. The mixture was stirred overnight and the bulk of the solvent removed by evaporation on the steam-bath. The solid product was filtered off, washed with acetone, and extracted with warm methanol. On evaporation to small bulk, the extract deposited crystalline material which was collected and recrystallised from methanol (yield, 2·65 g.); colourless plates, m. p. 222° (decomp.) (Found: C, 41·9; H, 7·0; N, 32·5; S, 18·5. $C_6H_{12}N_4S$ requires C, 41·9;

H, 7·0; N, 32·6; S, 18·6%). From the analysis the substance appeared to be 2-*amino*-4-*methylthio*-6-*dimethyldihydro*-1 : 3 : 5-*triazine* (XIII), and this was supported by the formation of the same substance in approximately the same yield in two separate experiments in which (*a*) dimethylcyanamide was employed in place of methyl*iso*propylcyanamide, and (*b*) no cyanamide was used.

The above compound (2 g.), *p*-chloroaniline hydrochloride (1·7 g.), and water (5 c.c.) were boiled under reflux for 18 hours. Unreacted *p*-chloroaniline was removed by distillation in steam, and the solution filtered from insoluble matter. Addition of the filtrate to sodium hydroxide precipitated a tarry solid which gradually solidified. This was collected, washed with water, and crystallised from 50% alcohol to give a compound which was presumed to be 2-*amino*-4-p-*chloroanilino*-6-*dimethyldihydro*-1 : 3 : 5-*triazine* (XIV), m. p. 130—131° undepressed by the material described below.

Condensation of p-*Chlorophenyldiguanide with Acetone.*—*p*-Chlorophenyldiguanide hydrate (32·5 g.) (Part IV, *loc. cit.*), acetone (130 c.c.), and piperidine (2 c.c.) were refluxed for 15 hours, cooled, treated with decolourising carbon, and filtered. The filtrate was poured into water (280 c.c.), allowed to stand for 2 hours, and the solid collected, washed with water, and crystallised from aqueous alcohol to give a product (believed to be 2-amino-4-*p*-chloroanilino-6-dimethyldihydro-1 : 3 : 5-triazine) as colourless prisms (yield, 13 g.), m. p. 130—131° (Found : C, 49·2; H, 5·4; N, 26·1. $C_{11}H_{14}N_5Cl,H_2O$ requires C, 49·0; H, 5·2; N, 26·0%). The substance loses water at its m. p., and recrystallisation of the resulting material from aqueous alcohol affords the original hydrate. It does not form a copper complex with ammoniacal copper sulphate.

Reaction of p-*Chlorophenylguanylthiourea with* iso*Propylamine in Presence of Mercuric Oxide.* (*a*) *p*-Chlorophenylguanylthiourea (23 g.) was dissolved in methanolic *iso*propylamine (200 c.c. of 32·5%), and the solution stirred with mercuric oxide (43 g.) for 48 hours at room temperature. It was then heated at 40—50° for 2 hours, cooled, and filtered. The filtrate was evaporated to dryness and the residue extracted twice with a mixture of water (50 c.c.) and 2N-hydrochloric acid (20 c.c.) at 60—65° for a few minutes and filtered cold. The residue was washed well with water, dried, and crystallised from methanol to give *p*-chlorophenyldicyandiamide (yield, 14·5 g., 74·5%), m. p. 203° undepressed by an authentic specimen. The above acid extracts were combined and added to sodium hydroxide solution to give a tarry precipitate which was collected, heated with 5% acetic acid at 90—100°, and then cooled. The insoluble material which was collected by filtration consisted of unchanged starting material (14·5%). The acetic acid extract was made alkaline with sodium hydroxide and extracted with benzene. The dried benzene extract was evaporated to dryness; a little acetic acid was added to the residue, and the excess removed by evaporation. On stirring the residue with acetone, a small amount of material remained undissolved which was identified as N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. and mixed m. p. 184—185° (yield, <0·5%).

(*b*) A suspension of *iso*propylamine hydrochloride (3·2 g.), *p*-chlorophenylguanylthiourea (6·9 g.), and mercuric oxide (6·5 g.) in nitrobenzene (20 c.c.) was stirred at 130—135° for 18 hours. After cooling the mixture was stirred with 2N-hydrochloric acid (40 c.c.) for 1 hour and filtered from mercuric sulphide. The acid layer was separated, and the nitrobenzene re-extracted with 2N-hydrochloric acid (20 c.c.). The combined acid extracts were freed from nitrobenzene by extraction with benzene, clarified by filtration through kieselguhr, and made alkaline (brilliant-yellow) with ammonia. The precipitated product was filtered off and crystallised from water; m. p. 243—244° undepressed in admixture with the hydrochloride of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (yield, 2 g.).

Reaction of p-*Chlorophenyldicyandiamide with* iso*Propylamine at Low Temperatures.*—*p*-Chlorophenyldicyandiamide (19·5 g.) in methanol (200 c.c.) containing *iso*propylamine (65·0 g.) was stirred at room temperature for 48 hours and then at 40—50° for 2 hours. The solution was then evaporated to dryness and extracted with 5% acetic acid (50 c.c.) at 50—60°. The insoluble material was unchanged *p*-chlorophenyldicyandiamide (18·4 g.). The acetic acid extract was poured into excess of sodium hydroxide solution and extracted with benzene. Evaporation of the dried benzene solution left a small quantity of oil which was dissolved in ether and the solution neutralised with acetic acid. On evaporation and lixiviation of the residue with acetone, a small amount of a substance was obtained which was identified as N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. 184—186° (yield, <0·5%).

A similar experiment performed with the addition of mercuric oxide (43 g.) gave a rather higher yield (2·5%) of diguanide.

Reaction of p-*Chlorophenylguanylthiourea with Mercuric Oxide.*—*p*-Chlorophenylguanylthiourea (1·15 g.), mercuric oxide (2·2 g.), and methanol (15 c.c.) were heated under reflux for 20 hours, and the mixture then filtered. Acidification of the filtrate with hydrochloric acid and dilution with water gave *p*-chlorophenyldicyandiamide (yield, 0·35 g.), m. p. and mixed m. p. 200—201°.

Reaction of p-*Iodophenylguanylthiourea with* iso*Propylamine.*—*p*-Iodophenylguanylthiourea hydrochloride (7·1 g.), *iso*propylamine (1·2 g.), and mercuric oxide (4·3 g.) were heated in nitrobenzene at 130—135° for 18 hours with stirring. The cooled mixture was stirred with 2N-hydrochloric acid and then filtered. The two layers were separated, and the nitrobenzene layer extracted again with 2N-hydrochloric acid. The combined acid extracts were shaken with benzene, separated, and made faintly alkaline (brilliant-yellow) with ammonia. The precipitated product crystallised from water to give N^1-*p*-iodophenyl-N^5-*iso*propyldiguanide hydrochloride (2·1 g.) (Part XXVIII), m. p. and mixed m. p. 237—239°.

Reaction of iso*Propylguanylthiourea with Mercuric Oxide.*—*iso*Propylguanylthiourea (2·0 g.) and mercuric oxide (6·0 g.) were stirred with a 25% solution of trimethylamine in alcohol (20 c.c.) for 18 hours at 50—60°. The resulting suspension was filtered, and the filtrate evaporated to small bulk and cooled. The crystalline material which separated was collected and crystallised from aqueous methanol; m. p. 203—208° [Found : C, 37·9; H, 6·5; N, 34·9; *M* (Rast), 155. Calc. for $C_5H_{10}N_4S$: C, 38·0; H, 6·35; N, 35·4%; *M*, 158], and was considered to be a mixture of two or more of the several possible oxidation products of *iso*propylguanylthiourea. The filtrate from this material was evaporated to dryness and dissolved in dioxan. On standing, crystals of *iso*propyldicyandiamide separated; m. p. 113—115° undepressed in admixture with authentic material ($\frac{1}{2}C_4H_8O_2$) (Part XXVIII).

Reaction of iso*Propylguanylthiourea with* p-*Bromoaniline.*—*p*-Bromoaniline (8·6 g.) was dissolved in

2N-hydrochloric acid (25 c.c.), and *iso*propylguanylthiourea (8 g.) and mercuric oxide (11 g.) added. After 1 hour's stirring the mixture was boiled under reflux for a further hour, then acidified with 2N-hydrochloric acid and cooled. To precipitate any soluble mercury a little sodium sulphide was added and the mixture filtered. The filtrate was neutralised with ammonia, and the precipitated product filtered off and crystallised from water. It had m. p. 243—244°, identical with the N^1-*p*-bromophenyl-N^5-*iso*propyldiguanide hydrochloride previously described (Part XXVIII).

Reaction of p-*Chlorophenylguanyl*-S-*methyliso*thiourea *with Alkylamines.*—(a) *Methylamine.* (i) In methanol. *p*-Chlorophenylguanyl-*S*-methyl*iso*thiourea hydriodide (2·6 g.) was added to a cooled methanolic methylamine solution (19 c.c. of 13%), the temperature being kept below 10°. After 4 days at room temperature the solution was evaporated to dryness and the residue treated with N-hydrochloric acid (20 c.c.) at 50—60°. After cooling, filtration left a residue which was identified as *p*-chlorophenyldicyandiamide, m. p. and mixed m. p. 202° (0·25 g.). The filtrate was poured into excess of sodium hydroxide to give an oil which was isolated by extraction with benzene followed by evaporation of the benzene extract. It was converted into the hydrochloride by suspending in warm water, neutralising with 2N-hydrochloric acid and allowing the filtered solution to cool. The product which crystallised (0·25 g.) was identified as N^1-*p*-chlorophenyl-N^5-methyldiguanide hydrochloride (Part X), m. p. and mixed m. p. 227—228°.

(ii) In aqueous methanol. *p*-Chlorophenylguanyl-*S*-methyl*iso*thiourea hydriodide (1 g.) was dissolved in methanol (15 c.c.) and aqueous methylamine (20 c.c. of 21%) added gradually with cooling (temperature below 20°). The mixture was left for 6 days at room temperature and then evaporated to dryness. Acid extraction of the residue with cold 2N-hydrochloric acid afforded no detectable diguanide. The acid-insoluble material was pure *p*-chlorophenyldicyandiamide (0·45 g.), m. p. and mixed m. p. 201—202°.

(b) *Dimethylamine.* The hydriodide of (IX; R = Cl, R′ = H, R″ = SMe) (2·6 g.) was added to methanolic dimethylamine (14 c.c. of 24%), the temperature being kept below 10°, and the mixture left for 4 days. Evaporation of the solution to dryness gave a residue which was completely soluble in N-hydrochloric acid. This acid solution was poured into excess of sodium hydroxide, to give a precipitate of almost pure N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide (yield, 90%), m. p. 168—169° undepressed by an authentic specimen (Part X).

(c) iso*Propylamine.* (i) *p*-Chlorophenylguanyl-*S*-methyl*iso*thiourea hydriodide (1 g.) was dissolved in methanol (10 c.c.), and *iso*propylamine added below 20°. After 6 days the mixture was evaporated to dryness, and the residue extracted with cold 2N-hydrochloric acid (10 c.c.), leaving undissolved *p*-chlorophenyldicyandiamide (yield, 20%), m. p. and mixed m. p. 200—201°. The acid extract was poured into excess of sodium hydroxide solution to give an oily precipitate which gradually solidified. This material was collected, washed with water, dried, and dissolved in a small quantity of acetone. Addition of an acetone solution of acetic acid to destroy the alkalinity to brilliant-yellow gave a precipitate of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate (yield, 20%), m. p. and mixed m. p. 184—185°.

(ii) *p*-Chlorophenylguanyl-*S*-methyl*iso*thiourea hydriodide (1·85 g.) was mixed into a thin paste with *iso*propylamine (0·5 g.) and water (1 c.c.), and the mixture heated to 130° during 1 hour under an air condenser. After a further 15 hours at 130—135°, the melt was boiled for a short time with 2N-sodium hydroxide, cooled, and extracted with ether. The ether extract was in turn extracted with 2N-acetic acid, the extract basified with sodium hydroxide, and the liberated base extracted with ether. This ether extract was shaken with 2N-hydrochloric acid, and the acid extract separated and made faintly alkaline (brilliant-yellow) with ammonia to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride, m. p. and mixed m. p. 243—244° (yield, 70%).

(d) *Methyliso*propylamine. *p*-Chlorophenylguanyl-*S*-methyl*iso*thiourea hydriodide (1 g.) dissolved in methanol (10 c.c.) was treated with methyl*iso*propylamine (4 c.c.), the mixture being kept below 20°. After 6 days the mixture was worked up by evaporation and extraction with cold 2N-hydrochloric acid to give *p*-chlorophenyldicyandiamide (0·3 g.) and an acid-soluble portion. The base obtained from the latter was converted by means of acetic acid in acetone into its acetate (0·05 g.) which was identical with N^1-*p*-chlorophenyl-N^5-methyl-N^5-*iso*propyldiguanide acetate (Part X), m. p. and mixed m. p. 212—213°.

Condensation of N-iso*Propylguanyl*-S-*methyliso*thiourea *Hydriodide with* p-*Chloroaniline.*—*p*-Chloroaniline (1·3 g.), the hydriodide of (XII; R = Pr$^\beta$, R′ = H, R″ = Me) (3·0 g.), and water (5 c.c.) were refluxed for 18 hours. Unreacted *p*-chloroaniline was removed by steam distillation, leaving the hydriodide of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (needles from water, m. p. 170—171°) which was converted into the base by dissolution in water and basification with sodium hydroxide. The base, isolated by ether extraction, afforded the hydrochloride of (III; R = Pr$^\beta$, R′ = H), m. p. and mixed m. p. 243—244° (yield, 30%).

Condensation of N-iso*Propylguanyl*-S-*methyliso*thiourea *Hydriodide with* p-*Anisidine.*—*p*-Anisidine (1·2 g.) and (XII; R = Pr$^\beta$, R′ = H, R″ = Me) hydriodide (3·0 g.) were boiled with water (5 c.c.) for 18 hours. The mixture was diluted with water (15 c.c.) and extracted with ether. The aqueous layer was made alkaline to Clayton-yellow with sodium hydroxide, and the resulting oil extracted with ether. The ethereal solution was neutralised with 2N-hydrochloric acid; crystals of N^1-*p*-methoxyphenyl-N^5-*iso*propyldiguanide hydrochloride (forthcoming publication) separated, m. p. and mixed m. p. 230—231° (yield, 47·5%).

Condensation of N-(N-*Methyl*-N-iso*propylguanyl*)-S-*methyliso*thiourea *Hydriodide with* p-*Chloroaniline.*—*N*-(*N*-Methyl-*N*-*iso*propylguanyl)-*S*-methyl*iso*thiourea hydriodide (3·2 g.), *p*-chloroaniline (1·3 g.), and water (5 c.c.) were refluxed for 20 hours. The resulting mixture was made faintly alkaline (brilliant-yellow) with ammonia, and unreacted *p*-chloroaniline removed by steam distillation. On cooling, the hydriodide of N^1-*p*-chlorophenyl-N^5-methyl-N^5-*iso*propyldiguanide separated (m. p. 224° after crystallisation from water) (yield, 13%); it was identified by conversion into the corresponding acetate (Part X), m. p. and mixed m. p. 212°.

Condensation of N-n-*Butylguanyl*-S-*methyliso*thiourea *Hydriodide with* p-*Bromoaniline.*—*p*-Bromoaniline (8·0 g.) was added to an aqueous solution of an equivalent quantity of crude *N*-*n*-butylguanyl-*S*-methyl*iso*thiourea hydriodide (see above) in water (25 c.c.), and the solution boiled under reflux for

22 hours. Ammonia was added to make the solution faintly alkaline to brilliant-yellow, followed by steam distillation to remove unreacted *p*-bromoaniline. After dilution with water to 80 c.c., hydrochloric acid was added until the mixture was acid to Congo-red. A little insoluble matter was removed by filtration, and the filtrate added to excess of sodium hydroxide solution. The precipitated base was extracted with benzene, and the product re-extracted from the benzene as its hydrochloride by shaking with 2N-hydrochloric acid. Addition of ammonia to this acid extract precipitated N^1-*p*-bromophenyl-N^5-*n*-butyldiguanide hydrochloride (first prepared by another route to be described in a forthcoming publication), m. p. and mixed m. p. 210°.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9. [*Received, November 26th*, 1947.]