Synthetic Antimalarials. Part XLIX. The Structure and Synthesis of the Dihydrotriazine Metabolite of Proguanil.*

By H. C. CARRINGTON, A. F. CROWTHER, and G. J. STACEY.

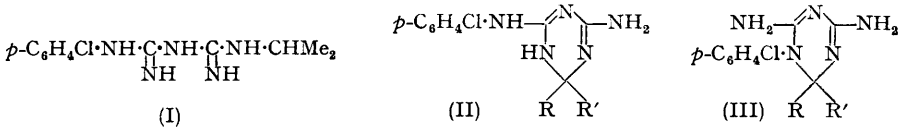
[Reprint Order No. 4755.]

The reaction between *p*-chlorophenyldiguanide and acetone under acid conditions yields a compound identical with the highly active metabolite (Crowther and Levi, *Brit. J. Pharmacol.*, 1953, **8**, 93) of the antimalarial drug "Paludrine" (proguanil, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide). The compound is readily converted under alkaline conditions into an inactive isomer, 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; R = R′ = Me) (cf. Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645), the structure of which has been confirmed by the optical resolution of its 2-ethyl-2-methyl homologue (II; R = Me, R′ = Et).

From a study of the reactions of the active metabolite of proguanil, and of the condensation under both acid and basic conditions of a number of N^1-aryldiguanides bearing other substituents on one or more of the nitrogen atoms, it is concluded that the active metabolite is 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (III; R = R′ = Me).

THE isolation of a metabolite of "Paludrine" (proguanil, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide) (I) with high antimalarial activity, from the urine of rabbits and of human volunteers receiving the drug, was described by Carrington, Crowther, Davey, Levi, and Rose (*Nature*, 1951, **168**, 1080), and a detailed account of this work has since been given by Crowther and Levi (*Brit. J. Pharmacol.*, 1953, **8**, 93). The present communication describes studies on the structure of this and related substances.

The active metabolite, strongly basic in nature, was characterised first as the picrate, and then as the free base, and was found to have the empirical formula $C_{11}H_{14}N_5Cl$, the molecule having two atoms of hydrogen less than that of proguanil itself. On treatment with warm dilute aqueous sodium hydroxide, it was readily converted into an isomeric compound which had no antimalarial activity and was identical with 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; R = R′ = Me) which Birtwell, Curd, Hendry, and Rose (*J.*, 1948, 1645) had already prepared both by heating *p*-chlorophenyldiguanide with



(I) (II) (III)

acetone in the presence of piperidine, and by the reaction of 4-amino-1 : 2-dihydro-2 : 2-dimethyl-6-methylthio-1 : 3 : 5-triazine with *p*-chloroaniline hydrochloride. The two isomers were differentiated by the melting points of the free bases and of the picrates. The bases differed markedly in solubility, the active metabolite being the more soluble in water and the less soluble in ether. Most convenient for identification were the characteristic differences between their ultra-violet absorption spectra, both in acid (see Fig. 1) and in alkaline solution. It was later found that additional alkali was unnecessary for the isomerisation of the active metabolite. Transformation to the inactive isomer occurred when an aqueous solution of the free base was warmed, or when the solid base was heated to its melting point. Neither isomer formed a complex with copper salts.

The difficulties involved in the isolation of the metabolite limited the structural studies that could be carried out with the natural product. However, since the active metabolite was stable in neutral solution, modification of the reaction conditions used by Birtwell *et al.* (*loc. cit.*) for preparation of the inactive isomer from *p*-chlorophenyldiguanide and acetone led to formation of the active compound : the latter was obtained in very small yield by

* Part XLVIII, *J.*, 1951, 1780.

heating *p*-chlorophenyldiguanide hydrochloride with acetone in aqueous solution, and in nearly theoretical yield in the presence of a small excess of acid. The identity of the synthetic with the natural material was confirmed by melting points of the base and of the picrate, by ultra-violet absorption spectra, by its similar antimalarial activity, and by conversion into the inactive isomer.

The synthetic method * could be modified in various ways. Thus, the diguanide hydrochloride was prepared from *p*-chloroaniline hydrochloride and dicyandiamide, and without isolation brought into reaction with acetone and hydrochloric acid to give the metabolite. Alternatively, the amine, dicyandiamide, acetone, and two equivalents of hydrochloric acid could be used. Acetone could be replaced by its bisulphite compound, diethyl acetal, or *iso*propenyl acetate. In all these condensations under acid conditions the inactive isomer was not formed, even in traces. In the absence of a catalyst, acetone failed to react with *p*-chlorophenyldiguanide base. The condensation in the pre-

FIG. 1.

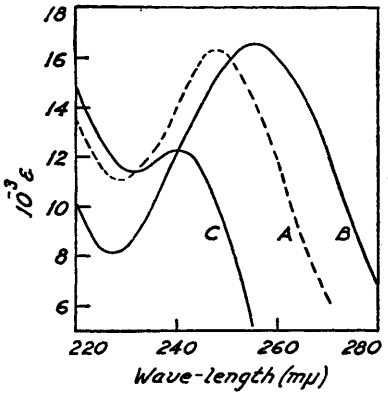


FIG. 2.

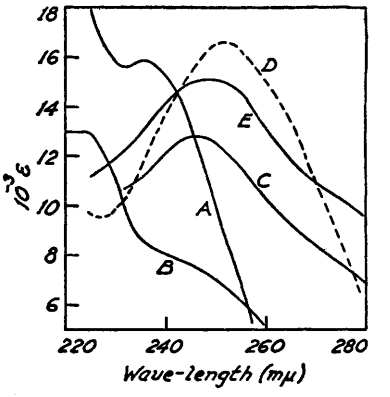


FIG. 1. *Absorption spectra in* 0·01N-HCl.
A, 4-*Amino*-6-(p-*chloro*-N-*methylanilino*)-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = Me, R′ = H, R″ = NH_2).
B, 4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (II; R = R′ = Me).
C, 4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (III; R = R′ = Me).

FIG. 2. *Absorption spectra of*: (a) 4-*Amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-6-*methylamino*-1 : 3 : 5-*triazine* (IX; X = Cl, R = NHMe, R′ = H): *A*, *In* 0·01N-HCl; *B*, *in* 0·1N-NaOH; *C*, *in* 0·1N-NaOH, *after* 20 *min. at* 100° *in* 0·1N-NaOH. (b) 4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = H, R′ = Me, R″ = NH_2) : *D*, *in* 0·01N-HCl; *E*, *in* 0·1N-NaOH.

sence of acid was a reversible reaction, for when heated with dilute aqueous acid the active compound was readily hydrolysed to acetone and the diguanide. Furthermore, the yield obtained in the condensation was dependent upon the excess of acetone used.

Somewhat later, it became known to us (personal communication from Dr. S. Farber) that workers at the Children's Hospital in Boston had independently discovered the synthetic reaction between aryldiguanides and acetone under acidic conditions, and had studied some biological properties of the products. A preliminary account of their work has been published (Modest, Farber, Foley, Pechet, and Diamond, *J. Amer. Chem. Soc.*, 1952, **74**, 855).

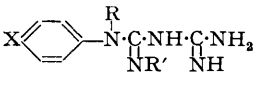
The synthesis of the active compound unfortunately made little direct contribution to a proof of its structure. It did, however, provide ample supplies of material for further study, and made possible the synthesis of analogous substances which were of great value in later structural work.

The conditions used by Birtwell *et al.* (*loc. cit.*) for the isolation of 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine from the reaction of *p*-chloroaniline

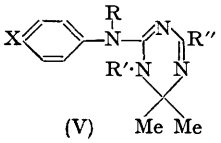
* Patent protection pending.

hydrochloride with 4-amino-1 : 2-dihydro-2 : 2-dimethyl-6-methylthio-1 : 3 : 5-triazine were such that the active metabolite, had it been the initial product, would have undergone isomerisation. The possibility existed, therefore, that the structure assigned to the inactive isomer was really that of the active substance. It was therefore decided first to seek further confirmatory evidence for the proposed structure of the inactive compound.

Valuable information was obtained from a study of the products of the condensation of N^1-aryl-N^1-methyldiguanides with acetone. For these products, structures of the type (III) are clearly impossible. N^1-*p*-Chlorophenyl-N^1-methyldiguanide (IV; X = Cl, R = Me, R′ = H) condensed with acetone in the presence of either piperidine or hydrochloric acid, giving the same product. It was considered to be 4-amino-6-(*p*-chloro-*N*-methylanilino)-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (V; X = Cl, R = Me, R′ = H, R″ = NH_2). The ultra-violet absorption spectrum of this compound was closely similar to that of the inactive isomer, and different from that of the active metabolite (see Fig. 1). Similar results were obtained from a parallel series of experiments with N^1-methyl-N^1-phenyldiguanide (IV; X = R′ = H, R = Me). A structure such as (III) is therefore excluded for the inactive isomer.

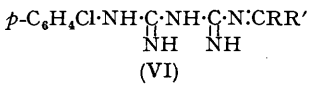


(IV)

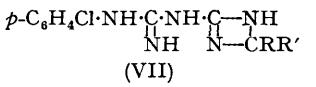


(V)

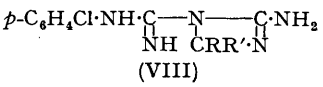
A study of analogues of the inactive isomer bearing two different substituents in the 2-position provided further evidence. *p*-Chlorophenyldiguanide condensed with ethyl methyl ketone in the presence of aqueous hydrochloric acid to give the analogue of the active body, which isomerised when heated as the base in aqueous solution. The 4-amino-6-*p*-chloroanilino-2-ethyl-1 : 2-dihydro-2-methyl-1 : 3 : 5-triazine (II; R = Me, R′ = Et) thus obtained was resolved by use of (+)-tartaric acid, the dextrorotatory base being isolated. This gave strong support to a 6-membered ring structure for the inactive isomer and its analogues. The Schiff's base form (VI) would not be resolvable, nor, in view of the tautomeric properties of the guanidine system, would the 4-membered ring structure (VII). A compound with the improbable structure (VIII) would be expected to form a copper complex. Since, of the two possible 6-membered ring structures, (III) has already been excluded, the formulation (II), suggested by Birtwell *et al.* (*loc. cit.*), seems to be well founded.



(VI)



(VII)



(VIII)

Several other derivatives of 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; R = R′ = Me) have been prepared. With acetic anhydride it formed a diacetyl derivative, and it reacted with *p*-chlorophenyl *iso*thiocyanate to give what is believed to be 6-*p*-chloroanilino-4-*p*-chlorophenylthioureido-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine. With nitrous acid it gave 6-*p*-chloroanilino-1 : 2-dihydro-4-hydroxy-2 : 2-dimethyl-1 : 3 : 5-triazine (V; X = Cl, R = R′ = H, R″ = OH), also obtained by heating *p*-chlorophenylguanylurea with acetone and piperidine. It is noteworthy that the group attacked by nitrous acid corresponds with N^4 of the diguanide from which (II) is derived, whereas the diguanides themselves are attacked at N^2 (Curd, Davey, and Richardson, *J.*, 1949, 1732). The isomeric *N*-*p*-chlorophenyl-*N*′-guanylurea with acetone and piperidine gave what appeared to be 4-amino-1-*p*-chlorophenyl-1 : 2-dihydro-6-hydroxy-2 : 2-dimethyl-1 : 3 : 5-triazine (IX; X = Cl, R = OH, R′ = H).

Attention was next directed to a study of the active metabolite. The most likely structure for this substance, provided that no major rearrangement had occurred during the removal in the animal of two hydrogen atoms from the proguanil molecule, appeared to be 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (III; R =

R′ = Me). In view of the ready reversibility of the synthetic reaction between *p*-chlorophenyldiguanide and acetone, it was thought unlikely that a hydrogen atom of the benzene ring was involved in the metabolic dehydrogenation. It was also considered probable that in the molecule of the active compound the three-carbon unit of acetone (the *iso*propyl group of proguanil) was linked to N^5 of the diguanide. With these restrictions, the number of possible formulæ, theoretically very large, was greatly reduced, and the next most likely structures were considered to be (VI; R = R′ = Me)—(VIII; R = R′ = Me).

The failure of the active compound to form a complex with ammoniacal copper sulphate was considered, as in the case of the inactive isomer (Birtwell *et al.*, *loc cit.*), to be evidence in favour of a cyclic structure.

In this series also, analogues with two different substituents in the 2-position should be capable of optical resolution, but efforts to carry out such resolutions have been unsuccessful. The compound (III; R = Me, R′ = Et) combined with (+)-tartaric acid to give a crystalline salt which, although prepared from equimolecular proportions of acid and base in ethanol, contained only one molecule of tartaric acid to two molecules of base. The salt appeared to be homogeneous, for it was unchanged on repeated crystallisation. Its rotation corresponded to that of the (+)-tartrate of an optically inactive base, and the base recovered from it was, in fact, inactive. Attempts to resolve (III; R = H, R′ = Pr^i) with (+)-tartaric acid, and (III; R = H, R′ = Et) with (+)-camphorsulphonic acid also failed.

Under mild conditions the active metabolite did not react with nitrous acid. Under more vigorous conditions far-reaching decomposition occurred, and no characteristic product was obtained. With *p*-chlorophenyl *iso*thiocyanate it gave only a monothiourea derivative.

It was shown by Crowther, Curd, and Rose (*J.*, 1951, 1780) that phenyldiguanide can be directly halogenated in the *p*-position of the aromatic nucleus. Halogenation experiments on the isomers formed from phenyldiguanide and acetone have shown an interesting difference in behaviour. Whereas the isomer of the inactive type resembles the diguanide in that it is readily chlorinated or brominated in the *p*-position, the compound of the active series is much more resistant.

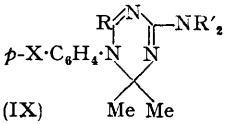
As it seemed unlikely that a rigid proof of the structure of this very labile substance would be obtained merely by degradative experiments, the condensation with acetone, under both acidic and basic conditions, of aryldiguanides bearing additional substituents in the diguanide grouping at N^2, N^4, and N^5 was studied. These substituents would be expected to limit the ways in which condensation with acetone could occur, but it should be borne in mind that, in general, the acid-catalysed condensations take place more smoothly, and in better yield, than those catalysed by bases. When condensation to an active type in acid conditions is impossible, an inactive type may be formed, as already noted in the case of the N^1-aryl-N^1-methyldiguanides. The condensation products were readily classified on the basis of their ultra-violet absorption spectra.

N^1-*p*-Chlorophenyl-N^5N^5-dimethyldiguanide (X; R = H, R′ = R″ = Me) reacted in the normal way, yielding one isomer under acidic, and the other under basic, conditions. In this case the active compound, which could not have a four-membered ring structure of the type (VII), was transformed into the inactive form with unusual facility in the presence of alkali, and the method of isolation had to be modified.

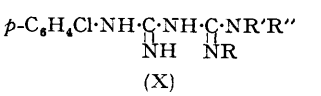
N^1-*p*-Chlorophenyl-N^2N^2-dimethyldiguanide (XI) did not condense with acetone, under either acidic or basic conditions. The failure to form an inactive isomer of type (II) was to be expected, but the failure to condense under acid conditions was surprising. The diguanide itself had certain unusual properties, as, for example, its high melting point and its low solubility in ether.

N^1-*p*-Chlorophenyl-N^4N^5-dimethyldiguanide (X; R = R′ = Me, R″ = H), with a basic catalyst, gave no condensation product that could be isolated. After a long reaction time under acid conditions there was obtained a small amount of the picrate of an ether-soluble base, which from its ultra-violet absorption spectrum and its stability to alkali appeared to have the structure (XII). Had a compound of the active type been formed, then the possibility of the metabolite's having a Schiff's base structure (VI) would have been elimin-

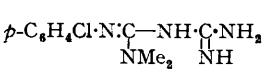
ated. In view of the difficulties experienced with this diguanide, it was not surprising that N^1-*p*-chlorophenyl-$N^2N^4N^5$-trimethyldiguanide did not condense with acetone under either basic or acidic conditions.



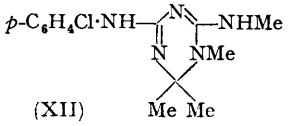
(IX)



(X)



(XI)



(XII)

The results obtained with N^1N^2-disubstituted diguanides were of great interest. With N^1-*p*-chlorophenyl-N^2-methyldiguanide (IV; X = Cl, R = H, R′ = Me) two products were obtained by the usual procedures. When however the isomerisation of the compound from the acid-catalysed condensation (IX; X = Cl, R = Me·NH, R′ = H) was studied, the ultra-violet absorption spectrum of the product suggested that it was an equilibrium mixture of the two isomeric forms, and this view was strengthened when it was found that caustic alkali-treatment of the base-catalysed condensation product (V; X = Cl, R = H, R′ = Me, R″ = NH_2) gave a similar mixture. The absorption spectrum of the equilibrium mixture indicated that it contained between three and four parts of the inactive to one part of the active isomer (see Fig. 2). Owing to the similar solubility of the two bases in ether the components of the mixture could not readily be separated in the usual way, but the mixed hydrochlorides were separated by counter-current distribution between water and butanol. The two fractions were again characterised by their absorption spectra.

Apart from the structural implications, these results with N^1-*p*-chlorophenyl-N^2-methyldiguanide show that the two types of condensation with acetone are quite distinct. If the reaction in the presence of piperidine had first given the aryl-dihydrotriazine which then, under the basic conditions obtaining, had rearranged to give the anilino-dihydrotriazine a mixture of the two would have been expected. Since however the anilino-compound was isolated readily in a pure state its formation must have been independent of that of its isomer. The formation of the *N*-methylanilino-type (V; R = Me, R′ = H, R″ = NH_2) from N^1-aryl-N^1-methyldiguanides mentioned above, which cannot proceed by way of an aryldihydrotriazine, bears out this conclusion.

N^1N^2-Di-*p*-chlorophenyldiguanide (IV; X = Cl, R = H, R′ = *p*-C_6H_4Cl), when condensed with acetone under either acidic or basic conditions, gave one and the same product. This was stable to alkali, the absence of any isomerisation being shown clearly by the ultra-violet absorption characteristics. A similar result was obtained with N^1N^2-diphenyldiguanide (IV; X = R = H, R′ = Ph).

The results with these N^1N^2-disubstituted diguanides gave the only positive evidence of structure obtained from the experiments on the condensation reactions of polysubstituted diguanides. Since members of the inactive series have already been shown to have the dihydrotriazine structure (II), the only ready explanation of the equilibrium between the two isomers in the condensation of N^1-*p*-chlorophenyl-N^2-methyldiguanide with acetone is found in the formulation of both as dihydrotriazine derivatives. Again, the failure to obtain, from the two N^1N^2-diaryldiguanides, isomers unstable to alkali indicated that acidic conditions for the condensation led directly to dihydrotriazines, which, in this case, were necessarily identical with those formed under basic conditions.

Attempts to synthesise the active metabolite by methods which would provide an unambiguous proof of structure have been unsuccessful. For example, the direct addition of dicyandiamide to compounds of the acetone anil type, would, if it gave compounds of the active type, be some confirmation of the triazine structure. The Schiff's bases from ketones and aromatic amines are not very well-characterised substances, and therefore the reaction between benzylideneaniline and dicyandiamide was chosen for study. In the absence of acid no reaction was observed, but, with acid present, a small yield of 4 : 6-

diamino-1 : 2-dihydro-1 : 2-diphenyl-1 : 3 : 5-triazine was obtained, identical with the product isolated from the condensation of phenyldiguanide with benzaldehyde in the presence of acid. Unfortunately, the Schiff's base itself is hydrolysed to its components under acid conditions, so that the synthesis has no real structural significance.

To sum up the evidence, the failure to form a copper complex, the halogenation experiments, and the results of the condensations of the N^1N^2-disubstituted diguanides, all favour the dihydrotriazine structure (III) for the active metabolite. Against this must be put the failure to resolve the condensation products with aldehydes or unsymmetrical ketones, and perhaps the formation of the inactive type of product from the acid condensation of N^1-*p*-chlorophenyl-N^4N^5-dimethyldiguanide and acetone. These results would best be explained by the Schiff's base structure (VI). On balance the evidence is considered to favour the structure (III), and this has been established beyond doubt by the *X*-ray crystallographic studies of Miss M. Bailey (*Acta Cryst.*, 1954, in the press).

Experimental

Rearrangement of 4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (III; R = R′ = Me).—4 : 6-Diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (crude base prepared from crude picrate isolated from the urine of rabbits dosed with proguanil) (Crowther and Levi, *loc. cit.*) (0·128 g.) was dissolved in warm water (4 c.c.). The solution was boiled for about 2 min., filtered whilst hot, and cooled. The colourless elongated parallelepipeds which separated were collected, washed with water, and dried; they had m. p. 135°, undepressed on admixture with 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine hydrate (Birtwell *et al.*, *loc. cit.*). Ultra-violet absorption in 0·005N-HCl: $\lambda_{max.}$ 255 mμ (ε 16,900). The picrate was prepared from aqueous solution and recrystallised from ethanol as orange-yellow needles, m. p. 233—235° undepressed on admixture with the picrate described below.

4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (II; R = R′ = Me).—This was prepared from *p*-chlorophenyldiguanide, acetone, and piperidine (*idem, ibid.*). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 255 mμ (ε 16,600) (see Fig. 1); in 0·005N-HCl, $\lambda_{max.}$ 255 mμ (ε 17,500); in 0·1N-NaOH, $\lambda_{max.}$ 258 mμ (ε 17,200). The picrate, prepared in water and crystallised from ethanol, formed orange-yellow needles, m. p. 236—237° (Found: C, 42·3; H, 3·7; N, 23·3; Cl, 7·35. Calc. for $C_{11}H_{14}N_5Cl,C_6H_3O_7N_3$: C, 42·5; H, 3·5; N, 23·3; Cl, 7·4%). Crounse (*J. Org. Chem.*, 1951, **16**, 492) gives m. p. 238°.

4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (III; R = R′ = Me).—(*a*) *p*-Chlorophenyldiguanide hydrochloride (100 g.), acetone (500 c.c.), and water (1 l.) were heated together under reflux for 15 hr. and then evaporated to 500 c.c. under reduced pressure and cooled. The crystals which separated were filtered off and the filtrate was stirred vigorously at 0—5° with ether (1 l.) whilst 10N-sodium hydroxide (100 c.c.) was added. The aqueous layer was separated and extracted with further amounts of ether until a test portion no longer gave a precipitate on the addition of ammonia and copper sulphate solution. The solution was neutralised with hydrochloric acid, and saturated aqueous picric acid was added. The picrate was collected, washed with water, and dried (0·6—1·2 g.). It crystallised from ethanol in long pale yellow needles, m. p. 209—210° undepressed on admixture with the picrate of the proguanil metabolite (Crowther and Levi, *loc. cit.*) (Found: C, 42·5; H, 3·8; N, 23·0. Calc. for $C_{11}H_{14}N_5Cl,C_6H_3O_7N_3$: C, 42·5; H, 3·5; N, 23·3%). A mixture of the picrate (171 mg.), water (5 c.c.), and hydrochloric acid (1 c.c.; *d* 1·18) was extracted exhaustively with ether. 40% Sodium hydroxide solution was then added to the aqueous solution until there was no further precipitation. The base was collected, washed with ice-cold water, and dried in a vacuum over sodium hydroxide flakes (yield 51 mg.; m. p. 145—146°). The crude base was dissolved, at room temperature, in chloroform (previously saturated with water) (4 c.c.). Ether (4 c.c.) was added to precipitate the pure base as colourless prisms, m. p. 146° (Found: N, 27·9. Calc. for $C_{11}H_{14}N_5Cl$: N, 27·8%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 240 mμ (ε 12,300).

The pure base (0·5 g.) was heated under reflux with water (20 c.c.) (pH of solution, 8—9) for 2 hr., and then cooled. The isomer which separated was collected, washed with water, and dried (0·47 g.); it had m. p. 140—141° undepressed in admixture with (II; R = R′ = Me). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 256 mμ (ε 16,900); in 0·1N-NaOH, $\lambda_{max.}$ 258 mμ (ε 17,400).

(*b*) *p*-Chlorophenyldiguanide hydrochloride (20 g.), water (200 c.c.), acetone (100 c.c.), and

hydrochloric acid (7·04 c.c., 1 equiv.; *d* 1·18) were heated together under reflux for 20 hr. The solution was evaporated to half its volume under reduced pressure and cooled. The solid which separated was removed and the filtrate was stirred at 0—5° with ether (200 c.c.) whilst 40% sodium hydroxide solution (30 c.c.) was added. The colourless solid thus precipitated was collected, washed with ether, and dried (9·8 g.). A portion of this crude base was crystallised as in (*a*) and then had m. p. 143° undepressed on admixture with pure base from (*a*). A further portion of the crude base was suspended in ethanol, and concentrated hydrochloric acid was added until the base had dissolved. The solution was filtered from a little solid, and ether was added to the filtrate. The precipitated *hydrochloride* was collected, washed with ether, dried, and crystallised from ethanol–ether or water, in prisms; the m. p. varied from 204° to 219° depending on rate of heating (Found: C, 45·75; H, 5·4; N, 23·9. $C_{11}H_{14}N_5Cl,HCl$ requires C, 45·8; H, 5·2; N, 24·3%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 240 mμ (ε 12,300). The hydrochloride of (III; R = R′ = Me) was more conveniently prepared by dissolution of the crude base in 7% hydrochloric acid, followed by neutralisation with ammonia. The hydrochloride then usually separated; otherwise, the addition of saturated salt solution caused its precipitation.

The *hydrobromide* was prepared similarly from the base and dilute hydrobromic acid. It formed prisms (from water), m. p. 213—214° (Found: C, 40·2; H, 4·8; N, 21·2. $C_{11}H_{14}N_5Cl,HBr$ requires C, 39·7; H, 4·5; N, 21·1%).

The yield of (III; R = R′ = Me) was increased by lowering the reaction temperature to 50°. Prolonged reaction at room temperature also gave a good yield. Variation of the amount of additional hydrochloric acid either to 0·1 equiv. or to 2·0 equivs. had little effect, but reduction in the amount of acetone used, to slightly more than the stoicheiometric proportion, resulted in inferior yields. *p*-Chlorophenyldiguanide, acetone, and water, with either sulphuric acid or hydrobromic acid in amounts in excess of 1 equiv., gave good yields of (III; R = R′ = Me). Treatment with acetone and hydrochloric acid of the mixture obtained by heating *p*-chloroaniline hydrochloride with dicyandiamide in water, without the diguanide initially formed being isolated, gave the same compound. It was also formed from *p*-chloroaniline hydrochloride, dicyandiamide, acetone, and hydrochloric acid on being heated together in water. Acetone diethyl acetal and *iso*propenyl acetate each gave (III; R = R′ = Me)) on reaction with *p*-chlorophenyldiguanide hydrochloride and hydrochloric acid, as did acetone–sodium hydrogen sulphite, but in this case only in the presence of a considerable excess of acid.

Acid Hydrolysis of 4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (III; R = R′ = Me).—The diamino-dihydrotriazine hydrochloride (5 g.) and 0·1N-hydrochloric acid (50 c.c.) were heated together under reflux for 30 min. The solution was evaporated to dryness under reduced pressure, leaving a crystalline residue (4·21 g.), which was crystallised from water, giving *p*-chlorophenyldiguanide hydrochloride, m. p. 239° undepressed on admixture with authentic material. The constitution of the hydrolysis product was confirmed by the formation of a water-insoluble complex on treatment with ammoniacal copper sulphate solution.

Prolonged heating of the diamino-dihydrotrizine with 7% hydrochloric acid gave *p*-chloroaniline in 75% yield.

N^1-p-*Chlorophenyl*-N^1-*methyldiguanide* (IV; X = Cl, R = Me, R′ = H).—*p*-Chloro-*N*-methylaniline hydrochloride (17·8 g.), dicyandiamide (10·6 g.), and water (35 c.c.) were heated together under reflux for 90 min. The cooled mixture was extracted with ether to remove unchanged base, carbon was added, and the mixture was filtered. The filtrate was made strongly alkaline with 40% sodium hydroxide solution, and the precipitated base was collected, washed with ice-cold water, and dried. Crystallisation from chlorobenzene gave N^1-p-*chlorophenyl*-N^1-*methyldiguanide* as colourless crystals, m. p. 156° (Found: C, 48·05; H, 5·3; N, 30·45. $C_9H_{12}N_5Cl$ requires C, 47·9; H, 5·3; N, 31·0%).

4-*Amino*-6-(p-*chloro*-N-*methylanilino*)-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = Me, R′ = H, R″ = NH_2).—(*a*) N^1-*p*-Chlorophenyl-N^1-methyldiguanide (3 g.), acetone (50 c.c.), and piperidine (0·3 c.c.) were heated together under reflux for 7 days. Water (100 c.c.) was added to the cooled mixture and the whole was made alkaline by the addition of ammonia. An excess of copper sulphate solution, to precipitate unchanged diguanide as the copper complex, was added. The mixture was filtered, the filtrate was acidified with hydrochloric acid, and sodium sulphide was added until there was no further separation of copper sulphide. Carbon was added and the mixture was filtered. Aqueous picric acid was added to the filtrate, and the *picrate* of the product was collected, washed with water, and dried (2·3 g.). It crystallised from ethanol in yellow platelets, m. p. 278° (Found: C, 43·25; H, 4·15; N, 22·45. $C_{12}H_{16}N_5Cl,C_6H_3O_7N_3$ requires C, 43·7; H, 3·85; N, 22·65%). The crude picrate was suspended in dilute hydrochloric acid and extracted with ether. The aqueous part was evaporated to dry-

ness under reduced pressure, and the residue was triturated with acetone, collected, washed with acetone and dried. The product crystallised from ethanol–ether, to give 4-*amino*-6-(p-*chloro*-N-*methylanilino*)-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine dihydrochloride*, m. p. 146—147° (Found: C, 39·3, 39·1; H, 5·95, 6·0; N, 19·6. $C_{12}H_{16}N_5Cl,2HCl,1·5H_2O$ requires C, 39·4; H, 5·7; N, 19·2%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 247·5 mμ (ε 16,300) (see Fig. 1); in 0·1N-NaOH, $\lambda_{max.}$ 260 mμ (ε 12,400).

(*b*) N^1-*p*-Chlorophenyl-N^1-methyldiguanide (3 g.), water (10 c.c.), acetone (5 c.c.), and hydrochloric acid (2·34 c.c.; *d* 1·18) were heated together under reflux for 16 hr. The solution was cooled, and basified with ammonia, and the small amount of oil which separated was removed by extraction with ether. The aqueous part was made strongly alkaline with 40% sodium hydroxide solution, and the solid precipitated was collected, dissolved in water, and filtered. Ammoniacal copper sulphate solution was added to the filtrate. The copper complex of the unchanged diguanide was filtered off, the filtrate was acidified with hydrochloric acid, and sodium sulphide was added. The precipitate was removed, the solution was neutralised with ammonia, and aqueous picric acid was added. The picrate thus formed was collected, washed with water, dried, and crystallised from ethanol, yielding pale yellow platelets, m. p. 275—276° undepressed in admixture with the picrate from (*a*).

N^1-*Methyl*-N^1-*phenyldiguanide* (IV; X = R′ = H, R = Me).—*N*-Methylaniline (53·5 g.), hydrochloric acid (43·7 c.c.; *d* 1·18), dicyandiamide (41·5 g.), and water were heated together under reflux for 1·5 hr. and then filtered after addition of carbon. The cooled filtrate was treated with sodium hydroxide solution, and the precipitated base was collected, washed with water, dried (H_2SO_4; vac.), and crystallised from benzene. The base could not be further purified but was sufficiently pure for the reaction below. It was characterised as the *hydrochloride*, colourless needles, m. p. 205°, from ethanol–ethyl acetate (Found: N, 30·55. $C_9H_{13}N_5,HCl$ requires N, 30·8%), and as the *picrate*, yellow platelets, m. p. 170—171°, from ethanol (Found: C, 43·25; H, 3·9; N, 27·65, 27·85. $C_9H_{13}N_5,C_6H_3O_7N_3$ requires C, 42·9; H, 3·8; N, 26·7%). Satisfactory nitrogen analyses could not be obtained. Cohn (*J. pr. Chem.*, 1911, **84**, 394) described this preparation but did not characterise the product.

4-*Amino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-6-(N-*methylanilino*)-1 : 3 : 5-*triazine* (V; X = R′ = H, R = Me, R″ = NH_2).—N^1-Methyl-N^1-phenyldiguanide (12 g.), dry acetone (50 c.c.), and piperidine (1 c.c.) were heated together under reflux for 22 hr. The solution was filtered, and evaporated under reduced pressure. The syrupy residue was dissolved in water, and aqueous picric acid was added. The *picrate* thus precipitated was collected, washed with water, dried, and crystallised from ethanol; it had m. p. 239—240° (Found: C, 47·05; H, 4·5; N, 23·95. $C_{12}H_{17}N_5,C_6H_3O_7N_3$ requires C, 46·95; H, 4·35; N, 24·3%). In order to measure the ultra-violet absorption of the product, a portion of the picrate was shaken with dilute hydrochloric acid and ether, and the aqueous part examined. Ultra-violet absorption: in 0·01N-HCl, λ_{max} 247 mμ (ε 15,600); in 0·1N-NaOH, $\lambda_{max.}$ 255 mμ (ε 12,000).

4 : 6-*Diamino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1-*phenyl*-1 : 3 : 5-*triazine* (IX; X = R′ = H. R = NH_2).—(*a*) Phenyldiguanide (35 g.), acetone (200 c.c.), and hydrochloric acid (34 c.c.; *d* 1·18) were heated in water (400 c.c.) under reflux on the steam-bath for 15 hr. The acetone was distilled off under reduced pressure, and the mixture was cooled to 3°. Ether (500 c.c.) was added, and the mixture was made strongly alkaline with 40% sodium hydroxide solution and shaken. The ethereal layer was decanted and a second ether-extraction was carried out. The residue was filtered and the solid was washed with ether and dried *in vacuo* (36 g.). Crystallisation from moist chloroform by addition of ether and light petroleum gave the *base*, m. p. 138—139° (Found: C, 56·2; H, 6·7; N, 29·4. $C_{11}H_{15}N_5,H_2O$ requires C, 56·2; H, 7·2; N, 29·8%). The base was dissolved in ethanol and concentrated hydrochloric acid, and ether was added until crystallisation of the *hydrochloride* occurred. Recrystallised from ethanol–ether, it formed colourless needles, m. p. 209—210° (Found: C, 50·05; H, 5·9; N, 26·3. $C_{11}H_{15}N_5,HCl,0·5H_2O$ requires C, 50·25; H, 6·45; N, 26·7%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 240 mμ (ε 7400).

(*b*) The dihydrotriazine was also conveniently prepared from aniline hydrochloride and dicyandiamide, with a subsequent similar reaction with acetone, without the isolation of phenyldiguanide hydrochloride.

4-*Amino*-6-*anilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = R = R′ = H, R″ = NH_2).—4 : 6-Diamino-1 : 2-dihydro-2 : 2-dimethyl-1-phenyl-1 : 3 : 5-triazine (3 g.), 40% sodium hydroxide solution (1 c.c.), and water (100 c.c.) were heated together on the steam-bath for 45 min. The solution was cooled, and 40% sodium hydroxide solution was added to precipitate a gum which crystallised on trituration with ethanol. The *base* crystallised from water,

m. p. 184—185° (Found: C, 61·4; H, 7·05; N, 32·0. $C_{11}H_{15}N_5$ requires C, 60·8; H, 6·9; N, 32·3%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 250 mμ (ε 14,800); in 0·1N-NaOH, $\lambda_{max.}$ 253 mμ (ε 15,100).

4 : 6-*Diamino*-1-p-*chlorophenyl*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine* (III; R = Me, R′ = Et).—*p*-Chlorophenyldiguanide hydrochloride (37 g.), ethyl methyl ketone (100 c.c.), and hydrochloric acid (12·9 c.c.; *d* 1·18) in water (200 c.c.) were kept at 70° for 15 hr. The unchanged ketone was distilled off under reduced pressure. The residue was cooled to 3°, ether (200 c.c.) was added, and the mixture was made strongly alkaline with 40% sodium hydroxide solution. The ethereal layer was separated, the aqueous suspension was extracted twice more with ether, and the solid product was separated by filtration. It was washed with water, and dried *in vacuo* (24 g.). Recrystallisation by addition of ether and light petroleum (b. p. 60—80°) to a solution in moist chloroform gave 4 : 6-*diamino*-1-p-*chlorophenyl*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine* as prisms, m. p. 139—140° (Found: C, 54·35; H, 6·45; N, 26·5. $C_{12}H_{16}N_5Cl$ requires C, 54·2; H, 6·05; N, 26·4%). Ultra-violet absorption in 0·01 N-HCl: $\lambda_{max.}$ 242 mμ (ε 11,600). Addition of ether to a solution of the base in ethanolic hydrogen chloride yielded the *hydrochloride*, needles (from ethanol–ether), m. p. 206—208° (Found: C, 48·0; H, 5·65; N, 22·9. $C_{12}H_{16}N_5Cl,HCl$ requires C, 47·7; H, 5·65; N, 23·2%).

The (+)-*tartrate* was prepared from the base (30 g.) and (+)-tartaric acid (16·9 g.) in ethanol (200 c.c.). The solution was filtered and evaporated under reduced pressure to a syrup, which crystallised on trituration with methanol and acetone (34 g.). After two recrystallisations from aqueous ethanol, the tartrate had m. p. 186—187° [Found: C, 49·5; H, 5·6; N, 20·25. $(C_{12}H_{16}N_5Cl)_2,C_4H_6O_6$ requires C, 49·3; H, 5·6; N, 20·6%], $[\alpha]_D^{20}$ + 4·2° (*c*, 5 in H_2O). Repeated crystallisation failed to effect resolution of this salt, and the base recovered from it was optically inactive.

4-*Amino*-6-p-*chloroanilino*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine* (II; R = Me, R′ = Et).—4 : 6-Diamino-1-*p*-chlorophenyl-2-ethyl-1 : 2-dihydro-2-methyl-1 : 3 : 5-triazine (10 g.) was suspended in water (100 c.c.), heated on the steam-bath for 1 hr., and then cooled. The oil, after being separated from the supernatant liquid, solidified. It was recrystallised twice from aqueous methanol, to give 4-*amino*-6-p-*chloroanilino*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine*, plates, m. p. 140—142° (Found: C, 52·0; H, 6·3; N, 25·8. $C_{12}H_{16}N_5Cl,0·5H_2O$ requires C, 52·0; H, 6·2; N, 25·5%). Ultra-violet absorption in 0·1N-NaOH: $\lambda_{max.}$ 258 mμ (ε 17,700).

Resolution of 4-*Amino*-6-p-*chloroanilino*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine*.—The above base (12 g.) was suspended in ethanol (25 c.c.), and a solution of (+)-tartaric acid (7·5 g.) in ethanol (25 c.c.) was added. The mixture was heated to 40° and the solution thus obtained was filtered and evaporated to half-bulk under reduced pressure. The solution was kept overnight at 0° and the crystals which separated were collected (5·7 g.), m. p. 80—82°. After two recrystallisations from ethanol the tartrate had m. p. 82—83°. The product, which was highly solvated, lost readily only part of its ethanol of crystallisation in air (Found, on material dried at 56° *in vacuo* over P_2O_5: C, 46·4; H, 6·4; N, 14·6. $C_{12}H_{16}N_5Cl,C_4H_6O_6,C_2H_5OH$ requires C, 46·8; H, 6·1; N, 15·2%), $[\alpha]_D^{20}$ +74° (*c*, 5 in H_2O). A solution of the tartrate in water was made strongly alkaline by addition of sodium hydroxide solution. The precipitated dextrorotatory *base* formed plates, m. p. 120—121°, from ethanol (Found: C, 53·8; H, 7·0; N, 22·5. $C_{12}H_{16}N_5Cl,C_2H_5OH$ requires C, 53·9; H, 7·05; N, 22·5%), $[\alpha]_D^{23}$ +16° (*c*, 5 in EtOH).

Derivatives of 4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine*.—4-Amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; R = R′ = Me) (4·05 g.), acetic anhydride (4 c.c.), and acetic acid (15 c.c.) were heated together under reflux for 1 hr. The mixture was then poured into water (100 c.c.) and cooled. The solid was collected, washed with water, dried, and crystallised from ethanol, giving the *diacetyl* derivative as hydrated colourless prisms, m. p. 214° (Found: C, 51·1; H, 5·45; N, 20·0; Cl, 10·2. $C_{15}H_{18}O_2N_5Cl,H_2O$ requires C, 51·0; H, 5·7; N, 19·8; Cl, 10·0%).

The 4-amino-triazine (1·35 g.) and *p*-chlorophenyl *iso*thiocyanate (2·54 g.) in acetone (30 c.c.) were heated under reflux for 3 hr. The solution was cooled, diluted with water (100 c.c.), and steam-distilled to remove excess of *iso*thiocyanate. The residue was filtered and the solid was washed with water and dried. It crystallised from ethanol to give colourless rods of the *thiourea*, m. p. 199—200° (Found: C, 51·1; H, 4·15; N, 20·05, 20·2; S, 8·2. $C_{18}H_{18}N_6Cl_2S$ requires C, 51·3; H, 4·3; N, 19·95; S, 7·6%).

6-p-*Chloroanilino*-1 : 2-*dihydro*-4-*hydroxy*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = R′ = H, R″ = OH).—(*a*) 4-Amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (2·5 g.) was warmed in 7% hydrochloric acid (20 c.c.) to 80°. Sodium nitrite solution (13·8 c.c.; 10%) was added during 30 min. and the mixture was kept at 80° for a further 10 min.

The solution was cooled, carbon was added, and the mixture was filtered. The filtrate was basified with 40% sodium hydroxide solution, and the liberated base was collected, washed with water, dried, and crystallised from ethanol, yielding fine colourless needles of the *hydroxy*-compound, m. p. 250° (decomp.) (Found: C, 52·45; H, 5·15; N, 22·35. $C_{11}H_{13}ON_4Cl$ requires C, 52·3; H, 5·15; N, 22·2%). The *hydrochloride* had m. p. 224° (effervescence), undepressed on admixture with the hydrochloride from (*b*) below; ultra-violet absorption: in 0·1N-HCl, $\lambda_{max.}$ 228—236 mμ (ε 10,500); in 0·1N-NaOH, $\lambda_{max.}$ 252—262 mμ (ε 15,500).

(*b*) *p*-Chlorophenyldicyandiamide (5 g.), *iso*propanol (12 c.c.), and hydrochloric acid (2·5 c.c.; *d* 1·18) were heated together under reflux for 30 min. A further amount of hydrochloric acid (1·5 c.c.) was then added and the heating was continued for a further 2 hr. The solution was poured into water (100 c.c.), and the solid precipitated was removed. The filtrate was basified with sodium hydroxide solution, and the base thus liberated was collected, washed with water, and dried. It crystallised from benzene containing a small amount of ethanol to give *p*-chlorophenylguanylurea of m. p. 133—134° (Found: N, 26·7. Calc. for $C_8H_9ON_4Cl$: N, 26·4%) (Walther and Griesshammer, *J. pr. Chem.*, 1915, **92**, 251, give m. p. 125°). *p*-Chlorophenylguanylurea (20 g.) and piperidine (2 c.c.) were heated in acetone (200 c.c.) under reflux for 20 hr. The solution was filtered, the filtrate was evaporated to dryness, and the syrupy residue was dissolved in ethanol and poured into water, to give a solid, which was collected, washed with water, and dried. It was dissolved in alcoholic hydrogen chloride, and ethyl acetate was added. The precipitate was collected, washed with ethyl acetate, and dried. Crystallisation from ethanol gave prisms of 6-p-*chloroanilino*-1 : 2-*dihydro*-4-*hydroxy*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine hydrochloride*, m. p. 223° (effervescence) (Found: C, 45·55; H, 4·75; N, 19·55. $C_{11}H_{13}ON_4Cl,HCl$ requires C, 45·7; H, 4·8; N, 19·4%). Ultra-violet absorption: in 0·1N-HCl, $\lambda_{max.}$ 226—236 mμ (ε 10,500); in 0·1N-NaOH, $\lambda_{max.}$ 257 mμ ε, 13,300).

N-p-*Chlorophenyl*-N′-*guanylurea*.—*p*-Chlorophenyldiguanide hydrochloride (5 g.) was stirred at room temperature in 7% hydrochloric acid (100 c.c.) whilst sodium nitrite (2 g.) was added. The mixture was kept at 20° for 1 hr. and then filtered. The solid residue was washed with a little water, drained, and dissolved in dilute hydrochloric acid. The solution was treated with carbon, filtered, and basified. The precipitate thus formed was collected, washed with water, and crystallised from water, to give *N*-*p*-chlorophenyl-*N*′-guanylurea as feathery needles, m. p. 140° (Found: C, 45·15; H, 4·4; N, 25·85. Calc. for $C_8H_9ON_4Cl$: C, 45·2; H, 4·2; N, 26·4%). Passerini (*Chem. Abs.*, 1951, **45**, 10208) since the completion of this work has reported m. p. 143°.

4-*Amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-6-*hydroxy*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (IX; X = Cl, R = OH, R′ = H).—*N*-*p*-Chlorophenyl-*N*′-guanylurea (10 g.) and piperidine (1·2 c.c.) were heated in acetone (65 c.c.) under reflux for 17 hr. The mixture was cooled and the solid was collected, washed with acetone, and dried. It crystallised from aqueous 2-ethoxyethanol as fine needles of the *dihydrotriazine*, m. p. 227° (decomp.) (Found: C, 52·25, 52·4; H, 5·4, 5·3; N, 21·7. $C_{11}H_{13}ON_4Cl$ requires C, 52·3; H, 5·15; N, 22·2%).

4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2-iso*propyl*-1 : 3 : 5-*triazine* (III; R = H, R′ = Pr^i).—*p*-Chlorophenyldiguanide hydrochloride (12·4 g.), *iso*butyraldehyde (50 c.c.), hydrochloric acid (4·3 c.c.; *d* 1·18), ethanol (20 c.c.), and water (100 c.c.) were heated together at 70° for 15 hr. The ethanol and excess of *iso*butyraldehyde were distilled under reduced pressure, and the residue was cooled to 3°. Ether (200 c.c.) was added, and the mixture was made strongly alkaline by addition of 40% sodium hydroxide solution. The solid product was separated by filtration, washed with ether and then with water, and dried *in vacuo* (15·2 g.), m. p. 144—146°. The base could not readily be recrystallised, but was dissolved in dilute aqueous hydrochloric acid, filtered, and then neutralised with ammonia; the *hydrochloride* separated as prisms, m. p. 226—227° (Found: C, 42·6; H, 6·2; N, 20·7. $C_{12}H_{16}N_5Cl,HCl,2H_2O$ requires C, 41·95; H, 5·8; N, 20·5%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 244 mμ (ε 10,600). The (+)-*tartrate* was prepared from the crude base (20·5 g.) and (+)-tartaric acid (11·6 g.) in ethanol (120 c.c.). The solution was set aside and then filtered to remove a small amount of gelatinous material. Addition of ethyl acetate (50 c.c.) caused separation of the crystalline salt (18 g.), which, when recrystallised from aqueous ethanol, had m. p. 196—197°, $[\alpha]_D^{20}$ +9·6° (*c*, 5 in H_2O) [Found: C, 48·4; H, 5·3; N, 20·0. $(C_{12}H_{16}N_5Cl)_2,C_4H_6O_6,H_2O$ requires C, 48·3; H, 5·7; N, 20·2%]. Repeated crystallisation failed to bring about any resolution of this salt.

4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-2-iso*propyl*-1 : 3 : 5-*triazine* (II; R = H, R′ = Pr^i).—The above hydrochloride (5 g.) was dissolved in hot water (100 c.c.), and the solution was made alkaline by addition of 40% sodium hydroxide solution. The mixture was heated on the steam-bath for 1 hr., and cooled. The gummy product was separated, and triturated with methanol. The solid obtained was crystallised from aqueous methanol, giving 4-*amino*-6-p-

chloroanilino-1 : 2-*dihydro*-2-iso*propyl*-1 : 3 : 5-*triazine* as a solvate (2·5 g.), m. p. 118—120° (Found : C, 52·4; H, 6·45; N, 22·8. $C_{12}H_{16}N_5Cl,CH_3{\cdot}OH$ requires C, 52·4; H, 6·7; N, 23·5%).

4 : 6-*Diamino*-1-p-*chlorophenyl*-2-*ethyl*-1 : 2-*dihydro*-1 : 3 : 5-*triazine* (III; R = H; R′ = Et).—*p*-Chlorophenyldiguanide hydrochloride (24·8 g.), propionaldehyde (25·6 g.), hydrochloric acid (8·73 c.c.; *d* 1·18), and water (75 c.c.) were stirred together at 50° for 17 hr. The cooled mixture was extracted with ether; the aqueous part was then stirred with ether (150 c.c.) at 0—5°, and sodium hydroxide solution was added until there was no further precipitation. The solid was collected, washed with ether, and dried. It was dissolved in dilute hydrochloric acid, the solution was filtered, and the filtrate was neutralised with aqueous ammonia. Saturated salt solution was added to complete precipitation and the solid was collected, washed with a little water, and dried. Crystallisation from water gave the *hydrochloride*, m. p. 244—245° (Found : C, 46·1; H, 5·3; N, 23·7. $C_{11}H_{14}N_5Cl,HCl$ requires C, 45·8; H, 5·2; N, 24·3%). Ultra-violet absorption in 0·01N-HCl : $\lambda_{max.}$ 244 mμ (ε 10,200). The crude base (6·06 g.) in ethanol (50 c.c.) was mixed with a solution of (+)-camphorsulphonic acid (5·65 g.) in ethanol (50 c.c.) at room temperature. The crystals which separated were collected, washed with ethanol, and dried (3·85 g.; m. p. 217°). The product was crystallised four times from ethanol (the optical rotation was unchanged) to give the (+)-*camphorsulphonate* as prisms, m. p. 217°, $[\alpha]_D^{20}$ + 19·8° (*c*, 2·22 in EtOH) (Found : C, 51·4; H, 6·3; N, 13·9; Cl, 7·0. $C_{11}H_{14}N_5Cl,C_{10}H_{16}O_4S,0{\cdot}5H_2O$ requires C, 51·2; H, 6·3; N, 14·2; Cl, 7·2%). The base recovered from the recrystallised salt was optically inactive.

4(or 6)-*Amino*-1-p-*chlorophenyl*-6(or 4)-p-*chlorophenylthioureido*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine*.—4 : 6-Diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (III; R = R′ = Me) (2·51 g.), *p*-chlorophenyl *iso*thiocyanate (5·08 g.), and acetone (100 c.c.) were heated together under reflux for 90 min. The solution was then evaporated to a small bulk and diluted with light petroleum (b. p. 60—80°) to precipitate an oil which readily crystallised. The solid was collected, washed with light petroleum (b. p. 60—80°), dried, and crystallised from ethanol to give the *thiourea*, m. p. 174—175° (Found : C, 51·05; H, 4·45; N, 19·35; S, 7·55. $C_{18}H_{18}N_6Cl_2S$ requires C, 51·3; H, 4·3; N, 19·95; S, 7·6%).

Chlorination of 4-*Amino*-6-*anilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = R = R′ = H, R″ = NH_2).—The anilino-dihydrotriazine (13·96 g.) was dissolved in acetic acid (90 c.c.), and chlorine (4·86 g.) was passed into the solution at 20° during 20 min. Addition of ether precipitated a gum which was separated, washed with ether, dissolved in water and basified with sodium hydroxide solution. The precipitated gummy base was converted into the picrate which crystallised from ethanol as orange-yellow needles of 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine picrate of m. p. 236—237° undepressed on admixture with authentic material.

6-*Amino*-1-p-*chlorophenyl*-4-*dimethylamino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (IX; X = Cl, R = NH_2, R′ = Me).—A mixture of N^1-*p*-chlorophenyl-N^5N^5-dimethyldiguanide hydrochloride hemihydrate (22·8 g.), acetone (200 c.c.), and 7% hydrochloric acid (40 c.c.) was heated under reflux for 18 hr. on a steam-bath. The solution was concentrated (to about 40 c.c.) below 50° and 7% aqueous ammonia was added to give a pH of 5. Addition of saturated aqueous sodium chloride (about 140 c.c.) to the filtered solution gave a gum which later solidified and was collected, dissolved in water (25 c.c.), and filtered. The filtrate was again treated with sufficient saturated aqueous sodium chloride to give a permanent turbidity. The solution was cooled in ice-water, the crystals obtained were collected and dissolved in ethanol (45 c.c.), and the clarified solution was mixed with ethyl acetate (250 c.c.) and ethanolic 16% hydrogen chloride (8 c.c.). The precipitated *dihydrochloride* was purified by dissolution in ethanol, and addition of an excess of ethyl acetate containing a little ethanolic hydrogen chloride. The small prisms thus obtained melted at 186—188°, resolidified almost at once, and remelted at 264·5° (Found : C, 43·85; H, 5·35; N, 20·1. $C_{13}H_{18}N_5Cl,2HCl$ requires C, 44·2; H, 5·7; N, 19·85%).

The crude dihydrochloride (7·5 g.) was dissolved in water (18 c.c.), the pH of the solution was adjusted to 5 with aqueous ammonia (*d* 0·88), and saturated aqueous sodium chloride (15 c.c.) was added, to give the *monohydrochloride*, prisms (from ethanol–ether), m. p., after previous melting at 120° and resolidification, 263—264°, not depressed by the isomeric hydrochloride below (Found : C, 48·45; H, 6·6; N, 21·35. $C_{13}H_{18}N_5Cl,HCl,0{\cdot}5H_2O$ requires C, 48·05; H, 6·2; N, 21·6%). Ultra-violet absorption : in 0·01N-HCl, $\lambda_{max.}$ 246 mμ (ε 22,300); in 0·1N-NaOH, $\lambda_{max.}$ 243 mμ (ε 17,000). The *hydriodide* was slightly less soluble than the hydrochloride in water. It formed small colourless rods which melted in the region of 110° and decomposed about 145° (Found : C, 36·85; H, 5·25; N, 16·2; loss in wt. in vacuum at

80°, 3·65. $C_{13}H_{18}N_5Cl,HI,H_2O$ requires C, 36·5; H, 4·95; N, 16·4; H_2O, 4·2%). The *picrate* crystallised as yellow prisms from ethanol. When heated fairly rapidly, it melted partially at about 180°, resolidified, and melted finally at 242—243° (Found: C, 45·3; H, 4·3; N, 21·9. $C_{13}H_{18}N_5Cl,C_6H_3O_7N_3$ requires C, 44·9; H, 4·15; N, 22·0%).

6-p-*Chloroanilino*-4-*dimethylamino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = R′ = H, R″ = NMe_2).—N^1-*p*-Chlorophenyl-N^5N^5-dimethyldiguanide (14·5 g.), acetone (60 c.c.), and piperidine (0·8 c.c.) were heated under reflux for 76 hr. The liquid was cooled, concentrated (to about 25 c.c.), and mixed with water (50 c.c.). Unchanged diguanide was filtered off, and the mother-liquors were freed from acetone by distillation under reduced pressure and acidified with 7% hydrochloric acid. The solid (4·0 g.) which separated was collected, and crystallised from dilute hydrochloric acid to give 6-p-*chloroanilino*-4-*dimethylamino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine hydrochloride* as needles, m. p. 265—266° (Found: C, 49·25; H, 5·85; N, 21·8. $C_{13}H_{18}N_5Cl,HCl$ requires C, 49·3; H, 6·05; N, 22·1%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 259 mμ (ε 19,800); in 0·1N-NaOH, $\lambda_{max.}$ 262 mμ (ε 21,500). The *picrate* crystallised from 2-ethoxyethanol as blunt yellow needles, m. p. 241—242° (Found: C, 45·05; H, 4·0; N, 21·5. $C_{13}H_{18}N_5Cl,C_6H_3O_7N_3$ requires C, 44·9; H, 4·15; N, 22·0%). Unlike the isomeric picrate described above, this compound showed no tendency to melt at about 180°.

N^1-p-*Chlorophenyl*-N^2N^2-*dimethyldiguanide* (XI).—This was prepared from *N*-*p*-chlorophenyl-*N*′-guanylthiourea (11·4 g.), aqueous dimethylamine (45 c.c.; 25%), ethanol (500 c.c.), and mercuric oxide (32·5 g.), stirred together for 15 hr. at room temperature. The filtered solution was evaporated under reduced pressure, and the residue, crystallised from aqueous ethanol, gave N^1-p-*chlorophenyl*-N^2N^2-*dimethyldiguanide*, m. p. 227° (decomp.) (Found: C, 49·9; H, 5·55; N, 29·3. $C_{10}H_{14}N_5Cl$ requires C, 50·2%; H, 5·85; N, 29·2%).

Reaction between N^1-p-*Chlorophenyl*-N^4N^5-*dimethyldiguanide and Acetone under Acidic Conditions.*—N^1-*p*-Chlorophenyl-N^4N^5-dimethyldiguanide hydrochloride (4·15 g.), 3·5% hydrochloric acid (15 c.c.), water (22 c.c.), and acetone (22 c.c.) were heated together for 70 hr. in a water-bath at 70°. The solution was concentrated (to about 30 c.c.) at 50°, cooled, mixed with ether (50 c.c.), and kept at 0—5° while an excess of aqueous 40% sodium hydroxide was added. The ethereal solution, combined with a second extract of the aqueous layer, was dried (Na_2SO_4). Removal of the ether left a solid which was dissolved in ethanol and treated with an excess of picric acid. The product (2·65 g.) was recrystallised from *n*-propanol and dried at 110°/20 mm., to give yellow 4-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-6-*methylamino*-1 : 3 : 5-*triazine picrate* (as XII), which melted partially at 168—169°, then resolidified, and later melted at 184—185° (Found: C, 45·4; H, 4·0; N, 21·8; $C_{13}H_{18}N_5Cl,C_6H_3O_7N_3$ requires C, 44·9; H, 4·15; N, 22·0%). The *base*, prepared from the picrate and crystallised from benzene and dried at 100°/20 mm., had m. p. 126—127° (Found: C, 55·3; H, 6·5; N, 24·5. $C_{13}H_{18}N_5Cl$ requires C, 55·8; H, 6·5; N, 25·1%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 265 mμ (ε 18,500); in 0·1N-NaOH, $\lambda_{max.}$ 265 mμ (ε 21,200).

N-(N-p-*Chlorophenyl*-N′-*methylguanyl*)-N′-*methylthiourea.*—*N*-*p*-Chlorophenyl-*N*′-methylguanidine (34 g.) and methyl *iso*thiocyanate (14·6 g.) were heated together on the steam-bath for 4 hr. The mixture was steam-distilled and the water was decanted from the residue which was then dissolved in hot ethanol (30 c.c.), treated with carbon, and filtered. The filtrate was stirred vigorously while 10% hydrochloric acid (100 c.c.) was slowly added. The precipitate was filtered off, washed with acetone, and dried. Recrystallisation from 85% methanol (carbon) gave N-(N-p-*chlorophenyl*-N′-*methylguanyl*)-N′-*methylthiourea hydrochloride* as colourless rectangular prisms (12·2 g.), m. p. 190—191° (decomp.) (Found: C, 41·1; H, 5·2; N, 18·75. $C_{10}H_{13}N_4ClS,HCl$ requires C, 41·0; H, 4·8; N, 19·15%).

N^1-p-*Chlorophenyl*-$N^2N^4N^5$-*trimethyldiguanide.*—A mixture of *N*-(*N*-*p*-chlorophenyl-*N*′-methylguanyl)-*N*′-methylthiourea hydrochloride (20·5 g.), aqueous methylamine (57 c.c.; 23% solution), mercuric oxide (45·4 g.), and ethanol (400 c.c.) was stirred at 30—40° for 16 hr., then heated on the steam-bath for 30 min. and filtered. The filtrate was evaporated to dryness under reduced pressure and the residual gum was dissolved in 7% hydrochloric acid (100 c.c.). The solution was clarified and an excess of aqueous 40% sodium hydroxide was added, to precipitate a sticky solid which was extracted with ether. The residue left after removal of the ether was redissolved in 7% hydrochloric acid (50 c.c.), and aqueous ammonia (*d* 0·88) was added to give a pH of 5. Addition of saturated aqueous sodium chloride to the carbon-treated solution caused precipitation of N^1-p-*chlorophenyl*-$N^2N^4N^5$-*trimethyldiguanide hydrochloride* (60%), m. p. 201—202°. Recrystallised from ethanol–ethyl acetate, it formed prisms of the same m. p. (Found: C, 46·1; H, 5·9; N, 23·8, 23·65. $C_{11}H_{16}N_5Cl,HCl$ requires C, 45·6; H, 5·9; N,

24·15%). The corresponding *base* crystallised from light petroleum (b. p. 60—80°) as small prisms, m. p. 114—116° (Found: C, 52·15; H, 5·85, N, 27·4. $C_{11}H_{16}N_5Cl$ requires C, 52·1; H, 6·35; N, 27·7%). The *picrate* crystallised from 50% aqueous ethanol as yellow rods, m. p. 150—151° (Found: C, 42·45; H, 4·25; N, 22·85. $C_{11}H_{16}N_5Cl,C_6H_3O_7N_3$ requires C, 42·3; H, 3·95; N, 23·2%).

N¹-p-*Chlorophenyl*-N²-*methyldiguanide* (IV; X = Cl, R = H, R′ = Me).—*N*-*p*-Chlorophenyl-*N*′-guanylthiourea (Ashworth, Crowther, Curd, Hendry, Richardson, and Rose, *J.*, 1949, 475) (22·85 g.), mercuric oxide (64·8 g.), and aqueous methylamine (66 c.c.; 23% solution) were stirred vigorously in ethanol (900 c.c.) for 16 hr. at room temperature and then for 30 min. on the steam-bath. The filtered solution was evaporated under reduced pressure, to leave a thick oil which set to a glass. This was dissolved in ethyl acetate (500 c.c.), and the solution clarified with kieselguhr. Ethanolic hydrogen chloride precipitated the crude hydrochloride, which was collected, stirred with water (60 c.c.), and filtered. The filtrate was made alkaline by addition of aqueous sodium hydroxide and the precipitated N¹-p-*chlorophenyl*-N²-*methyldiguanide*, after several recrystallisations from benzene, formed prisms, m. p. 169—170° (Found: C, 48·6; H, 5·4; N, 30·9. $C_9H_{12}N_5Cl$ requires C, 48·0; H, 5·35; N, 31·1%).

4-*Amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-6-*methylamino*-1 : 3 : 5-*triazine* (IX; X = Cl, R = MeNH, R′ = H).—When *N*¹-*p*-chlorophenyl-*N*²-methyldiguanide (4·5 g.), 3·5% hydrochloric acid (40 c.c.), water (10 c.c.), and acetone (25 c.c.) were kept at 50° for 18 hr. and the mixture was worked up in the usual manner, a base was obtained (2·1 g.), melting at 154—155°, then resolidifying and melting with decomposition at 217—219°. This was dissolved in dilute hydrochloric acid and salted out at pH 5 as the monohydrate of 4-*amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-6-*methylamino*-1 : 3 : 5-*triazine hydrochloride*, small prisms, m. p. 228—230° (decomp.), shrinking at 185° (Found: C, 44·75; H, 5·8; N, 22·7. $C_{12}H_{16}N_5Cl,HCl,H_2O$ requires C, 44·9; H, 6·0; N, 22·9%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 236 mμ (ε 15,800) (see Fig. 2). In one experiment in which dilute sulphuric acid was used instead of hydrochloric acid, an improved yield of the base was obtained. The *picrate* crystallised from ethanol as yellow prisms, m. p. 179—181° (Found: C, 43·85; H, 3·85; N, 22·3. $C_{12}H_{16}N_5Cl,C_6H_3O_7N_3$ requires C, 43·8, H, 3·9; N, 22·7%).

4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = H, R′ = Me, R″ = NH_2).—*N*¹-*p*-Chlorophenyl-*N*²-methyldiguanide (5·65 g.), acetone (25 c.c.), and piperidine (0·4 c.c.) were heated together under reflux for 68 hr. The mixture was cooled and the solid obtained (5·1 g.) was collected, and recrystallised from 50% aqueous methanol to give 4-*amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-1 : 3 : 5-*triazine*, prisms, m. p. 223—224° (decomp.) (Found: C, 54·15; H, 5·8; N, 25·95. $C_{12}H_{16}N_5Cl$ requires C, 54·3; H, 6·1; N, 26·4). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 252 mμ (ε 16,600); in 0·1N-NaOH, $\lambda_{max.}$ 249 mμ (ε 15,100). The *picrate* crystallised from ethanol as blunt yellow needles, m. p. 192—195° (Found: C, 44·1; H, 4·05; N, 22·2. $C_{12}H_{16}N_5Cl,C_6H_3O_7N_3$ requires C, 43·8; H, 3·9; N, 22·7%).

When each of the two dihydrotriazines derived from *N*¹-*p*-chlorophenyl-*N*²-methyldiguanide was heated at 100° for 20 min. in 0·1N-sodium hydroxide, the ultra-violet absorption of the solutions ($\lambda_{max.}$ 247 mμ; ε, 13,000) (see Fig. 2) corresponded in each case with that of a mixture of the two isomers containing about 75% of 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-1 : 2 : 2-trimethyl-1 : 3 : 5-triazine.

Isomerization of 4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = H, R′ = Me, R″ = NH_2) *to Form an Equilibrium Mixture*.—The anilino-dihydrotriazine (0·2 g.) in 0·1N-sodium hydroxide (65 c.c.) was heated for 20 min. in a bath at 100°. The cooled solution was made faintly acid (pH 6) with hydrochloric acid and extracted with *n*-butanol (4 × 65 c.c.). The extracts were concentrated under reduced pressure to about 15 c.c. and the volume was made up to 25 c.c. with butanol and enough water to saturate the butanol solution. This was submitted to counter-current distribution in an all-glass machine of the Craig type, employing 48 transfers between 25 c.c. quantities of *n*-butanol (the traversing solvent) and of 0·01N-hydrochloric acid which had previously been equilibrated with each other. The ultra-violet absorption at 236 and 252 mμ (the wave-lengths corresponding with peak absorption for the two isomers in 0·01N-hydrochloric acid) was determined in the aqueous phase from a number of tubes sufficient to give the pattern of the distribution. The concentrations of the two isomers were calculated by the solution of simultaneous equations derived from these values and from the absorption of the pure isomers. Tube 34 provided a solution whose absorption was identical with that of the starting material, and which, on treatment with hot alkali, again gave an equilibrium mixture. Absorption curves typical of the isomeric methylamino-dihydrotriazine (IX;

X = Cl, R = MeNH, R′ = H) were obtained from tubes 20 and 21. The solution in the latter tube was basified and heated for 20 min. at 100° to give again an equilibrium mixture.

N^1N^2-*Di*-p-*chlorophenyldiguanide* (IV; X = Cl, R = H, R′ = *p*-C_6H_4Cl).—Guanidine nitrate (19·6 g.) was added to ethanol (200 c.c.) in which sodium (3·7 g.) had been dissolved and the whole was boiled for 30 min. and filtered. More ethanol (300 c.c.) was added to the filtrate, together with *NN′*-di-*p*-chlorophenylthiourea (23·6 g.) and mercuric oxide (52 g.). After being stirred vigorously at room temperature for 18 hr. and then on the steam-bath for 15 min., the suspension was filtered, and the filtrate was concentrated under reduced pressure (to about 100 c.c.) and mixed with hydrochloric acid (600 c.c.; 2%) which precipitated a mixture of hydrochloride and base. The product was triturated with concentrated hydrochloric acid, collected, dried, dissolved in methanol, and reprecipitated by addition of ethyl acetate, to give N^1N^2-*di*-p-*chlorophenyldiguanide hydrochloride*, rods, m. p. 239—240° (decomp.) (Found: C, 47·0; H, 3·5; N, 20·25. $C_{14}H_{13}N_5Cl_2$,HCl requires C, 46·8; H, 3·95; N, 19·55%).

4-*Amino*-6-p-*chloroanilino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (IX; X = Cl, R = *p*-NH·C_6H_4Cl, R′ = H).—(*a*) A mixture of N^1N^2-di-*p*-chlorophenyldiguanide hydrochloride (10·8 g.), acetone (55 c.c.), water (45 c.c.), and N-hydrochloric acid (30 c.c.) was stirred and heated under reflux on the steam-bath for 20 hr. Acetone was distilled off under reduced pressure and the residual suspension was mixed with ether and treated, in the cold, with an excess of aqueous sodium hydroxide. The undissolved solid was still mainly hydrochloride which was recrystallised from 40% aqueous ethanol and then dissolved in ethanol and reprecipitated by addition of dilute hydrochloric acid, to give the sesquihydrate of 4-*amino*-6-p-*chloroanilino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine hydrochloride*, decomp. 134° (Found: C, 47·9; H, 5·2; N, 16·1; loss in wt. in a vacuum at 110°, 5·8. $C_{17}H_{17}N_5Cl_2$,HCl,1·5H_2O requires C, 47·9; H, 4·95; N, 16·5; H_2O, 6·3%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 248 mμ (ε 19,600); in 0·1N-NaOH, $\lambda_{max.}$ 244 mμ (ε 17,200). The absorption was unchanged after treatment with 0·1N-sodium hydroxide at 100° for 20 min. The *base* crystallised from 40% aqueous ethanol as irregular prisms, m. p. 196—197° (Found: C, 55·55; H, 4·9; N, 19·55. $C_{17}H_{17}N_5Cl_2$ requires C, 56·3; H, 4·75; N, 19·35%). The *picrate* formed yellow rods (from ethanol), m. p. 247—249° (Found: C, 47·1; H, 3·3; N, 18·8. $C_{17}H_{17}N_5Cl_2$,$C_6H_3O_7N_3$ requires C, 46·7; H, 3·4; N, 18·95%).

(*b*) A mixture of N^1N^2-di-*p*-chlorophenyldiguanide (from the hydrochloride and ethanolic sodium ethoxide) (3·2 g.), acetone (12 c.c.), and piperidine (0·2 c.c.) was heated under reflux for 66 hr. The hot solution was treated with carbon and filtered. The filtrate was diluted with water (30 c.c.) to precipitate a crude base (2·25 g.). This was converted into a hydrochloride and a picrate, each of which was identical (m. p. and mixed m. p.) with the corresponding derivative obtained by method (*a*) above.

4-*Amino*-6-*anilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1-*phenyl*-1 : 3 : 5-*triazine* (IX; X = H, R = NHPh, R′ = H).—N^1N^2-Diphenyldiguanide (Cramer, *Ber.*, 1901, **34**, 2597) (3·15 g.), N-hydrochloric acid (25 c.c.), acetone (15 c.c.), and water (5 c.c.) were heated together for 20 hr. on the steam-bath. Concentration of the solution under reduced pressure, followed by basification and ether-extraction under ice-cold conditions, left an insoluble base (1·35 g.), m. p. 171—174°. It was dissolved in 10% hydrochloric acid, and aqueous ammonia was added to give a pH of 5. The solid thus precipitated was collected, dissolved in water, and salted out with saturated aqueous sodium chloride, to give very small colourless rods of the dihydrate of 4-*amino*-6-*anilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1-*phenyl*-1 : 3 : 5-*triazine hydrochloride*, m. p. 236—237° (Found: C, 55·25; H, 6·35; N, 18·9. $C_{17}H_{19}N_5$,HCl,2H_2O requires C, 55·75; H, 6·6; N, 19·15%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 248 mμ (ε 20,500); in 0·1N-NaOH, $\lambda_{max.}$ 246 mμ (ε 12,800). The yellow *picrate*, crystallised from 2-ethoxyethanol, had m. p. 236—238° (decomp.) (Found: C, 52·65; H, 4·45; N, 21·4. $C_{17}H_{19}N_5$,$C_6H_3O_7N_3$ requires C, 52·9; H, 4·25; N, 21·5%).

4 : 6-*Diamino*-1 : 2-*dihydro*-1 : 2-*diphenyl*-1 : 3 : 5-*triazine*.—Aniline hydrochloride (25·9 g.) and dicyandiamide (21 g.) were stirred together in water (50 c.c.) on the steam-bath for 1 hr. A solution of benzaldehyde (42·4 g.) in ethanol (100 c.c.), and hydrochloric acid (17·5 c.c.; *d* 1·18) were added and the mixture was stirred at 70° for 17 hr. Carbon was then added and the mixture was filtered, and evaporated almost to dryness under reduced pressure. Water (200 c.c.) was added and the solution was evaporated under reduced pressure to half its volume. The solid which separated on keeping at 0° for some time was collected, washed with water, then dissolved in water, cooled to 0°, and shaken with ether whilst sodium hydroxide solution was added. The precipitated base was collected, washed with ether, and dried. It was dissolved in dilute hydrochloric acid, and the solution was clarified, and neutralised with aqueous ammonia

to precipitate the colourless *hydrochloride*, m. p. 232—233° (from water) (Found : C, 59·65; H, 5·4; N, 23·2. $C_{15}H_{15}N_5$,HCl requires C, 59·75; H, 5·3; N, 23·2%). Ultra-violet absorption in 0·01N-HCl : $\lambda_{max.}$ 249 mμ (ε 8,600).

Reaction of Benzylideneaniline with Dicyandiamide.—(*a*) Benzylideneaniline (10 g.) was added to a solution of dicyandiamide (4·65 g.) in water (125 c.c.) and 7% hydrochloric acid (27·7 c.c.). The mixture was stirred at 70° for 24 hr. and cooled and the oil present was discarded. Carbon was added and the mixture was filtered. The filtrate was cooled to 0° and made strongly alkaline with sodium hydroxide solution. The precipitate was collected, washed with ether, and dried. The base was dissolved in dilute hydrochloric acid, and the solution was clarified, and neutralised with aqueous ammonia. The solid was collected, washed with water, and crystallised from water, to give 4 : 6-diamino-1 : 2-dihydro-1 : 2-diphenyl-1 : 3 : 5-triazine hydrochloride, m. p. 221—224° undepressed by the product of the preceding experiment (Found : C, 59·45; H, 5·55; N, 23·45%). Ultra-violet absorption in 0·01N-HCl : $\lambda_{max.}$ 249 mμ (ε 9300).

(*b*) The initial mixture as in (*a*) was neutralised by the addition of aqueous ammonia and then stirred at 70° for 18 hr. The benzylideneaniline was unchanged.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, DYESTUFFS DIVISION,
HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9. [*Received, October 28th,* 1953.]