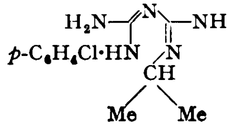
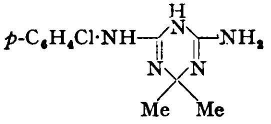
231. *Attempts to Prepare a Possible Metabolite of " Paludrine " (Proguanil) and Related* 1 : 3 : 5-*Triazines.*

By Stanley Birtwell.

It is suggested that the metabolite of " Paludrine " (proguanil), which Hawking (*Nature*, 1947, **159**, 409) and others suggest is responsible for the antimalarial activity, may be an effective antagonist for folic acid. Proguanil itself is only a moderate folic acid antagonist (Falco *et al.*, *ibid.*, 1949, **164**, 107). If this is so, the metabolite may well be 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine. Attempts to prepare this and related triazines such as 4-amino-1-*p*-chlorophenyl-1 : 2-dihydro-2-imino-6-methyl-1 : 3 : 5-triazine, however, gave in all cases the inactive, isomeric compounds 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine and, *e.g.*, 2-amino-4-*p*-chloroanilino-6-methyl-1 : 3 : 5-triazine respectively, owing (in the latter case, and possibly in the former) to isomerisation of the 1-*p*-chlorophenyltriazines to the 6-*p*-chloroanilino-compounds.

There is much evidence to support the view that a metabolite, produced from the antimalarial drug " Paludrine " (proguanil) (I) in the animal body, is responsible for its plasmodicidal action (Hawking, *Nature*, 1947, **159**, 409, and later workers). Its constitution has previously been debated (Fraser and Kermack, *J.*, 1951, 2682) and *inactive* metabolites have been isolated, one of which is considered to be 2-amino-6-*p*-chloroanilino-1 : 4-dihydro-4 : 4-dimethyl-1 : 3 : 5-triazine (II) (Crounse, *J. Org. Chem.*, 1951, **16**, 492). In this connection, the present work on antimalarials containing the 1 : 3 : 5-triazine nucleus, and the underlying theory are of interest.


(I)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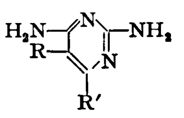
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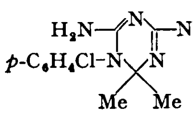
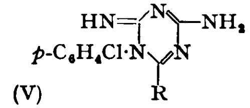

(IV)

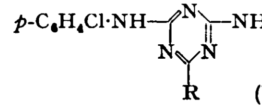
Falco, Hitchings, Russell, and Vanderwerff (*Nature*, 1949, **164**, 107) have shown that proguanil (I) in common with many 2 : 4-diaminopyrimidines (III), is a folic acid antagonist with respect to *L. casei*. However, they observed that correlation between antifolic acid activity and antimalarial activity was obscure. A rational explanation of their results would follow if (*a*) the effective folic acid antagonist were the (animal) metabolite of proguanil and (*b*) *L. casei* were capable of metabolising the drug in this way only to a limited extent. Furthermore, since oxidation is a relatively common mode of detoxication, 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (IV) is probably the metabolite in question. This compound also shows greater similarity to folic acid and the aminopyrimidines (III) than does proguanil (I).

Owing to the difficulties in devising unambiguous routes to (IV) and the rather scanty evidence for the structure of (II) (Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645; Crounse *loc. cit.*), which does not preclude many alternative structures, notably of the Schiff's base and four-membered ring types, syntheses of triazines of type (V) were first attempted.

When amidines react with dicyanimide (cf. Curd, Hendry, Kenny, Murray, and Rose, *J.*, 1948, 1630, for the reaction of amines with dicyanimide), the dicyanimide salt of the amidine is first formed, which on being heated alone or in a solvent rearranges to the 1 : 3 : 5-triazine. 2 : 4-Diamino-6-methyl- and 2 : 4-diamino-6-phenyl-1 : 3 : 5-triazine were prepared in this way from acetamidine and benzamidine respectively, and it appeared that the use of *N*-*p*-chlorophenylamidines in this reaction would afford an unambiguous route to 6-alkyl-4-amino-1-*p*-chlorophenyl-1 : 2-dihydro-2-imino-1 : 3 : 5-triazines (V). In fact, *N*-*p*-chlorophenyl-acetamidine and -propionamidine gave the anilino-compounds 2-amino-4-*p*-chloroanilino-6-methyl- and -6-ethyl-1 : 3 : 5-triazine (VI ; R = Me and R = Et respectively). *N*-*p*-Chlorophenyl-*N'*-cyanoguanidine was isolated as a by-product, but does not appear to be involved in the formation of the anilino-triazine (VI) : it does not

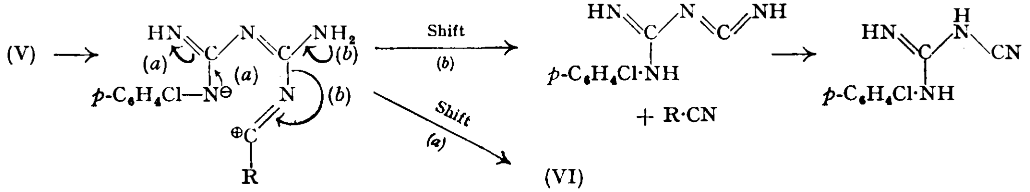


(V)



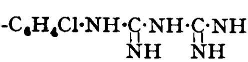
(VI)

combine with methyl or ethyl cyanide under the conditions applying in the above reaction, and yields only a trace of (VI ; R = Et) when similarly treated with *N*-*p*-chlorophenyl-propionamidine. The known processes for the preparation of triazines from cyano-guanidines and nitriles or amidines involve much higher temperatures and pressures and usually an alkaline catalyst (*e.g.*, Ostrogovich, *Chem. Abs.*, 1911, 2099; U.S.P. 2 302 162; B.P. 583 720). Therefore, in the reaction between substituted amidines and dicyanimide, compounds of type (V) are first formed but, being unstable at the temperature of the reaction, undergo fission of the $N_{(1)}$–$C_{(6)}$ bond, subsequently cyclising on the free amino-group to give the more stable, aromatic structures (VI). It is believed that fission of the $N_{(1)}$–$C_{(6)}$ bond is also a necessary preliminary for the formation of the by-products *N*-*p*-chlorophenyl-*N'*-cyanoguanidine and alkyl cyanide (not isolated), the mechanism of decomposition and isomerisation of the unstable dihydrotriazines (V) being :



Compounds (VI ; R = Me and Et) had no plasmodicidal activity when tested against *P. gallinaceum* in chicks.

Attempts to prepare the dihydrotriazine (IV) by methods which, it was recognised, might lead only to isomers or mixtures of isomers, were then made. Three main routes, commencing respectively from proguanil (I), *p*-chlorophenyldiguanide (VII), and *N*-amidino-N'-*p*-chlorophenylthiourea (VIII), have been explored.

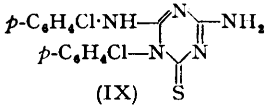


$$p\text{-}C_6H_4Cl\cdot NH\cdot\underset{\underset{NH}{\|}}{C}\cdot NH\cdot\underset{\underset{NH}{\|}}{C}\cdot NH_2$$

(VII)

$$p\text{-}C_6H_4Cl\cdot NH\cdot\underset{\underset{S}{\|}}{C}\cdot NH\cdot\underset{\underset{NH}{\|}}{C}\cdot NH_2$$

(VIII)

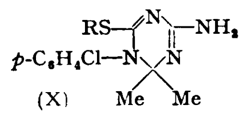


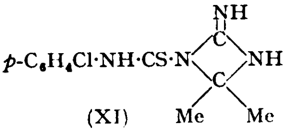
(IX)

Oxidation of (I) by acid or alkaline permanganate, lead tetra-acetate, hydrogen peroxide, or potassium ferricyanide gave no recognisable products.

Acetone and (VII) under reflux in acetic acid gave the triazine (II); the hydrochloride of (VII) failed to condense with acetone although the related but much less basic dithiobiurets condense readily, in the presence of strong acid, to give keturets (Fromm, *Annalen*, 1893, **275**, 30). Acetone diethyl acetal and (VII) at 130° gave a complex mixture from which two substances were isolated with difficulty. Analytical data in neither case corresponded to (IV) and identification was not completed.

The method of Slotta, Tschesche, and Dressler (*Ber.*, 1930, **63**, 208) was used for the preparation of (VIII) from *p*-chlorophenyl *iso*thiocyanate and guanidine. A compound $C_{15}H_{11}N_5SCl_2$ was also isolated which, it is believed, is (IX) (cf. Crowther, Curd, Richardson, and Rose, *J.*, 1948, 1636, who isolated similar compounds from the reaction of *p*-chlorophenyl *iso*thiocyanate with alkylguanidines). Acetone reacted readily with (VIII) in the presence of piperidine : the yield of condensation product varied with the amount of catalyst used, being a maximum (85%) with 50 c.c. of piperidine per mole of (VIII). The same product was obtained in poor yield when the reaction was catalysed by hydrochloric acid. It has been assigned structure (X; R = H) in view of its alkali solubility, its retention of sulphur in the presence of reagents such as ammoniacal silver nitrate, mercuric oxide, etc., its ready *S*-alkylation, and in particular the reaction with chloroacetic acid which does not give a cyclic structure as is the case with substituted thioureas containing two replaceable hydrogen atoms (Johnson, Pfau, and Hodge, *J. Amer. Chem. Soc.*, 1912, **34**, 1041). Although alkali solubility is doubtful it is possible that structure (XI) would also possess these properties, but it might be expected to give the same colour reaction with ammoniacal nickel salts as an amidinothiourea. Our compound does not do so, and as subsequent stages of the synthesis failed to give the desired (IV), more rigorous proof has not been sought. Replacement of the ethylthio-group of (X; R = Et) by amino has been tried under a variety of conditions, *viz.*, boiling the hydriodide with alcoholic ammonia, heating the hydriodide or the free base with methanolic ammonia in sealed tubes at 55—60°, and fusion of the hydriodide with ammonium acetate. In all cases, the anilino-triazine considered to be (II) was isolated, accompanied by decomposition products such as guanidine, *p*-chlorophenylguanidine, and, in the ammonium acetate fusion, *p*-chloroacetanilide, as well as a number of compounds which have been identified only as far as their empirical formulæ. A clear explanation of these results cannot be given. It may be that (IV) and not (II) is the correct formula for the reaction product of *p*-chlorophenyldiguanide and acetone in the presence of piperidine. Alternatively, (II) may be formed by reaction of ammonia with intermediates arising by decomposition of (X), or more probably as a result of a rearrangement such as has been suggested for the conversion of the unstable (V) into (VI).


(X)


(XI)

Other reactions which have been tried in order to obtain the desired type of compound include the condensation of *N*¹-diethylaminoethyl-*N*²-phenyldiguanide with acetone, and reaction of benzoyl-*p*-chlorophenylcyanamide with guanidine. The materials isolated appear to be hydrolysis products of the desired compounds—as determined from analytical data—6-diethylaminoethylamino(or 1-diethylaminoethyl)-1 : 2-dihydro-4-hydroxy-2 : 2-dimethyl-1-phenyl(or 6-anilino)-1 : 3 : 5-triazine in the former, and 1-*p*-chlorophenyl-1 : 2-dihydro-4-hydroxy-2-keto-6-phenyl-1 : 3 : 5-triazine in the latter case.

[Note added in proof.] Carrington, Crowther, Davey, Levi, and Rose recently reported (*Nature*, 1951, **168**, 1080) the isolation of a metabolite having ten times the activity of the parent drug. Its structure (IV), predicted by us on theoretical grounds, has been confirmed by *X*-ray analysis. Ready conversion of the metabolite into the inactive isomer (II), by the action of heat or alkali, confirms our suspicion that the failure to obtain (IV) by the methods adopted was, in fact, due to such an isomerisation. The synthesis of (IV) from *N'*-*p*-chlorophenyldiguanide and acetone has been accomplished (*loc. cit.*), under unspecified conditions.

EXPERIMENTAL

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss of Oxford.

N-p-*Chlorophenylacetamidine.*—An ethereal solution of methylmagnesium iodide (120 c.c., 0·25 mole) was added during 5 minutes to a stirred solution of *p*-chlorophenylcyanamide (15·2 g., 0·1 mole) in anisole (100 c.c.). Methane was evolved and ether distilled. The mixture was heated to 90—100°, more ether being distilled off, and this temperature was maintained for 2½ hours. After cooling, the whole was poured into dilute hydrochloric acid and ice. The aqueous layer was separated and basified with sodium hydroxide solution (addition of ice), and the precipitate filtered off (gravity). The filtrate and the filter paste were extracted with chloroform (300 c.c.). The extract, after being dried (Na_2SO_4), was evaporated to small bulk, *N*-*p*-chlorophenylacetamidine crystallising. Last traces of solvent were removed on a porous tile, and the product was obtained as pale brown prisms (12·6 g.), m. p. 112—115° (Gage, *J.*, 1949, 221, gives m. p. 116—117° after crystallisation from *cyclo*hexane).

Reaction of Dicyanimide with Amidines.—(a) *Benzamidine.* Benzamidine hydrochloride (1·6 g.) was added to sodium dicyanimide (0·9 g.) in water (20 c.c.). The *dicyanimide* salt of benzamidine, which crystallised, was collected and dried *in vacuo* ($CaCl_2$) (1·0 g.; m. p. 154°). When it was heated to 160° in an oil-bath, a vigorous reaction set in and the temperature rose spontaneously to 250°. After it had subsided, the temperature was kept at 150—160° for 10 minutes. The product was cooled and digested with 2N-hydrochloric acid (20 c.c.) at 60°, and the filtered extract poured into excess of dilute sodium hydroxide solution (ice), 2 : 4-diamino-6-phenyl-1 : 3 : 5-triazine being precipitated (0·7 g.; m. p. 221—225°). After crystallisation from alcohol it had m. p. 223—225° (Found: C, 57·4; H, 5·1; N, 37·2. Calc. for $C_9H_9N_5$: C, 57·7; H, 4·8; N, 37·4%).

(b) *Acetamidine.* Acetamidine hydrochloride (9·4 g.) and sodium dicyanimide (9·0 g.) were stirred in absolute alcohol (100 c.c.) and heated under reflux for 1 hour. After cooling, the sodium chloride was filtered off, and the filtrate evaporated to dryness *in vacuo.* A crystalline residue of the dicyanimide salt of acetamidine (12·5 g.) remained, m. p. 94° after drying at 80—90°.

A portion (5·0 g.) was stirred in dry benzene (75 c.c.), and traces of alcohol and water were removed as azeotropes by distillation of about two-thirds of the solution. Nitrobenzene (25 c.c.) was added and the mixture heated to the b. p. for about 5 minutes, with the apparatus set for distillation. Much ammonia was evolved. The suspension was then filtered, and the solid washed with benzene, dried, and dissolved in water (50 c.c.) containing 2N-sodium hydroxide (5 c.c.) at 60°. Some insoluble material was removed, and the concentration of sodium hydroxide in the filtrate increased to about 10% by addition of a concentrated solution of the alkali. Crystalline 2 : 4-diamino-6-methyl-1 : 3 : 5-triazine, giving the characteristic blue colour with iodine–potassium iodide solution, was precipitated. It was collected, washed with a small amount of 2N-sodium hydroxide, then with alcohol, and finally crystallised from alcohol, whereafter it had m. p. 270—272° (Found: C, 38·25; H, 5·7. Calc. for $C_4H_7N_5$: C, 38·4; H, 5·6%).

(c) N-p-*Chlorophenylacetamidine.* 2N-Hydrochloric acid (30 c.c.) was added to a suspension of the amidine (10·5 g.) in water (50 c.c.) until an acid reaction to Congo-red was obtained. The solution was clarified and treated with sodium dicyanimide (5·5 g.) in water (30 c.c.). Scratching caused separation of the *dicyanimide* salt of *N-p*-chlorophenylacetamidine which was filtered off, washed with water, and dried on a porous title *in vacuo* over phosphoric oxide (11·3 g.; m. p. 144—146°). A sample, recrystallised from water at 70—80°, was obtained as small, almost colourless, needles, m. p. 145—146° (Found: C, 50·75; H, 4·25; N, 29·4. $C_{10}H_{10}N_5Cl$ requires C, 51·0; H, 4·25; N, 29·7%). A portion of this salt (7·0 g.) in dry butanol (K_2CO_3) (35 c.c.) was heated under reflux for 2 hours. The butanol was distilled in steam, and the residual hot suspension acidified (hydrochloric acid) and cooled. A crystalline precipitate (1·3 g.; m. p. 189—200°) which separated was filtered off and washed with water to a total volume of filtrate of 90—100 c.c. After purification through dilute sodium hydroxide solution, and three crystallisations from 33% alcohol, it had m. p. 208°, undepressed on admixture with *N-p*-chlorophenyl-*N'*-cyanoguanidine (Found: C, 49·35; H, 3·7; N, 29·0; Cl, 18·0. Calc. for $C_8H_7N_4Cl$: C, 49·4; H, 3·6; N, 28·8; Cl, 18·3%). The aqueous, acid filtrate was clarified after being warmed to 25—30°, and treated with concentrated nitric acid (14 c.c.) with good stirring. The crystalline nitrate which separated was collected, washed with dilute nitric acid, dissolved in hot water (50 c.c.), and poured into excess of sodium hydroxide solution and ice. The precipitate of 2-amino-4-*p*-chloroanilino-6-methyl-1 : 3 : 5-triazine (VI; R = Me) was dried and crystallised from chlorobenzene; it was obtained as almost colourless prisms (2·6 g.; m. p. 198—199°) (Curd, Landquist, and Rose, *J.*, 1947, 154, give m. p. 195—196°) (Found: C, 51·3; H, 4·4; N, 30·0. Calc. for $C_{10}H_{10}N_5Cl$: C, 51·0; H, 4·25; N, 29·7%).

(d) N-p-*Chlorophenylpropionamidine.* The *dicyanimide* salt (4·0 g.; m. p. 120—122°), prepared as in (c) from *p*-chlorophenylpropionamidine (Birtwell, *J.*, 1949, 2561) (4·8 g.), sodium dicyanimide (2·5 g.), and 2N-hydrochloric acid (12·5 c.c.), crystallised from water in almost colourless prisms, m. p. 121—122° (Found: C, 53·0; H, 4·9; N, 28·2. $C_{11}H_{12}N_5Cl$ requires C, 52·9; H, 4·8; N, 28·1%). A portion of the salt (3·5 g.) was heated under reflux in dry butanol (K_2CO_3) for 2 hours. The butanol was distilled off in steam and the residual solution acidified with hydrochloric acid. Insoluble material was filtered off, washed with water (total filtrate volume, 50 c.c.) and extracted with water (50 c.c.) at 50—60°. The filtered extract was poured into excess of sodium hydroxide solution and ice, 2-amino-4-*p*-chloroanilino-6-ethyl-1 : 3 : 5-triazine (VI; R = Et) (1·4 g.; m. p. 171—172°) separating. A further amount (0·35 g.; m. p. 169—170°) was obtained by addition of nitric acid to the filtrate from the steam-distillation as in (c). The combined crops, after crystallisation from toluene, had m. p. 174—175°, undepressed on admixture with an authentic specimen (Birtwell, *loc. cit.*) (Found : C, 53·1; H, 5·0; Cl, 14·0. Calc. for $C_{11}H_{12}N_5Cl$: C, 52·9; H, 4·8; Cl, 14·2%).

Attempted Reaction of N-p-*Chlorophenyl*-N′-*cyanoguanidine with Ethyl Cyanide*.—A mixture of *N*-*p*-chlorophenyl-*N*′-cyanoguanidine (2·0 g.), ethyl cyanide (1·0 c.c.), and butanol (15 c.c.) was heated under reflux for 3 hours. Unchanged *N*-*p*-chlorophenyl-*N*′-cyanoguanidine (1·65 g.; m. p. 210—211°) crystallised on cooling. No basic material was obtained by dilution of the filtrate with benzene and extraction with hydrochloric acid.

The course of the reaction was unaffected by the addition of acid (HCl, NH_4Cl) or basic (NaOEt) catalysts, or by slight modifications in the experimental procedure.

Reaction of N-p-*Chlorophenyl*-N′-*cyanoguanidine with* N-p-*Chlorophenylpropionamidine*.—*N*-*p*-Chlorophenyl-*N*′-cyanoguanidine (1·4 g.) and *N*-*p* chlorophenylpropionamidine (1·3 g.) were heated under reflux for 3 hours in butanol (10 c.c.) containing a trace of hydrochloric acid. Unchanged *N*-*p*-chlorophenyl-*N*′-cyanoguanidine (1·0 g.; m. p. 210—212°) which crystallised on cooling was filtered off, and the filtrate was distilled in steam. The residue was acidified with hydrochloric acid, and filtered at the boil. The filtrate, on cooling, deposited crystals which were collected, dissolved in hot water, and poured into sodium hydroxide solution, 2-amino-4-*p*-chloroanilino-6-ethyl-1 : 3 : 5-triazine (VI; R = Et) (0·1 g.; m. p. 171—172°) being obtained.

Preparation of 2-*Amino*-6-p-*chlorophenyl*-1 : 4-*dihydro*-4 : 4-*dimethyl*-1 : 3 : 5-*triazine* (II) *in Acetic Acid Solution* (cf. Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645).—*p*-Chlorophenyldiguanide (VII) (10·5 g.), acetone (10 c.c.), and glacial acetic acid (10 c.c.) were mixed, whereupon the acetate crystallised. The suspension was heated under reflux for 40 hours until almost homogeneous, and, after cooling, was poured into sodium hydroxide solution and ice, an oil being precipitated. The addition of benzene caused the mixture to separate into two layers with 2-amino-6-*p*-chlorophenyl-1 : 4-dihydro-4 : 4-dimethyl-1 : 3 : 5-triazine (II) at the interphase. This was collected and crystallised from aqueous alcohol, the hydrate of the base (1·0 g.) being obtained m. p. 135—136° (Birtwell *et al.*, *loc. cit.*, give m. p. 130—131°).

Reaction of p-*Chlorophenyldiguanide* (VII) *with Acetone Diethyl Acetal*.—A paste of *p*-chlorophenyldiguanide (VII) (10·5 g.) in acetone diethyl acetal (10·0 g.) was heated under reflux ($CaCl_2$ tube) in an oil-bath at 120°, so that the acetal was boiling gently. After 18 hours, benzene (100 c.c.) was added, and moist carbon dioxide was passed through the cooled, filtered solution. The precipitated carbonates, on treatment with cold, dilute hydrochloric acid gave an insoluble *hydrochloride*, which after two crystallisations from butanol had m. p. 288—289° (Found : C, 40·7; H, 4·0; N, 29·5; Cl, 24·8. $C_{10}H_{11}N_6Cl,HCl$ requires C, 41·8; H, 4·2; N, 29·3; Cl, 24·8%). The benzene filtrate from the carbonates was treated with dry hydrogen chloride. The precipitated hydrochlorides, suspended in warm alcohol, and treated with sodium hydroxide solution, gave a crude *base* on dilution with water. After three crystallisations from aqueous dioxan it had m. p. 203—205° (Found : C, 53·0; H, 5·1; N, 19·1; Cl, 16·0. $C_{10}H_{12}ON_3Cl$ requires C, 53·2; H, 5·3; N, 18·6; Cl, 15·7%).

N-*Amidino*-N′-p-*chlorophenylthiourea* (VIII).—Guanidine hydrochloride (29·0 g.) and a solution of sodium (6·0 g.) in acetone (200 c.c.) were stirred at room temperature for 1 hour. *p*-Chlorophenyl *iso*thiocyanate was added gradually with cooling, and after 24 hours' stirring the mixture was heated under reflux for 1 hour, then cooled and filtered. When the filtrate was poured into water an oil separated, which became slowly semi-solid. The water was decanted and the residue treated with a small amount of alcohol, giving a solid, m. p. 189° (decomp.) (19·0 g.). After being dried for a short time at 100°, it was boiled with methanol (*ca.* 300 c.c.), and the insoluble 4-*amino*-6-p-*chloroanilino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2-*thio*-1 : 3 : 5-*triazine* (IX) filtered off; it had m. p. 290° (decomp.) after two crystallisations from 2-ethoxyethanol (Found : C, 49·5; H, 3·3; N, 19·0. $C_{15}H_{11}N_5SCl_2$ requires C, 49·5; H, 3·0; N, 19·2%). The methanol filtrate on cooling gave N-*amidino*-N′-p-*chlorophenylthiourea* (VIII), m. p. 191° (decomp.) (10·3 g.) (Found : C, 42·2; H, 3·6; N, 24·5. $C_8H_9N_4SCl$ requires C, 42·0; H, 3·9; N, 24·5%). A further small amount was obtained by evaporation of the filtrate.

4-*Amino*-1 : 2-*dihydro*-6-*mercapto*-2 : 2-*dimethyl*-1-*phenyl*-1 : 3 : 5-*triazine*.—*N*-Amidino-*N*′-phenylthiourea (Slotta *et al.*, *Ber.*, 1930, **63**, 208) (2·3 g.), acetone (15 c.c.), and piperidine (0·1 c.c.) were heated under reflux for 20 hours. Complete solution was not obtained. After cooling, the insoluble material was filtered off and recrystallised from butanol, to give the *mercaptotriazine*, m. p. 240° (decomp.) (Found : C, 56·3; H, 5·9; N, 23·9; S, 13·4 $C_{11}H_{14}N_4S$ requires C, 56·4; H, 6·0; N, 23·9; S, 13·7%).

4-*Amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-6-*mercapto*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (X; R =

H).—*N*-Amidino-N′-*p*-chlorophenylthiourea (VIII) (34·3 g.), acetone (300 c.c.), and piperidine (7·5 c.c.) were heated under reflux with stirring for 3 hours. The insoluble *mercaptotriazine* was collected, washed with acetone, and dried at 100°; it (34·0 g.) had m. p. 229° (decomp.), unchanged on recrystallisation from butanol (Found: N, 21·4; S, 12·3. $C_{11}H_{13}N_4SCl$ requires N, 20·9; S, 11·9%).

*4-Amino-*1-p-*chlorophenyl-*1 : 2-*dihydro-*2 : 2-*dimethyl-*6-*methylthio-*1 : 3 : 5-*triazine* (X; R = Me).—The triazine (X; R = H) (1·3 g.), dimethyl sulphate (1·0 c.c.), and 2N-sodium hydroxide solution were shaken together for 3 hours, then warmed on the steam-bath for 15 minutes. The product was filtered off after cooling, washed with water, stirred with ether, and collected on a porous tile. It was taken up in acetone, filtered from insoluble material, and evaporated to dryness. The residue, recrystallised twice from *cyclo*hexane–benzene (3 : 1), gave the required *base* (X; R = Me), m. p. 171° (Found: C, 50·9; H, 5·6; N, 19·2. $C_{12}H_{15}N_4SCl$ requires C, 51·0; H, 5·3; N, 19·8%)

*4-Amino-*1-p-*chlorophenyl-*6-*ethylthio-*1 : 2-*dihydro-*2 : 2-*dimethyl-*1 : 3 : 5-*triazine* (X; R = Et).—(*a*) The mercapto-triazine (X; R = H) (4·0 g.), ethyl iodide (4·0 c.c.), and absolute alcohol (40 c.c.) were heated under reflux for 30 minutes, a homogeneous solution being obtained. The bulk of the solvent was evaporated off, and benzene (75 c.c.) added. Distillation of a further 20—25 c.c. removed the remaining alcohol, and the solution when cooled and scratched gave *4-amino-*1-p-*chlorophenyl-*6-*ethylthio-*1 : 2-*dihydro-*2 : 2-*dimethyl-*1 : 3 : 5-*triazine hydriodide* (5·6 g.; m. p. 181—182°). After crystallisation from water it had m. p. 182—183° (Found: C, 37·3; H, 4·4. $C_{13}H_{17}N_4SCl$ requires C, 36·8; H, 4·2%). A portion of the hydriodide, dissolved in hot water and poured into dilute sodium hydroxide solution and ice, gave the *base* (X; R = Et), which was dried *in vacuo* over sulphuric acid, then crystallised twice from *cyclo*hexane; it had m. p. 173—174° (Found: C, 52·9; H, 5·9; N, 18·3; S, 10·6. $C_{13}H_{17}N_4SCl$ requires C, 52·6; H, 5·7; N, 18·9; S, 10·8%). The picrate had m. p. 191—193°.

(*b*) *N*-Amidino-*N′*-*p*-chlorophenylthiourea (11·4 g.), 10N-hydrochloric acid (6·0 c.c.), and acetone (50 c.c.) were heated under reflux for 20 hours, then cooled, and insoluble material filtered off. The filtrate was poured into excess of 2N-sodium hydroxide solution, and the supernatant liquid decanted from the resulting oily precipitate. On acidification of the solution, and then basification with ammonia, a precipitate of crude (X; R = H) (3·2 g.) was obtained. After drying, it was converted into 4-amino-1-*p*-chlorophenyl-6-ethylthio-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine hydriodide as in (*a*) above, which after recrystallisation from chlorobenzene had m. p. 180—182° and gave a picrate, m. p. 191—193°, identical with the picrate obtained in (*a*).

*4-Amino-*6-*carboxymethylthio-*1-p-*chlorophenyl-*1 : 2-*dihydro-*2 : 2-*dimethyl-*1 : 3 : 5-*triazine* (X; R = $CH_2{\cdot}CO_2H$).—The mercapto-triazine (X; R = H) (1·0 g.), chloroacetic acid (1·0 g.), and water (10 c.c.) were boiled under reflux. At no time was a homogeneous solution obtained. The reaction mixture was cooled, and the insoluble material filtered off [0·15 g.; m. p. 241° (decomp.)]. The filtrate was basified with sodium hydroxide solution, and a stream of carbon dioxide passed through the solution, giving a further quantity of the same product [0·75 g.; m. p. 222° (decomp.)]. This substance was soluble in acids and alkalis but insoluble in all the usual solvents. It was converted into the *picrate* of 4-amino-6-carboxymethylthio-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine by boiling it with aqueous-alcoholic picric acid, and after recrystallisation from 66% alcohol this had m. p. 153—155° (decomp.) (0·5 g.) (Found: C, 41·5; H, 3·6; S, 5·7. $C_{13}H_{15}O_2N_4SCl,C_6H_3O_7N_3$ requires C, 41·0; H, 3·2; S, 5·7%).

*Reactions of the Hydriodide of 4-Amino-*1-p-*chlorophenyl-*6-*ethylthio-*1 : 2-*dihydro-*2 : 2-*dimethyl-*1 : 3 : 5-*triazine* (X; R = Et).—(a) *With ammoniacal methanol solution.* The hydriodide (6·0 g.) of (X; R = Et) in a saturated solution of ammonia in methanol (40 c.c.) was heated in a sealed tube at 55—60° for 6 hours. After cooling, the solution was filtered and evaporated to dryness. The residue was separated from a small amount of oil by dissolution in dilute hydrochloric acid. Mineral acidity was removed by sodium acetate, then a solution of picric acid in aqueous sodium acetate was added. The bulky picrate was collected and washed with warm water (A) (3·0 g.; m. p. 200—220°). The mother-liquors on being kept overnight gave a further picrate (B) [0·2 g.; m. p. 310° (decomp.)]. Product (A) was treated with a small amount of boiling ethyl acetate, then cooled, and the insoluble material filtered off. After several recrystallisations from alcohol, the picrate of 2-amino-6-*p*-chloroanilino-1 : 4-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine, m. p. and mixed m. p. 239—240°, was obtained. The ethyl acetate mother-liquors were evaporated to dryness, and the residue recrystallised from glacial acetic acid, then from aqueous alcohol, giving *p*-chlorophenylguanidine picrate, m. p. 230°, not depressed on admixture with an authentic specimen. Product (B) was recrystallised from glacial acetic acid to give guanidine picrate, m. p. 320° (decomp.).

(b) *With ammonium acetate.* Ammonium acetate (4·0 g.) was fused at 160° and the hydriodide (1·0 g.) of (XI; R = Et) added. The temperature was kept at 160—180° for 1 hour. The reaction mixture was cooled and diluted with water, *p*-chloroacetanilide crystallising (0·1 g.; m. p. 177—179°). Aqueous picric acid was added to the boiling filtrate, and the solution allowed to cool overnight; a picrate (0·85 g.) crystallised. It was extracted with a small amount of acetone, and the insoluble (0·15 g.) material crystallised from a large volume of acetone, giving guanidine picrate, m. p. and mixed m. p. 325° (decomp.) (Found: C, 29·7; H, 2·8; N, 29·2. Calc. for $CH_5N_3,C_6H_3O_7N_3$: C, 29·2; H, 2·8; N, 29·2%). The acetone extract was evaporated to dryness and re-extracted with boiling water (50 c.c.). The insoluble material was filtered off, recrystallised from alcohol, and extracted with a small amount of ethyl acetate, leaving 2-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine picrate, m. p. and mixed m. p. 238—239°. The aqueous extract, on cooling, deposited crystals of *p*-chlorophenylguanidine picrate, which after successive crystallisations from water and ethyl acetate had m. p. 235° (Found: C, 39·1; H, 2·3; N, 21·0; Cl, 9·6. Calc. for $C_7H_8N_3Cl,C_6H_3O_7N_3$: C, 39·2; H, 2·3; N, 21·0; Cl, 8·9%).

*Reaction of 4-Amino-*1-p-*chlorophenyl-6-ethylthio-*1 : 2-*dihydro-*2 : 2-*dimethyl-*1 : 3 : 5-*triazine* (X; R = Et) *with Ammonia.*—The triazine (X; R = Et) (4·0 g.), dissolved in a saturated solution of ammonia in methanol (40 c.c.), was heated in a sealed tube at 55—60° for 6 hours. The reaction mixture was evaporated to dryness after clarification, and the tarry residue extracted with tepid benzene, leaving a small amount of sparingly soluble, semi-solid material (A). Carbon dioxide was passed through the solution, and the precipitated carbonate (B) collected and boiled with benzene; some carbon dioxide was then evolved and a portion of the material dissolved. The insoluble material (C) was filtered off, and carbon dioxide was passed through the cold filtrate. The precipitated carbonate (D) (hygroscopic) was filtered off and dried *in vacuo*. Hydrogen chloride was passed through the main benzene filtrate (from B), and the hydrochloride which separated was filtered off. It was extracted with acetone, with decantation from a small amount of oil, and the residue, after evaporation of the acetone, was dissolved in water. Addition of a sodium acetate–picrate acid solution gave the picrate (E). Product (A), treated with alcoholic picric acid gave 2-amino-6-*p*-chloroanilino-1 : 4-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine picrate, m. p. and mixed m. p. 239—240° after two recrystallisations from alcohol. A further quantity of this compound was obtained by warming the carbonate (C) with aqueous picric acid and recrystallising the salt several times from alcohol. The material (D), treated with aqueous-alcoholic picric acid, gave a *picrate* which, after several crystallisations from glacial acetic acid, had m. p. 197—198°. It has not been identified (Found: C, 36·7; H, 2·5; N, 22·0; Cl, 5·5. $C_8H_9N_4Cl,2C_6H_3O_7N_3$ requires C, 36·7; H, 2·3; N, 21·4; C, 5·4%). Picrate (E) was extracted with cold acetone, and the residue recrystallised several times from glacial acetic acid, to give an unidentified *picrate*, m. p. 257° (Found: C, 38·0; H, 2·5; N, 21·8; Cl, 9·2%). The acetone extract was evaporated to dryness and the product crystallised twice from absolute alcohol, to give the picrate, m. p. and mixed m. p. 192—193°, of the starting material (X; R = Et).

*Reaction of Guanidine and Benzoyl-*p-*chlorophenylcyanamide.*—Guanidine hydrochloride (0·95 g.), sodium methoxide (0·54 g.), and benzoyl-*p*-chlorophenylcyanamide (3·5 g.) were heated under reflux in butanol (20 c.c.) for 2 hours. After cooling, the product, mixed with sodium chloride, was filtered off, washed with butanol, and dried at 100°. Sodium chloride was extracted with water, and the residue (0·6 g.; m. p. 235—238°) recrystallised from glacial acetic acid, to give 1-*p*-chlorophenyl-1 : 2-dihydro-4-hydroxy-2-keto-6-phenyl-1 : 3 : 5-triazine (Found: C, 60·2; H, 3·9; N, 14·2. $C_{15}H_{10}O_2N_3Cl$ requires C, 60·1; H, 3·4; N, 14·0%).

N^1-*2′-Diethylaminoethyl-*N^2-*phenyldiguanide and a Hydroxy-triazine.*—*N*-Amidino-*N′*-phenylthiourea (Slotta *et al.*, *loc. cit.*) and diethylaminoethylamine (5·0 g.) in absolute alcohol (50 c.c.) were stirred and heated under reflux for 5 hours with mercuric oxide (12·0 g.). The mixture was cooled, mercury salts were filtered off, and the amber-coloured filtrate was evaporated to dryness under diminished pressure (bath-temp. ≯90°). The residue was taken up in 2N-hydrochloric acid, clarified, and made alkaline with ammonia. The precipitate was filtered off and discarded. The filtrate gave a yellow oil on basification (sodium hydroxide solution), which was extracted into ether and dried (KOH). A yellow, gummy residue remained on evaporation of the solvent. Without further purification it was heated in acetone (25 c.c.) for 24 hours, then cooled, and carbon dioxide was passed through the solution. A carbonate was obtained (0·9 g.; m. p. 98—99° after shrinking), which dissolved in boiling acetone with evolution of carbon dioxide. On retreatment of the cooled solution with carbon dioxide, the carbonate of N^1-*2′-diethylaminoethyl*-N^2-*phenyldiguanide* crystallised (m. p. 98—100° after shrinking) (Found : C, 53·0; H, 8·1; N, 24·2. $C_{14}H_{24}N_6,H_2CO_3,\frac{1}{2}H_2O$ requires C, 53·3; H, 7·6; N, 24·8%). The *picrate* separated from alcohol in yellow prisms, m. p. 186—187° (Found : C, 41·9; H, 4·0; N, 22·6. $C_{14}H_{24}N_6,2C_6H_3O_7N_3,H_2O$ requires C, 42·5; H, 4·1; N, 22·9%). The main acetone filtrate was evaporated to dryness and converted into the picrate by treament with alcoholic picric acid. After several recrystallisations from acetone–alcohol 6-*diethylaminoethylamino*- (or 1-*diethylaminoethyl*)-1 : 2-*dihydro*-4-*hydroxy*-2 : 2-*dimethyl*-1-*phenyl*-(or 6-*anilino*)-1 : 3 : 5-*triazine picrate* crystallised; it had m. p. 196—198° (Found: C, 43·9; H, 4·5; N, 18·9. $C_{17}H_{27}ON_5,2C_6H_3O_7N_3,H_2O$ requires C, 43·8; H, 4·4; N, 19·4%).

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