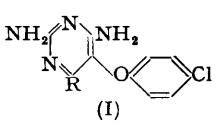
759. *Antimalarial Activity in 2 : 4-Diamino-5-arylpyrimidines. Some Reactions of α-Formylphenylacetonitrile.*

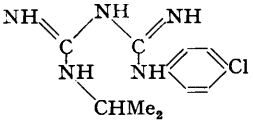
By B. H. CHASE, (MISS) J. P. THURSTON, and JAMES WALKER.

The effects of various agents on *Plasmodium gallinaceum* are briefly outlined in so far as " Paludrine " and certain pyrimidine types are concerned.

Reaction between α-formylphenylacetonitrile and diazomethane yielded a mixture of products containing the solid epoxide, βγ-epoxy-α-phenylbutyronitrile, as well as a solid enol methyl ether. Other methods for the preparation of enol ethers in good yield are described, and condensation of these ethers with guanidine affords, irrespective of their stereochemistry, good yields of 2 : 4-diamino-5-phenylpyrimidine. Direct condensation of α-formylphenylacetonitrile with guanidine gives the isomeric guanidinomethylenephenylacetonitrile, which, unexpectedly, passes into phenylacetylguanidine on treatment with acids. Similar reactions have been applied to *p*-chlorophenyl-α-formylacetonitrile. 2 : 4-Diamino-5-*p*-chlorophenylpyrimidine is highly active against *P. berghei* and *P. gallinaceum*, being about twice as active as " Paludrine " against both parasites in their respective hosts.

ALTHOUGH Curd and Rose and their colleagues proceeded in theory from sulphadiazine to pyrimidines and thence to diguanides in their development of " Paludrine " (proguanil) (*J.*, 1946, 343, 729), the connection between pyrimidines and proguanil was purely speculative until Bishop and McConnachie (*Nature*, 1948, **162**, 541) linked sulphadiazine experimentally with proguanil by showing that certain proguanil-resistant strains of *P. gallinaceum* were cross-resistant to sulphadiazine and *vice versa*. Since that time it has been found that the antimalarial activity of proguanil was potentiated by *p*-aminobenzoic acid competitors, such as sulphadiazine (Greenberg, *J. Pharmacol.*, 1949, **97**, 238), that 2 : 4-diamino-6 : 7-diphenylpteridine could suppress parasitæmia in doses tolerated by chicks infected with *P. gallinaceum*, and that this action was potentiated by sulphadiazine and significantly inhibited by pteroylglutamic acid (*idem, ibid.*, p. 484), while the antimalarial action of sulphadiazine was potentiated by 2 : 4-diamino-5-aryloxypyrimidines (Greenberg and Richeson, *ibid.*, 1950, **99**, 444), which had previously been found to be powerful antagonists of pteroylglutamic acid in cultures of *L. casei* (cf. Hitchings, Elion, Falco, Russell, and VanderWerff, *Ann. N.Y. Acad. Sci.*, 1950, **52**, Art. 8, 1330). Falco, Hitchings, Russell, and VanderWerff (*Nature*, 1949, **164**, 107) noted that 2 : 4-diamino-5-*p*-chlorophenoxypyrimidine (I; R = H) showed a certain formal resemblance to proguanil (II), which they found also to be an effective antagonist of pteroylglutamic acid; conversely, the former (I; R = H) and a homologue (I; R = Me) were found to have antimalarial activity (Falco *et al.*, *loc. cit.*; Goodwin, *ibid.*, p. 1133).


(I)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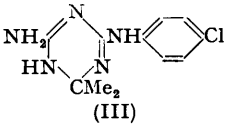
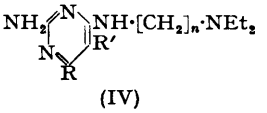
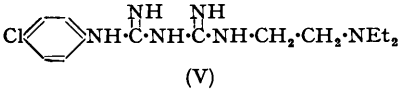

(III)

It may be recalled that it had been shown in these laboratories (Hawking, *Nature*, 1947, **159**, 409; Hawking and Perry, *Brit. J. Pharmacol.*, 1948, **3**, 320; Tonkin, *ibid.*, 1946, **1**, 163) that proguanil (II) *per se* does not appear to possess marked antimalarial activity but that it

undergoes activation in the animal body to give a substance of high intrinsic activity. The possibility that this activation product might be a cyclic structure is fairly obvious, having regard to the nature of the polyfunctionality of the diguanide chain in (II), although we have confirmed the fact that 6-amino-4-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-*s*-triazine (III), isolated by Crounse (Abst. of Papers, 117th Meeting, Amer. Chem. Soc., 1950, p. 28 L; *J. Org. Chem.*, 1951, **16**, 492) as a metabolite of proguanil, is devoid of activity (cf. Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645). Nevertheless, the possibility of a formal resemblance between the unknown active metabolite and 2 : 4-diaminopyrimidines did not appear to be excluded, and, together with the chain of circumstantial evidence outlined above, seemed to indicate the desirability for a further study of 2 : 4-diaminopyrimidines as antimalarials. Quite marked antimalarial activity had previously been observed in 4-dialkylaminoalkylamino-2-aminopyrimidines (IV) (Hull, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 357), and it was hoped that simplification of this type of compound by elimination of the dialkylaminoalkyl group to give simple 2 : 4-diaminopyrimidines would have a beneficial effect on activity similar to that produced by omitting the corresponding basic centre in passing from the inactive 1-*p*-chlorophenyl-5-2′-diethylaminoethyldiguanide (V) to the active compounds of the proguanil type (II) (Curd, Davey, and Rose, *Ann. Trop. Med. Parasitol.*, 1945, **39**, 208). The type selected for study was (VI; R = H or Cl), and we were unaware of the interest of others in this direction, but the appearance of a communication * by Falco, Goodwin, Hitchings, Rollo, and Russell (*Brit. J. Pharmacol.*, 1951, **6**, 185), following a brief preliminary report (*Chem. Eng. News*, 1951, **29**, 1508), obliges us to submit an account of a less extensive investigation along similar lines upon which we have recently been engaged.



(IV)



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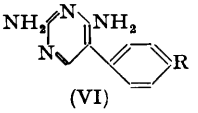
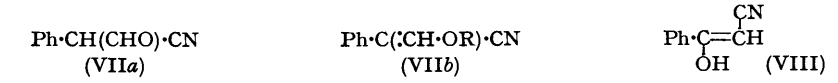
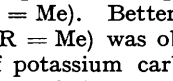


(VI)

The structure of α-formylphenylacetonitrile (VII*a*) has not been studied with the same thoroughness as has that of the less conveniently prepared ethyl α-formylphenylacetate, which exists almost entirely as the enol (cf. Eistert, Arndt, Loewe, and Ayça, *Chem. Ber.*, 1951, **84**, 159). The linearity of the cyano-group in (VII), however, prevents any contribution, through chelation, to the stability of the *cis*-form of the tautomeric hydroxymethylene-phenylacetonitrile (VII*b*; R = H) (cf. Hendricks, Wulf, Hilbert, and Liddel, *J. Amer. Chem. Soc.*, 1936, **58**, 1991), although it gives a strong ferric reaction, whereas the isomeric ω-cyanoacetophenone gives no ferric reaction and is believed to form only a *trans*-enol (VIII) (Arndt and Loewe, *Ber.*, 1938, **71**, 1627). On the one hand, the reaction between ω-cyano-



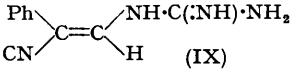
(VII*a*) (VII*b*) (VIII)

acetophenone and diazomethane proceeds quantitatively and homogeneously, both chemically and stereochemically, to give a solid enol ether (Arndt and Loewe, *ibid.*, p. 1631), while (VII), on the other hand, afforded with diazomethane two isomeric crystalline products together with oily material. One of these products, m. p. 176—178°, was methoxyl-free and, as it did not appear to react with the 2 : 4-dinitrophenylhydrazine reagent, was probably βγ-epoxy-α-phenylbutyronitrile,  ; rearrangement to β-keto-α-phenylbutyronitrile, $Ph{\cdot}CH(CN){\cdot}CO{\cdot}CH_3$, is implicit in its facile hydrolysis to phenylacetic acid with alkali. The other crystalline product, m. p. 67—68°, was a pure stereoisomeric form of the enol methyl ether (VII*b*; R = Me). Better conversion into a mixture of the two stereoisomeric enol methyl ethers (VII*b*; R = Me) was obtained by etherification in dry acetone with methyl iodide in the presence of potassium carbonate (cf. von Auwers, *Ber.*, 1938, **71**, 2082), and excellent yields in the case of the enol *iso*butyl ether (VII*b*; R = Bu^i) were obtained by azeotropic distillation of (VII*a*) with *iso*butanol in benzene in the presence of a trace of toluene-*p*-sulphonic acid, following the technique used by Seifert and Schinz (*Helv. Chim. Acta*, 1951, **34**, 728) for hydroxymethylene ketones.

Reaction between the alkoxymethylenephenylacetonitriles (VII*b*; R = Me or Bu^i) and

* [*Added in proof, October 24th*, 1951.] Since this communication was submitted, three further relevant papers by Hitchings and his collaborators have come to hand (*J. Amer. Chem. Soc.*, 1951, **73**, 3753, 3758, 3763).

guanidine proceeded smoothly, and without being dependent, as far as yields were concerned, on the stereochemistry of the enol ether, to give 2 : 4-diamino-5-phenylpyrimidine (VI; R = H), as shown by comparison with an authentic specimen. The direct reaction, however, between formylphenylacetonitrile [(VII*a*) or (VII*b*; R = H)] and guanidine afforded in rather poor yield a product isomeric with (VI; R = H), which, as it was oxygen-free, must have been the *trans*-form (IX) of α-(guanidinomethylene)phenylacetonitrile, and, surprisingly, this substance passed readily into phenylacetylguanidine (X; Z = O) on acid hydrolysis. As a tentative mechanism for this transformation, which we hope to examine more closely, it may be that (IX) undergoes hydrolysis into its components with subsequent reaction of the guanidine with the cyano-group (cf. Russell and Hitchings, *J. Amer. Chem. Soc.*, 1950, **72**, 4922), fission of the formyl group, and hydrolysis of the resulting phenylacetimidoguanidine (X; Z = NH) to (X; Z = O).



(IX)

$Ph{\cdot}CH_2{\cdot}CZ{\cdot}NH{\cdot}C(:NH){\cdot}NH_2$ (X)

To establish the identity of (VI; R = H), an authentic specimen was prepared by dehalogenation of 2 : 4-diamino-6-chloro-5-phenylpyrimidine. In the preparation of 2 : 4 : 6-trichloro-5-phenylpyrimidine from 5-phenylbarbituric acid, following the technique of Baddiley and Topham (*J.*, 1944, 678), the extent to which the side reaction between the product and dimethylaniline interfered seemed to be greater than has hitherto been described (King, King, and Spensley, *J.*, 1947, 1247; Marshall and Walker, *J.*, 1951, 1004); the by-product was presumably 4 : 6-dichloro-2-methylanilino-5-phenylpyrimidine (cf. King, King, and Spensley, *loc. cit.*) rather than the 4-methylanilino-isomer. Reaction between the trichloropyrimidine and ammonia under suitable conditions stopped, as expected (cf. Basford, Curd, and Rose, *J.*, 1946, 714), with the introduction of two amino-groups, and dehalogenation of the resulting 2 : 4-diamino-6-chloro-5-phenylpyrimidine to (VI; R = H) took place smoothly on catalytic hydrogenation, in contrast with the difficulty experienced in effecting similar dehalogenation of 4-chloro- and 2 : 4-dichloro-5-phenylpyrimidine (Davies and Piggott, *J.*, 1945, 347). Application of reactions analogous to those described above to *p*-chlorophenyl-α-formylacetonitrile afforded successively α-*iso*butoxymethylene-*p*-chlorophenylacetonitrile and 2 : 4-diamino-5-*p*-chlorophenylpyrimidine (VI; R = Cl), and direct interaction with guanidine gave *p*-chlorophenyl-α-guanidinomethyleneacetonitrile, analogous with (IX).

Against *P. berghei* in the mouse, (VI; R = Cl) was active at a minimum effective dose of 0·1 mg./20 g. mouse (given intraperitoneally once daily for 4 days), whereas the minimum effective dose of proguanil under the same conditions was 0·2 mg./20 g.; (VI; R = Cl) was likewise about twice as effective as proguanil in *P. gallinaceum* infections in chicks, the minimum effective doses respectively being 0·5 mg./100 g. and 1 mg./100 g. *per os* b.i.d. × 3½. These results are comparable with those of Falco, Goodwin, Hitchings, Rollo, and Russell (*Brit. J. Pharmacol.*, 1951, **6**, 185), except that their strains of *P. berghei* and *P. gallinaceum* appear to be respectively rather less and rather more sensitive to proguanil than ours. The morphological changes in the parasites after being treated with (VI; R = Cl) were similar to those observed after treatment with proguanil or sulphadiazine; instead of dividing normally, the chromatin of the schizonts becomes greatly subdivided and there is no formation of merozoites. Furthermore, (VI; R = Cl) readily cleared the blood of mice infected with *P. berghei*, whereas proguanil only does so at the maximum tolerated dose. The activity of (VI; R = Cl) against *P. berghei*, in the mouse (at 0·3 mg./20 g., intraperitoneally, once daily × 4) was not antagonised by *p*-aminobenzoic acid (10 mg./20 g., *per os*, b.i.d. × 4), or by pteroylglutamic acid (2 mg., similarly), and it was equally active against normal and sulphadiazine-resistant strains of the parasite. The activity of (VI; R = Cl) against *P. gallinaceum* in the chick (at 2 mg./100 g., *per os*, b.i.d. × 3½) was likewise not antagonised by *p*-aminobenzoic acid (10 mg., similarly) or by pteroylglutamic acid (3 mg., similarly). Against *P. berghei*, (VI; R = H), which was rather more toxic to mice, showed a trace of activity, and against *P. gallinaceum* in the chick it was active at a minimum effective dose of 4 mg./100 g., *per os*, b.i.d. × 3½. None of the other compounds described, including the 6-chloro-derivative of (VI; R = H), showed any activity against either parasite with the exception of *p*-chlorophenylguanidinomethyleneacetonitrile, which showed a trace of activity against *P. berghei* in the mouse. As active compounds of the 2 : 4-diaminopyrimidine type are also active against proguanil-resistant laboratory strains (Falco *et al.*, *loc. cit.*), their mode of action must be complementary to that of the activated metabolite of proguanil.

Experimental.

α-(Methoxymethylene)phenylacetonitrile (VII*b*; R = Me).—(*a*) An ice-cold solution of diazomethane (from 25 g. of nitrosomethylurea) in ether (200 c.c.) was added in portions with swirling to a suspension of α-formylphenylacetonitrile (14·5 g.) in ether (100 c.c.) at 0°. The formyl compound dissolved with evolution of nitrogen, and the solution rapidly deposited colourless fibres. After being kept at 0° (2 hours) and at room temperature (overnight), the solid (1·82 g.) was collected and washed with ether (20 c.c.). Recrystallisation from aqueous alcohol yielded long colourless threads of *βγ-epoxy-α-phenylbutyronitrile*, m. p. 176—178° (Found: C, 75·3; H, 5·3; N, 8·9; OMe, 0. $C_{10}H_9ON$ requires C, 75·4; H, 5·7; N, 8·8%). Removal of the ether and excess of diazomethane by distillation, and trituration of the residue with ethanol–light petroleum gave *α-(methoxymethylene)phenylacetonitrile* (3·4 g.), which separated from light petroleum in lustrous, colourless plates, m. p. 67—68° (Found: C, 75·3; H, 6·0; N, 9·1; OMe, 19·0. $C_{10}H_9ON$ requires C, 75·4; H, 5·7; N, 8·8; OMe, 19·5%). Extraction of the evaporated mother-liquors with boiling light petroleum yielded a further quantity of the enol methyl ether (1·2 g.; total yield, 4·6 g., 29%).

The epoxide showed no signs of reacting with Brady's reagent in the usual manner. It (250 mg.) was refluxed with 2N-potassium hydroxide (5 c.c.) for 5 hours and the solution, when diluted with water, yielded only a trace of brown gum to ether. Acidification and extraction with ether gave phenylacetic acid (165 mg.), m. p. after recrystallisation from light petroleum, and mixed m. p., 75·5—76·5°.

(*b*) Anhydrous potassium carbonate (14 g.), followed by methyl iodide (21·3 g.), was added to a solution of formylphenylacetonitrile (14·5 g.) in dry acetone, and the mixture was refluxed for 8 hours. Ether (150 c.c.) was added, and the solution filtered and evaporated. The product was distributed between ether and 0·5N-sodium hydroxide, and the ethereal layer was dried and evaporated, giving a residue (12·9 g.) which crystallised in the refrigerator. Fractionation gave: (i) oil (3·17 g.), b. p. up to 110°/0·5 mm.; (ii) oil (4·24 g.), b. p. 110—112°/0·5 mm.; (iii) oil (3·89 g.), b. p. 112°/0·5 mm.; (iv) oil (0·45 g.), which rapidly crystallised, b. p. 112—114°/0·5 mm.; (v) still residue which crystallised and gave the enol ether (1·0 g.), m. p. 67—68°, on crystallisation from light petroleum. Fraction (iii) did not crystallise on nucleation with fraction (iv); (ii), (iii), and (iv) were bulked and then had n_D^{20} 1·5786 (Found: OMe, 18·8%).

α-(isoButoxymethylene)phenylacetonitrile (VII*b*; R = Bu^i).—A mixture of formylphenylacetonitrile (7·25 g.), *iso*butanol (7·4 g.), and toluene-*p*-sulphonic acid (0·1 g.) in benzene was boiled under reflux for 20 hours in a conventional Dean and Stark apparatus. The cooled solution was washed with N-sodium hydroxide solution (50 c.c.) and with water, and dried ($CaCl_2$). Fractionation afforded *α-(isobutoxymethylene)-phenylacetonitrile* as a colourless viscous oil (9·1 g., 90%), b. p. 119—120°/0·1 mm., n_D^{22} 1·5445 (Found: C, 77·6; H, 7·7; N, 7·2. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%).

2 : 4-*Diamino-5-phenylpyrimidine* (VI; R = H).—(*a*) Guanidine nitrate (1·83 g.), followed by methoxymethylenephenylacetonitrile (1·59 g.), was added to a solution of sodium ethoxide (from 0·46 g. of sodium) in absolute alcohol (50 c.c.), and the mixture was refluxed for 5 hours. The residue after removal of the solvent under reduced pressure was shaken with ether (50 c.c.) and water (50 c.c.). The crystalline product (0·95 g.) was filtered off and a further quantity (0·61 g.; total yield, 1·56 g., 84%) was recovered from the ether. Crystallisation from benzene afforded colourless laths of 2 : 4-*diamino-5-phenylpyrimidine*, m. p. 162·5—163·5° (Found: C, 64·3; H, 5·4; N, 30·2. $C_{10}H_{10}N_4$ requires C, 64·3; H, 5·4; N, 30·1%).

(*b*) Under precisely similar conditions guanidine nitrate and *iso*butoxymethylenephenylacetonitrile afforded an identical product in 69% yield.

(*c*) A suspension of 2 : 4-diamino-6-chloro-5-phenylpyrimidine (1 g.) (see below) in ethanol (120 c.c.) containing 2N-potassium hydroxide (3 c.c.) was shaken with 2% palladised strontium carbonate (0·5 g.) in hydrogen at atmospheric pressure. The theoretical volume of hydrogen was absorbed in 8 hours and the filtered solution was evaporated to dryness. The residue was extracted with boiling benzene (100 c.c.), and the filtered extract was concentrated to small bulk (15 c.c.). On cooling, 2 : 4-diamino-5-phenylpyrimidine (0·77 g., 91%) separated, m. p. 162—163°, alone and in admixture with the products isolated in experiments (*a*) and (*b*) (above).

α-(Guanidinomethylene)phenylacetonitrile (IX).—Dry, powdered guanidine nitrate (6·7 g.), followed by formylphenylacetonitrile (7·25 g.), was added to a solution of sodium ethoxide (from 1·4 g. of sodium) in absolute alcohol (100 c.c.), and the solution was boiled under reflux for 8 hours. After removal of the alcohol under reduced pressure, the solid product was distributed between water (100 c.c.) and a large volume of ether. Evaporation of the dried ethereal solution and crystallisation of the residue from benzene gave colourless needles (3·05 g.) of *α-(guanidinomethylene)phenylacetonitrile*, m. p. 138·5—139·5° (Found: C, 64·4; H, 5·3; N, 29·5. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%).

The substance (500 mg.) was boiled under reflux with 0·5N-hydrochloric acid (25 c.c.) for 1½ hours. The cooled solution was basified with 2N-sodium hydroxide and thoroughly extracted with ether. Removal of the ether and crystallisation of the residue from methanol–ethyl acetate afforded colourless needles (345 mg.) of phenylacetylguanidine, m. p. 170—171°, alone and in admixture with an authentic specimen prepared from ethyl phenylacetate and guanidine (Simons and Weaver, U.S.P. 2,408,694) (Found: C, 61·3; H, 6·3; N, 23·7. Calc. for $C_9H_{11}ON_3$: C, 60·9; H, 6·3; N, 23·8%). Prolonged hydrolysis (17 hours) under the same conditions yielded phenylacetic acid, m. p. and mixed m. p. 75—76°.

Attempts to prepare (IX) from aminomethylenephenylacetonitrile (Davies and Piggott, *J.*, 1945, 351) and either *S*-methyl*iso*thiourea or *O*-methyl*iso*urea under standard conditions were abortive, the aminomethylenephenylacetonitrile being recovered unchanged.

2 : 4 : 6-*Trichloro-5-phenylpyrimidine*.—5-Phenylbarbituric acid (2·04 g.) (Lund, *Chem. Zentr.*, 1936, I, 2095) was added to a mixture of phosphoryl chloride (7·7 g.) and redistilled dimethylaniline (2·7 g.).

After refluxing for 20 minutes, the red solution was poured on crushed ice (250 g.) and extracted with ether. Removal of the ether from the dried extract gave a buff-coloured solid (2·55 g.). Sublimation at 170—180° (bath-temp.)/15 mm. gave two colourless fractions : (i) (1·75 g.) m. p. 153—158°, and (ii) (0·27 g.) m. p. 157—162°, subliming more slowly. Recrystallisation of (i) from alcohol afforded large plates of 2 : 4 : 6-*trichloro-5-phenylpyrimidine*, m. p. 159—160° (Found : C, 46·5; H, 2·1; N, 10·8; Cl, 39·9. $C_{10}H_5N_2Cl_3$ requires C, 46·3; H, 1·9; N, 10·8; Cl, 41·1%). Recrystallisation of (ii) from alcohol gave colourless needles of 4 : 6-*dichloro-2-methylanilino-5-phenylpyrimidine*, m. p. 167—167·5° (Found : N, 12·4; Cl, 21·4. $C_{17}H_{13}N_3Cl_2$ requires N, 12·7; Cl, 21·5%).

Omission of the dimethylaniline and prolonged boiling with phosphoryl chloride gave only a trace of the desired trichlorophenylpyrimidine, and substitution of quinoline for dimethylaniline gave a 15% yield of the trichloro-compound. The awkward separation of trichlorophenylpyrimidine and dichloromethylanilinophenylpyrimidine could be avoided by using the mixture directly (following experiment).

2 : 4-*Diamino-6-chloro-5-phenylpyrimidine*.—2 : 4 : 6-Trichloro-5-phenylpyrimidine (2·1 g.) and ethanolic ammonia (70 c.c.; saturated at 0°) were heated at 120° for 6 hours in a stainless-steel tube. After being kept at 0° overnight, the solution and solid were washed out with ethanol, and the mixture was taken to dryness under reduced pressure. The colourless residue was shaken with a mixture of ether (50 c.c.) and water (100 c.c.) and filtered off. Recrystallisation of the residue from alcohol gave colourless plates (1·55 g., 87%) of 2 : 4-*diamino-6-chloro-5-phenylpyrimidine*, m. p. 244—245° (Found : C, 54·5; H, 4·3; N, 25·5. $C_{10}H_9N_4Cl$ requires C, 54·4; H, 4·1; N, 25·4%). The compound was practically insoluble in water, ether, or chloroform.

Alternatively, the mixture of 2 : 4 : 6-trichloro-5-phenylpyrimidine and 4 : 6-dichloro-2-methylanilino-5-phenylpyrimidine was ammonolysed and the 4-*amino-6-chloro-2-methylanilino-5-phenylpyrimidine*, formed from the latter, was readily separated from the 2 : 4-diamino-6-chloro-5-phenylpyrimidine by taking advantage of the sparing solubility of the latter in cold ethanol; it separated from ethanol in colourless needles, m. p. 166—167° (Found : C, 65·9; H, 4·8; N, 18·3. $C_{17}H_{15}N_4Cl$ requires C, 65·7; H, 4·8; N, 18·0%).

p-*Aminophenylacetonitrile*.—A suspension of *p*-nitrophenylacetonitrile (100 g.) (*Org. Synth.*, Coll. Vol. I, 1932, p. 389) in a mixture of ethyl acetate (450 c.c.) and ethanol (150 c.c.) was shaken with 2% palladised strontium carbonate (1 g.) in hydrogen at a pressure of 10 atm. The theoretical volume of hydrogen was absorbed in 24 hours and the filtered solution was evaporated to dryness. The addition of 5N-hydrochloric acid to a stirred solution of the residue in chloroform (250 c.c.) afforded the colourless hydrochloride (91·5 g., 88%) of *p*-aminophenylacetonitrile, m. p. 228°, which was collected, washed, and dried. The hydrochloride crystallised from aqueous alcohol in plates, m. p. 229—231°. Czumpelik (*Ber.*, 1870, **3**, 474) describes this substance as crystallising in plates but records no m. p.

p-*Chlorophenyl-α-formylacetonitrile*.—*p*-Chlorophenylacetonitrile (50·5 g.), prepared in 68% yield from the foregoing amine by the method of Davies, Johnson, and Piggott (*J.*, 1945, 352), in absolute alcohol (75 c.c.) was added to sodium ethoxide (from 11·5 g. of sodium) in absolute alcohol (500 c.c.). The stirred solution was cooled in melting ice while ethyl formate (50 g.) was added dropwise. The mixture was then stirred at room temperature for 4 hours and refluxed finally for an hour before removal of most of the solvent under reduced pressure. The residue was taken up in water (750 c.c.) and extracted with ether. Acidification of the aqueous alkaline layer, extraction with ether, and evaporation of the dried extract yielded *p*-chlorophenyl-α-formylacetonitrile (53·8 g., 90%), which separated from aqueous alcohol or from ethyl acetate–light petroleum in colourless plates, m. p. 163—164°. Walther and Hirschberg (*J. pr. Chem.*, 1903, **67**, 393) record m. p. 159—161°.

α-iso*Butoxymethylene*-p-*chlorophenylacetonitrile*.—A solution of *p*-chlorophenylformylacetonitrile (20 g.), *iso*butanol (20 g.), and toluene-*p*-sulphonic acid (0·1 g.) in benzene (250 c.c.) was boiled under reflux for 16 hours in the Dean and Stark apparatus, cooled, and washed with N-sodium hydroxide (100 c.c.). Unchanged starting material (2·8 g., 14%) was recovered by acidifying the alkaline washings. Fractionation of the benzene solution yielded α-iso*butoxymethylene*-p-*chlorophenylacetonitrile* as a colourless oil (20·3 g., 78%), b. p. 139—141°/0·1 mm. On storage at 0° the product partly crystallised; the oil was drained off and recrystallisation of the solid from light petroleum afforded colourless, flattened prisms (5·1 g.), m. p. 62—63° (Found : C, 66·4; H, 6·0; N, 6·2. $C_{13}H_{14}ONCl$ requires C, 66·2; H, 6·0; N, 5·9%).

2 : 4-*Diamino*-5-p-*chlorophenylpyrimidine* (VI; R = Cl).—*iso*Butoxymethylene-*p*-chlorophenylacetonitrile (20·1 g., mixed stereoisomerides) was added to a solution of sodium ethoxide (from 2·35 g. of sodium) in absolute ethanol (200 c.c.), followed by guanidine nitrate (11·5 g.). A reddish-brown colour appeared on mixing and the solution was boiled under reflux for 21 hours. The solvent was removed and the residue shaken with a mixture of ether (100 c.c.) and water (200 c.c.), the solid product (13·9 g., 74%) being collected. Recrystallisation from *n*-butanol afforded colourless needles of 2 : 4-*diamino*-5-p-*chlorophenylpyrimidine*, m. p. 188—190° (Found : C, 54·7; H, 4·4; N, 25·8. $C_{10}H_9N_4Cl$ requires C, 54·4; H, 4·1; N, 25·4%). In another experiment the product separated from the same solvent in colourless plates, m. p. 195—196°, alone and in admixture with the form of m. p. 188—190°; either form could be converted into the other by seeding. The separate use of either the solid or the liquid fractions of the enol *iso*butyl ether afforded similar yields. No other product could be isolated.

p-*Chlorophenyl-α-(guanidinomethylene)acetonitrile*.—*p*-Chlorophenylformylacetonitrile (9 g.), followed by guanidine nitrate (9·15 g.), was added to sodium ethoxide (from 2·3 g. of sodium) in absolute alcohol (150 c.c.), and the mixture was boiled under reflux before being worked up in the manner described for the phenyl analogue (IX). On crystallisation from *n*-butanol the product (3·85 g.) afforded colourless prisms of p-*chlorophenyl-α-(guanidinomethylene)acetonitrile*, m. p. 206—207° (Found : C, 54·8; H, 4·3; N, 25·5. $C_{10}H_9N_4Cl$ requires C, 54·4; H, 4·1; N, 25·4%).

6-*Amino*-4-p-*chloroanilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-s-*triazine* (III).—The following method afforded much better yields than those recorded by Birtwell *et al.* (*J.*, 1948, 1655), who used a longer period of heating, or by Crounse (*J. Org. Chem.*, 1951, **16**, 500). A mixture of *p*-chlorophenyldiguanide (10·8 g.), piperidine (1 c.c.), and acetone (45 c.c.) was boiled under reflux for ½ an hour, kept at 37° overnight, and again refluxed for 2 hours. The solution was then treated with charcoal, filtered, and washed through with acetone. Concentration (to 35 c.c.) and addition of water (140 c.c.) precipitated a rapidly crystallising oil. The solid was collected after 1 hour at 0°, and recrystallisation from aqueous alcohol gave colourless prisms (10·7 g.), m. p. 129·5—131·5°.

The same product was obtained by boiling a mixture of *p*-chlorophenyldiguanide (9 g.), acetone (6·5 c.c.), and acetic acid (15 c.c.) under reflux for 24 hours. Removal of the solvent under reduced pressure gave a product which could not be made to crystallise satisfactorily. Treatment with 5N-hydrochloric acid (20 c.c.), followed by evaporation and crystallisation of the residue from alcohol–ether, gave the crude hydrochloride (4·4 g.), yielding the free base (3·25 g.) on treatment in hot aqueous solution with excess of concentrated aqueous ammonia.

The *dihydrochloride* separated from methanol–ethyl acetate in hard clumps of colourless prisms, m. p. 190° (decomp.) (Found : C, 40·1; H, 4·6; N, 21·5. $C_{11}H_{14}N_5Cl,2HCl$ requires C, 40·7; H, 4·9; N, 21·6%).

The authors are indebted to Mr. R. J. Clark for technical assistance.

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[*Received, August 22nd,* 1951.]