## 120. *Synthetic Antimalarials. Part XXIV. Some 2-Phenylureido- and 2-Phenylthioureido-4-dialkylaminoalkylamino-6-methylpyrimidines.*

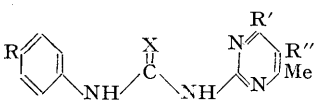
By R. DE B. ASHWORTH, A. F. CROWTHER, F. H. S. CURD, and F. L. ROSE.

The condensation of aryl *iso*cyanates and aryl *iso*thiocyanates with 2-aminopyrimidines has been shown to give 2-arylureido- and 2-arylthioureido-pyrimidines respectively. Compounds of these types carrying dialkylaminoalkylamino-groups in the 4-position which have now been prepared were found to be without significant activity against *P. gallinaceum* in chicks, in contrast to the activity of the corresponding 2-arylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines.

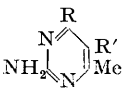
As a result of the discovery of antimalarial activity in 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine (Part IV, *J.*, 1946, 362) it was considered to be of interest to determine whether or not such activity was retained in the corresponding compounds in which the guanidine linkage was replaced by urea or thiourea linkages. Previous work indicated three methods by which arylureido- and arylthioureido-pyrimidines might be made. Wheeler and Bristol (*Amer. Chem. J.*, 1905, **33**, 448) first brought a chloropyrimidine into reaction with potassium thiocyanate to give an *iso*thiocyanatopyrimidine, and showed that 2-ethylthio-6-*iso*thiocyanopyrimidine reacted with aniline to give 2-ethylthio-4-phenylthioureidopyrimidine. Reinvestigation of the reaction of 4-chloro-2-ethylthiopyrimidine with potassium thiocyanate by Johnson and Storey (*ibid.*, 1908, **40**, 131) revealed that in this, as in other cases, the first product is the normal thiocyanate which can be isolated under certain conditions and subsequently isomerised to the *iso*thiocyanate. Similar preparations of arylthioureidopyrimidines from *iso*thiocyanatopyrimidines and arylamines have been described by Johnson and McCollum (*ibid.*, 1906, **36**, 136), Johnson and Chi (*J. Amer. Chem. Soc.*, 1930, **52**, 1580), and Chi and his co-workers [*ibid.*, 1932, **54**, 2058; 1933, **55**, 4183, 4655; 1936, **58**, 771, 773; *J. Chem. Eng.* (*China*), 1938, **5**, 35; *Chem. Abs.*, 1939, **33**, 6855], but it would appear that the method is limited in its application since certain chloropyrimidines fail to react with potassium thiocyanate (cf. Johnson and Storey, *loc. cit.*). An analogous method has been used by Chi and Ming (*Trans. Science Soc. China*, 1934, **8**, 77; *Chem. Abs.*, 1935, **29**, 472) for the preparation of a 4-phenylureidopyrimidine, namely ethyl 2-ethylthio-4-phenylureidopyrimidine-5-carboxylate; this involved, at the last stage, condensation of ethyl 2-ethylthio-4-*iso*cyanatopyrimidine-5-carboxylate with aniline. The second method, by which only arylureidopyrimidines have been made, involves the condensation of an aminopyrimidine with an aryl *iso*cyanate (cf. Keller, *J. pr. Chem.*, 1885, **31**, 373; Herfeldt, *ibid.*, 1896, **53**, 249; Johnson, Johns, and Heyl, *Amer. Chem. J.*, 1906, **36**, 160). The reaction of an aminopyrimidine with ethyl chloroformate followed by condensation of the product with aniline is recorded by von Meyer (*J. pr. Chem.*, 1884, **30**, 118).

Although there seemed no reason to doubt the constitution of the products obtained by the first method mentioned above, the other two were not held to be unambiguous. Nevertheless we considered that the condensation of an aminopyrimidine with an aryl *iso*cyanate would be the most suitable for the purpose we had in mind, and *p*-chlorophenyl *iso*cyanate was accordingly

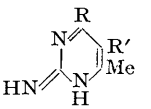
condensed with 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine. The product obtained from a reaction in xylene solution had all the properties expected of the desired 2-p-*chlorophenylureido*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = H), but, as in the condensation product of 4-amino-2 : 6-dimethylpyrimidine (" Kyanmethin ") with phenyl *iso*cyanate (cf. Keller, *loc. cit.*), later formulated as 4-phenylureido-2 : 6-dimethylpyrimidine (Beilstein, **24**, 89), it was conceivable that the *iso*cyanate had reacted with one of the tautomeric forms (II*a*) or II*b*) and that condensation had taken place on one or other of the pyrimidine nitrogen atoms to give one of the alternative structures (III and IV; X = O, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = H).



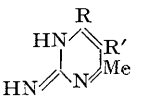
(I.)



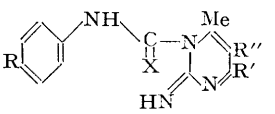
(II.)



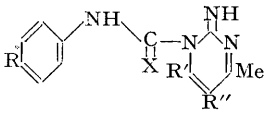
(II*a*.)



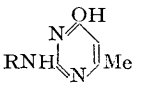
(II*b*.)



(III.)



(IV.)



(V.)

These alternative structures were, however, ruled out in the following way. *p*-Chlorophenyl *iso*cyanate was condensed with 2-amino-4-hydroxy-6-methylpyrimidine (II; R = OH, R′ = H) to give 4-*hydroxy*-2-p-*chlorophenylureido*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = OH, R″ = H), the constitution of which was proved by an alternative synthesis from *p*-chloroaniline and 4-hydroxy-2-ureido-6-methylpyrimidine (V; R = CO·$NH_2$), the latter being prepared by hydrolysis of 2-cyanoamino-4-hydroxy-6-methylpyrimidine (V; R = CN) (cf. Pohl, *J. pr. Chem.*, 1908, **77**, 542) of which there can no longer be any constitutional doubts in view of the work described in the following paper. When (I; X = O, R = Cl, R′ = OH, R″ = H), made by either method, was treated with phosphoryl chloride it was converted into 4-*chloro*-2-p-*chlorophenylureido*-6-*methylpyrimidine* (I; X = O, R = R′ = Cl, R″ = H), identical with the product of interaction of 4-chloro-2-amino-6-methylpyrimidine (II; R = Cl, R′ = H) with *p*-chlorophenyl *iso*cyanate, and this on interaction with β-diethylaminoethylamine gave 2-*p*-chlorophenylureido-4-β-diethylaminoethylamino-6-methylpyrimidine identical with that originally made from *p*-chlorophenyl *iso*cyanate and (II; R = NH·$[CH_2]_2$·$NEt_2$, R′ = H). These interconversions not only establish that both 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine and 2-*p*-chlorophenylureido-4-β-diethylaminoethylamino-6-methylpyrimidine, like (I; X = O, R = Cl, R′ = OH, R″ = H), have the structures assigned to them and not the possible alternative structures of types (III) and (IV), but also that the condensation of *p*-chlorophenyl *iso*cyanate and 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine does not involve reaction at the secondary amino-group of the side chain.

The conversion of 2-cyanoamino-4-hydroxy-6-methylpyrimidine into 4-hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine, although effected in the first instance *via* 4-hydroxy-2-ureido-6-methylpyrimidine, was also carried out through the corresponding *O*-ethyl-*iso*urea. 2-Cyanoamino-4-hydroxy-6-methylpyrimidine, treated with hydrogen chloride in dry alcohol, was converted into [V; R = C(:NH)·OEt] which when heated with *p*-chloroaniline hydrochloride unexpectedly gave (I; X = O, R = Cl, R′ = OH, R″ = H), but with *p*-chloroaniline the anticipated reaction took place and 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine (I; X = NH, R = Cl, R′ = OH, R″ = H) was formed.

4-Chloro-2-*p*-chlorophenylureido-6-methylpyrimidine was also formed by the interaction of 4-chloro-2-amino-6-methylpyrimidine with *p*-chlorophenylurea and with ethyl *p*-chlorophenylurethane, and condensation of (I; X = O, R = R′ = Cl, R″ = H) with γ-diethylaminopropylamine, δ-diethylaminobutylamine, and γ-di-*n*-butylaminopropylamine afforded further examples of 2-*p*-chlorophenylureido-4-dialkylaminoalkylamino-6-methylpyrimidines for test as antimalarials. One compound of the same type, but carrying an alkyl group in the 5-position of the pyrimidine nucleus, namely 2-p-*chlorophenylureido*-4-β-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = Et) was made by condensing *p*-chlorophenyl *iso*cyanate with 2-amino-4-β-diethylaminoethylamino-6-methyl-5-ethylpyrimidine (II; R = NH·$[CH_2]_2$·$NEt_2$, R′ = Et).

In addition to the above 2-*p*-chlorophenylureido-4-dialkylaminoalkylamino-6-methylpyrimidines the following were made by condensation of 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine with piperidine, morpholine, and di-*n*-butylamine respectively: 2-p-*chlorophenylureido*-4-*piperidino*-, 2-p-*chlorophenylureido*-4-*morpholino*-, and 2-p-*chlorophenylureido*-4-*di*-n-*butylamino*-6-*methylpyrimidine*. These compounds were not considered worth testing as antimalarials in view of the fact that the aforementioned dialkylaminoalkylamino-compounds showed only doubtful activity against *P. gallinaceum* in chicks at maximum tolerated doses.

The behaviour of *p*-chlorophenyl *iso*thiocyanate when brought into reaction with 2-amino-4-dialkylaminoalkylamino-6-methylpyrimidines parallelled that of *p*-chlorophenyl *iso*cyanate. Thus, *p*-chlorophenyl *iso*thiocyanate with (II; R = NH·$[CH_2]_2$·$NEt_2$, R′ = H) and 2-*amino*-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* (II; R = NH·$[CH_2]_3$·$NEt_2$, R′ = H) gave 2-p-*chlorophenylthioureido*-4-β-*diethylaminoethylamino*- (I; X = S, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = H) and 2-p-*chlorophenylthioureido*-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·$[CH_2]_3$·$NEt_2$, R″ = H). The constitutions of these substances were established by their conversion, with the aid of alcoholic ammonia and mercuric oxide, into the corresponding guanidino-compounds, 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine (I; X = NH, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R ″= H) (Part IV, *loc. cit.*) and 2-*p*-chlorophenylguanidino-4-*γ*-diethylaminopropylamino-6-methylpyrimidine (I; X = NH, R = Cl, R′ = NH·$[CH_2]_3$·$NEt_2$, R″ = H) (Part XXIII, preceding paper). (The constitutions of these guanidinopyrimidines are unequivocally proved by the work described in the following paper.)

The above thioureidopyrimidines and other similar compounds synthesised, namely 2-p-*bromophenylthioureido*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = S, R = Br, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = H), 2-p-*chlorophenylthioureido*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·CHMe·$[CH_2]_3$·$NEt_2$, R″ = H), and 2-p-*chlorophenylthioureido*-4-β-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (I; X = S, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = Et) were found to be inactive against *P. gallinaceum* in chicks when tested by our colleague, Dr. D. G. Davey.

The above work suggested that *p*-chlorophenylcyanamide should condense with 2-aminopyrimidines to give 2-*p*-chlorophenylguanidinopyrimidines, and after numerous abortive attempts it was found that condensation with 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine dihydrochloride did occur in boiling butanol solution to give 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine (3349).

## Experimental.

4-*Hydroxy*-2-p-*chlorophenylureido*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = OH, R″ = H).—(*a*) *p*-Chlorophenyl *iso*cyanate (1·6 g.) (Vittenet, *Bull. Soc. chim.*, 1899, **21**, 954), 2-amino-4-hydroxy-6-methylpyrimidine (1·2 g.) (Gabriel and Colman, *Ber.*, 1899, **32**, 2924), and dry xylene (5 c.c.) were boiled under reflux for ½ hour. After cooling, the insoluble material was filtered off, dried, and extracted twice with boiling water (50 c.c.) to leave a white powder which was crystallised first from dimethylformamide and then from nitrobenzene, giving 4-*hydroxy*-2-p-*chlorophenylureido*-6-*methylpyrimidine* as a colourless micro-crystalline powder, m. p. 294° (Found: C, 51·8; H, 4·1; Cl, 12·7. $C_{12}H_{11}O_2N_4Cl$ requires C, 51·7; H, 3·95; Cl, 12·75%).

(*b*) 4-Hydroxy-2-ureido-6-methylpyrimidine (5·4 g.) (Pohl, *loc. cit.*) and *p*-chloroaniline (3·9 g.) were heated in boiling *o*-dichlorobenzene (30 c.c.) for 1½ hours. Ammonia was evolved. The product was collected hot, washed successively with toluene and light petroleum, and dried. Recrystallisation from formodimethylamide and then from nitrobenzene gave the same product as in (*a*), m. p. and mixed m. p. 294° (Found: N, 20·5. $C_{12}H_{11}O_2N_4Cl$ requires N, 20·1%).

4-*Chloro*-2-p-*chlorophenylureido*-6-*methylpyrimidine* (I; X = O, R = R′ = Cl, R″ = H).—(*a*) A solution of *p*-chlorophenyl *iso*cyanate (32 g.) and 4-chloro-2-amino-6-methylpyrimidine (28 g.) (Gabriel and Colman, *loc. cit.*) in dry xylene (150 c.c.) was boiled under reflux for ½ hour. The product, which separated during the reaction, was filtered off after cooling, dried, and crystallised from toluene, giving 4-*chloro*-2-p-*chlorophenylureido*-6-*methylpyrimidine* as a colourless microcrystalline powder, m. p. 224—225° (Found: C, 48·8; H, 3·6; N, 18·6; Cl, 23·6, 24·0. $C_{12}H_{10}ON_4Cl_2$ requires C, 48·5; H, 3·4; N, 18·85; Cl, 23·9%).

(*b*) 4-Hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine (4 g.) [made by method (*a*) above] and phosphoryl chloride (8 c.c.) were refluxed for 6 minutes and the brownish-yellow solution, after cooling, poured on to a mixture of ice (120 g.) and sodium hydroxide solution (28 c.c. of 35%). The resulting yellowish granular solid was filtered off, dried, and crystallised twice from xylene–butanol (decolorisation being effected with a little activated alumina) to give the same product as in (*a*), m. p. and mixed m. p. 225° (Found: C, 48·2; H, 3·3; Cl, 23·7%).

4-Hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine, prepared by method (*b*) above, when treated with phosphoryl chloride in exactly the same manner also gave 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine, m. p. and mixed m. p. 225°.

(*c*) *p*-Chlorophenylurea (0·8 g.) (Young and Dunstan, *J.*, 1908, **93**, 1058) and 4-chloro-2-amino-6-methylpyrimidine (0·7 g.) were heated in boiling *o*-dichlorobenzene (10 c.c.) until ammonia ceased to be evolved. The product which separated on cooling was filtered off, dried, and crystallised from butanol. It then had m. p. 223—224° alone or admixed with the product made by method (*a*).

(*d*) Ethyl *p*-chlorophenylurethane (2 g.) (Vittenet, *loc. cit.*) was dissolved in *o*-dichlorobenzene (10 c.c.) and the solution added to 4-chloro-2-amino-6-methylpyrimidine (1·4 g.) dissolved in the same solvent (12·5 c.c.). The resulting mixture was refluxed for 3 hours, part of the solvent being allowed to distil off. The product which separated on cooling was filtered off, dried, and crystallised from butanol; m. p. 224° undepressed on admixture with material made by method (*a*).

2-p-*Chlorophenylureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = H).—(*a*) *p*-Chlorophenyl *iso*cyanate (3·2 g.) in dry xylene (10 c.c.) was added to 2-amino-4-*β*-diethylaminoethylamino-6-methylpyrimidine (4·4 g.) (Part III, *J.*, 1946, 357) in dry xylene (15 c.c.). On heating to boiling, reaction occurred and the product crystallised out. It was filtered off and crystallised from toluene (yield, 51·2%). Recrystallisation from ethyl acetate gave the *product* as colourless prisms, m. p. 199—200° (Found: C, 57·2; H, 6·6; N, 22·6; Cl, 9·4. $C_{18}H_{25}ON_6Cl$ requires C, 57·3; H, 6·6; N, 22·3; Cl, 9·4%) (3921).

(*b*) 4-Chloro-2-*p*-chlorophenylureido-6-methylpyrimidine (9 g.) was added to *β*-diethylaminoethylamine (10·4 g.) in acetic acid (13 c.c.) and the mixture boiled gently under reflux until complete solution was obtained. The mixture was then poured into water (100 c.c.), insoluble material filtered off, and the filtrate added to excess of sodium hydroxide. The washed and dried product was crystallised from toluene and then from dilute alcohol, giving 2-*p*-chlorophenylureido-4-*β*-diethylaminoethylamino-6-methylpyrimidine, m. p. 199—200° undepressed on admixture with material made by method (*a*).

2-p-*Chlorophenylureido*-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_3$·$NEt_2$, R″ = H), prepared by method (*b*) above using *γ*-diethylaminopropylamine in place of *β*-diethylaminoethylamine, crystallised from light petroleum (b. p. 100—120°) in colourless flat prisms, m. p. 188—190° (Found: N, 21·5. $C_{19}H_{27}ON_6Cl$ requires N, 21·5%) (4636).

2-p-*Chlorophenylureido*-4-*δ*-*diethylaminobutylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_4$·$NEt_2$, R″ = H), prepared similarly from 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine and *δ*-diethylaminobutylamine, was obtained as colourless needles from ethyl acetate, m. p. 185—186° (Found: N, 20·8. $C_{20}H_{29}ON_6Cl$ requires N, 20·8%) (4637).

2-p-*Chlorophenylureido*-4-*γ*-*di*-n-*butylaminopropylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_3$·$NBu^a_2$, R″ = H).—4-Chloro-2-*p*-chlorophenylureido-6-methylpyrimidine (3 g.), *γ*-di-*n*-butylaminopropylamine (2·3 g.), chlorobenzene (10 c.c.), water (10 c.c.), and sodium hydroxide (0·6 g.) were refluxed for 1 hour, and the chlorobenzene then removed by steam distillation. The insoluble residue was filtered off, washed with water, and dried. Crystallised first from light petroleum (b. p. 100—120°) and then from ethyl acetate, it was obtained as colourless needles, m. p. 153—154° (Found: N, 19·1. $C_{23}H_{35}ON_6Cl$ requires N, 19·2%) (4638).

2-p-*Chlorophenylureido*-4-*β*-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = Et).—*p*-Chlorophenyl *iso*cyanate (3·1 g.), 2-amino-4-*β*-diethylaminoethylamino-6-methyl-5-ethylpyrimidine (2·5 g.) (Part III, *loc. cit.*), and dry xylene (10 c.c.) were refluxed for 10 minutes and, after cooling, the *product* was filtered off and crystallised from toluene. It separated as tiny colourless plates, m. p. 169° (Found: N, 20·8; Cl, 9·4. $C_{20}H_{29}ON_6Cl$ requires N, 20·8; Cl, 8·8%) (4105).

2-p-*Chlorophenylureido*-4-*piperidino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = N<$[CH_2]_4$>$CH_2$, R″ = H).—A mixture of 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine (1·5 g.), piperidine (2 g.), chlorobenzene (5 c.c.), water (5 c.c.), and sodium hydroxide (0·3 g.) was refluxed for 1 hour. The mixture was then steam distilled and the residual *product* collected, dried, and crystallised from light petroleum (b. p. >120°). It separated as small colourless needles, m. p. 178—179° (Found: N, 20·2. $C_{17}H_{20}ON_5Cl$ requires N, 20·3%).

2-p-*Chlorophenylureido*-4-*morpholino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = N<$[CH_2]_4$>O, R″ = H), prepared similarly using morpholine in place of piperidine, crystallised from butanol–xylene as colourless plates, m. p. 223° (Found: N, 20·3. $C_{16}H_{18}O_2N_5Cl$ requires N, 20·1%).

2-p-*Chlorophenylureido*-4-*di*-n-*butylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = $NBu^a_2$, R″ = H).—This was prepared in an exactly analogous manner and separated from ethyl acetate as colourless plates, m. p. 157—158° (Found: N, 17·7. $C_{20}H_{28}ON_5Cl$ requires N, 18·0%).

2-p-*Chlorophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = H).—A solution of *p*-chlorophenyl *iso*thiocyanate (37·2 g.) (*Org. Synth.*, Coll. Vol. I, 1st. Edn., 159) and 2-amino-4-*β*-diethylaminoethylamino-6-methylpyrimidine (44·6 g.) in dry xylene (100 c.c.) was refluxed for 1 hour and then cooled. The product was filtered off, washed first with xylene and then with light petroleum (b. p. 40—60°), and dried. Crystallisation from benzene gave 2-p-*chlorophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (yield, 73%) as small colourless plates, m. p. 121—122° (Found: N, 21·4; Cl, 9·5; S, 8·3. $C_{18}H_{25}N_6ClS$ requires N, 21·4; Cl, 9·0; S, 8·15%) (4113).

2-p-*Bromophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = S, R = Br, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = H), prepared similarly from *p*-bromophenyl *iso*thiocyanate (5 g.) (Dyson and George, *J.*, 1924, **125**, 1702) and 2-amino-4-*β*-diethylaminoethylamino-6-methylpyrimidine (5 g.) in dry xylene (40 c.c.), crystallised from light petroleum (b. p. 100—120°) as colourless plates, m. p. 132° (yield, 62%) (Found: N, 19·0. $C_{18}H_{25}N_6BrS$ requires N, 19·2%) (3978).

2-p-*Chlorophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (I; X = S, R = Cl, R′ = NH·$[CH_2]_2$·$NEt_2$, R″ = Et), from *p*-chlorophenyl *iso*thiocyanate (7 g.) and 2-amino-4-*β*-diethylaminoethylamino-6-methyl-5-ethylpyrimidine (5 g.) in dry xylene (15 c.c.), crystallised from toluene in colourless plates, m. p. 181° (Found: Cl, 8·6. $C_{20}H_{29}N_6ClS$ requires Cl, 8·6%) (4106).

*Conversion of* 2-p-*Chlorophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine into* 2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine.*—The thioureido-compound

(1·0 g.) was stirred with mercuric oxide (1·0 g.) and methanolic ammonia (20 c.c. of 18%) at room temperature for 2 hours. The mercuric sulphide which had been formed was filtered off and washed with methanol. The filtrate and washings were combined and evaporated on the steam-bath to leave a glassy residue. This was dissolved in dilute acetic acid, the solution treated with decolorising carbon, filtered, and the filtrate added slowly to excess of dilute sodium hydroxide solution. The resulting solid product was filtered off, washed with water, and dried in a vacuum (yield, 84%). Crystallisation from acetone gave 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine, m. p. 155°, either alone or mixed with an authentic specimen (Part IV, *loc. cit.*) (Found : N, 25·8. Calc. for $C_{18}H_{26}N_7Cl$ : N, 26·1%). With litharge instead of mercuric oxide the same product was obtained crude, in a yield of 87%. Similarly, copper sulphate pentahydrate gave a yield of 84%.

2-*Amino*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (II; R = NH·$[CH_2]_3$·$NEt_2$, R′ = H).—A mixture of 4-chloro-2-amino-6-methylpyrimidine (29·85 g.), γ-diethylaminopropylamine (34·8 g.), chlorobenzene (105 c.c.), sodium hydroxide solution (75 c.c. of 35%), and water (105 c.c.) was refluxed with vigorous stirring for 4 hours. After cooling, sodium hydroxide (60 g.) was added with stirring. The two layers were separated and the aqueous layer extracted twice with chlorobenzene (50 c.c.). The chlorobenzene layer and the extracts were combined, dried (NaOH), and the solvent removed by distillation. The residual oil was purified by vacuum distillation, giving 2-*amino*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* as a colourless oil, b. p. 217—218°/11 mm., which gradually solidified (yield, 51·5%). It then crystallised from benzene–light petroleum (b. p. 40—60°) as colourless rods, m. p. 80—82° (Found : C, 60·6; H, 9·0. $C_{12}H_{23}N_5$ requires C, 60·7; H, 9·7%).

2-p-*Chlorophenylthioureido*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·$[CH_2]_3$·$NEt_2$, R″ = H).—The preceding compound (11·85 g.) and *p*-chlorophenyl *iso*thiocyanate (9·35 g., 1·1 mols.) were boiled in xylene (20 c.c.) for 45 minutes. The mixture was then cooled, diluted with light petroleum (b. p. 100—120°) (20 c.c.), and the product filtered off, washed with benzene, and dried (yield, 90%). Crystallisation from light petroleum (b. p. 100—120°) containing a little toluene gave the *thioureido*-compound as clusters of pale fawn needles, m. p. 140° (Found : C, 56·4; H, 6·5; N, 20·5; Cl, 8·7; S, 8·1. $C_{19}H_{27}N_6ClS$ requires C, 56·2; H, 6·6; N, 20·6; Cl, 8·7; S, 7·9%) (5219).

*Conversion of* 2-p-*Chlorophenylthioureido*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine into* 2-p-*Chlorophenylguanidino*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine*.—The above compound (1·0 g.), mercuric oxide (1·0 g.), and methanolic ammonia (20 c.c. of 18%) were stirred at 30—40° for 4 hours. After cooling, the mixture was acidified with 2N-hydrochloric acid and excess of sodium sulphide added. With stirring, the filtered solution was run dropwise into excess of sodium hydroxide at 0—5°. The resulting precipitate was filtered off, washed with water, and dried. Crystallisation from acetone afforded 2-*p*-chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methylpyrimidine, m. p. 147°, undepressed on admixture with an authentic sample (see previous paper) (Found : C, 58·2; H, 6·8. Calc. for $C_{19}H_{28}N_7Cl$ : C, 58·5; H, 7·2%).

2-p-*Chlorophenylthioureido*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·CHMe·$[CH_2]_3$·$NEt_2$, R″ = H).—2-Amino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (8·2 g.) (Hull *et al.*, Part III, *loc. cit.*), *p*-chlorophenyl *iso*thiocyanate (5·8 g., 1·1 mols.), and xylene (13 c.c.) were boiled for 45 minutes and then cooled. The mixture was diluted with benzene and extracted with dilute acetic acid. The acid extract was decolorised with carbon and then run dropwise into excess of ice-cold 2N-sodium hydroxide. The precipitated base was collected, washed with water, and dried. It was converted into its *dihydrochloride*, m. p. 184°, by dissolving it in a slight excess of alcoholic hydrogen chloride and adding ethyl acetate, followed by crystallisation from alcohol–ethyl acetate (yield, 12·0 g.) (Found : C, 48·0; H, 6·6; N, 15·6; Cl, 20·8; S, 6·5. $C_{21}H_{31}N_6ClS,2HCl,H_2O$ requires C, 47·8; H, 6·6; N, 15·9; Cl, 20·2; S, 6·1%) (5241).

2-p-*Chlorophenylguanidino*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (I; X = NH, R = Cl, R′ = NH·CHMe·$[CH_2]_3$·$NEt_2$, R″ = H).—2-*p*-Chlorophenylthioureido-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine dihydrochloride (5 g.) was stirred with mercuric oxide (5 g.) and alcoholic ammonia (50 c.c. of 13%) at 35—40° for 4 hours. The mixture was acidified with dilute hydrochloric acid and excess of sodium sulphide added. The mercuric sulphide was filtered off and the filtrate run into ice-cold 2N-sodium hydroxide. The resulting precipitate was collected, washed with water, and dried (yield, 3·6 g.). The base was soluble in cold light petroleum (b. p. 40—60°) and could not be purified by crystallisation from a solvent. It was partly purified by dissolution in dilute acid and reprecipitation with sodium hydroxide (Found : C, 59·2; H, 7·3; N, 22·5; Cl, 8·3; ash, 0·6. $C_{21}H_{32}N_7Cl$ requires C, 60·3; H, 7·6; N, 23·5; Cl, 8·5%). It gave a *dipicrate* which crystallised from 2-ethoxyethanol as a yellow microcrystalline powder, m. p. 204—205° (Found : C, 45·6; H, 4·2; N, 20·8. $C_{21}H_{32}N_7Cl$, $2C_6H_3O_7N_3$ requires C, 45·2; H, 4·3; N, 20·8%).

*Condensation of* p-*Chlorophenylcyanamide and* 2-*Amino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine*.—2-Amino-4-β-diethylaminoethylamino-6-methylpyrimidine (9·92 g.) and alcoholic hydrogen chloride (26·4 c.c. of 12·4% w/v) were mixed and evaporated to dryness. To the residual dihydrochloride, butanol (25 c.c.) was added (the hydrochloride solidified) followed by *p*-chlorophenylcyanamide (6·8 g.) (to be described in a forthcoming communication) and the mixture refluxed for 8 hours. The cooled clear mixture was diluted with benzene and extracted with 0·5N-hydrochloric acid. The acid extract was shaken with a little benzene, separated, decolorised with carbon, and filtered. It was then made strongly alkaline by the addition of 10N-sodium hydroxide and the liberated oil extracted with benzene. Unchanged aminopyrimidine was removed by repeated extraction with water (6 × 500 c.c.), and the benzene solution dried ($K_2CO_3$) and evaporated. The residual solid was finally crystallised from benzene–light petroleum (b. p. 40—60°) and then from acetone to give 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine, m. p. and mixed m. p. 155°.

(Experiments by Dr. E. C. Owen.) N-(4-*Hydroxy*-6-*methyl*-2-*pyrimidyl*)-O-*ethyl*isou*rea* [V; R = C(:NH)·OEt].—2-Cyanoamino-4-hydroxy-6-methylpyrimidine (10 g.) was suspended in dry alcohol (50 c.c.), and dry hydrogen chloride passed into the mixture with rapid stirring, the temperature being kept below 10°. When saturated, the mixture was left at room temperature for 2 days. The

solid was then filtered off, washed with alcohol, and dissolved in water (100 c.c.). After filtration from insoluble material the solution was neutralised with sodium hydroxide. On standing, the *product* crystallised. It was filtered off, dried, and crystallised from alcohol, m. p. 212—213° (Found: C, 49·0; H, 6·1; N, 28·6. $C_8H_{12}O_2N_4$ requires C, 49·0; H, 6·1; N, 28·6%).

*Condensation of* N-(4-*Hydroxy*-6-*methyl*-2-*pyrimidyl*)-O-*ethyl*iso*urea with* p-*Chloroaniline Hydrochloride.*—The above *O*-ethyl*iso*urea (2 g.) and *p*-chloroaniline hydrochloride (1·65 g.) were fused at 170° for 20 minutes. The fluid melt gradually crystallised during the reaction. After cooling, it was boiled twice with alcohol, and the insoluble material collected, dried, and crystallised from nitrobenzene, giving 4-hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine, m. p. and mixed m. p. 293—295° (Found: N, 20·1; Cl, 12·8. Calc. for $C_{12}H_{11}O_2N_4Cl$: N, 20·1; Cl, 12·75%).

*Condensation of* N-(4-*Hydroxy*-6-*methyl*-2-*pyrimidyl*)-O-*ethyl*iso*urea with* p-*Chloroaniline.*—The *O*-ethyl*iso*urea (2 g.) and *p*-chloroaniline (1·33 g.) were heated for 1·5 hours at 170°. The cooled mixture was repeatedly extracted with boiling alcohol, and the insoluble residue crystallised from nitrobenzene. The product was identified as 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine, m. p. and mixed m. p. 286—287°, depressed on admixture with 4-hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9.

[*Received, May 16th,* 1947.]