371. *Synthetic Antimalarials. Part XLII. The Preparation of Guanylureas and Biurets corresponding to "Paludrine" and related Diguanides.*

By (the late) F. H. S. Curd, D. G. Davey, and (Miss) D. N. Richardson.

Deamination of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide to give N-p-*chlorophenyl*-N′-iso*propylguanylurea* is effected by prolonged standing in acid solution or by treatment with excess of nitrous acid. The constitution of this guanylurea was proved by its synthesis from *p*-chlorophenyl *iso*cyanate and *iso*propylguanidine. In common with a number of related *N*-*p*-chlorophenyl-*N*′-alkylguanyl- and -*N*′*N*′-dialkylguanyl-ureas, also synthesised, it showed activity against the erythrocytic, but not against the exo-erythrocytic, forms of *P. gallinaceum*, whereas the isomeric N-p-*chlorophenylguanyl*-N′-iso*propylurea* was inactive.

A number of related 1-*p*-chlorophenyl-5-alkyl- and -5 : 5-dialkyl-biurets has also been prepared, but none of these compounds exhibited any antimalarial activity.

It has been shown by Spinks and Tottey (*Ann. Trop. Med. Parasit.*, 1945, **39**, 220) (see also Spinks, *ibid.*, 1946, **40**, 101) that the antimalarial "Paludrine" (I; R = H, R′ = Pr^i) is quantitatively hydrolysed to *p*-chloroaniline by heating with 0·25N-hydrochloric acid in an autoclave at 20—25 lb./sq. in. steam-pressure.

More recently, the observation has been made in these laboratories by Mr. R. S. Neal that when N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide was kept in 2N-hydrochloric acid, gradual deposition of the hydrochloride of another compound occurred. This latter salt gave analytical figures which suggested that it was one or other of the corresponding guanylureas (II) and (III; R = Cl, R′ = H, R″ = Pr^i). It was therefore decided to undertake the unambiguous synthesis of these compounds, not only in an attempt to establish the constitution of the transformation product, but also in order to examine them for antimalarial activity since it seemed possible that they might be implicated in the *in vivo* degradation of "Paludrine" through deamination. It may be noted that the corresponding guanylthioureas were without antimalarial activity (Parts XXIX and XXX, *J.*, 1948, 1636, 1645), but it was thought that this might be due to internal-salt formation which would be less likely in the case of the guanylureas.

Unsuccessful attempts to prepare arylguanylureas by the condensation of aryl *iso*cyanates with guanidine have been recorded in the literature by Slotta, Tschesche, and Dressler (*Ber.*, 1930, **63**, 208); *e.g.*, phenyl *iso*cyanate afforded only the bis-condensation product, *NN*′-bisphenylcarbamylguanidine. No reference could be found to the reaction of aryl *iso*cyanates with substituted guanidines, but in an earlier paper (Part XXIX, *loc. cit.*) it was shown that aryl *iso*thiocyanates in general condense with mono- and di-alkylguanidines to give *N*-aryl-*N*′-alkyl-(or -*N*′*N*′-dialkyl-)guanylthioureas, although in certain cases substances arising from the condensation of 2 molecules of *iso*thiocyanate with one molecule of guanidine were formed, either as the main product or as a by-product. It has now been found that aryl *iso*cyanates interact under similar conditions, in acetone solution, with mono- or di-alkylguanidines to give *N*-aryl-*N*′-alkyl- (or -*N*′*N*′-dialkyl-)guanylureas. Thus *p*-chlorophenyl *iso*cyanate with methylguanidine gave N-p-*chlorophenyl*-N′-*methylguanylurea* (III; R = Cl, R′ = H, R″ = Me), and with ethylguanidine afforded the corresponding *ethyl* compound (III; R = Cl, R′ = H, R″ = Et). Similarly, phenyl *iso*cyanate condensed with *NN*-dimethylguanidine to give N-*phenyl*-N′-(NN-*dimethylguanyl*)*urea* (III; R = H, R′ = R″ = Me). However, when *p*-chlorophenyl *iso*cyanate was condensed with *iso*propyl- or *n*-butyl-guanidine the respective products, N-p-*chlorophenyl*-N′-iso*propylguanylurea* and N-p-*chlorophenyl*-N′-n-*butylguanylurea*, were accompanied by small amounts of less soluble, higher-melting, materials, but the nature of these was not investigated.

N-*p*-Chlorophenyl-*N*′-*iso*propylguanylurea prepared by this method was found to be identical with the hydrolysis product of (I; R = H, R′ = Pr^i), formed, as mentioned above, by prolonged standing in acid solution.

An alternative method for the preparation of this type of compound was opened up by the observation of our colleague, Dr. J. A. Hendry, that N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide with excess of nitrous acid in aqueous solution afforded *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylurea identical with material made by the method mentioned above. Similarly, N^1-*p*-chlorophenyl-

N^5N^5-dimethyldiguanide on treatment with nitrous acid gave N-p-*chlorophenyl*-N′-(NN-*dimethylguanyl*)*urea* (III; R = Cl, R′ = R″ = Me), indistinguishable from the product of interaction of *p*-chlorophenyl *iso*cyanate and *NN*-dimethylguanidine, and the method was then used to prepare N-p-*chlorophenyl*-N′-(N-*methyl*-N-iso*propylguanyl*)*urea* (III; R = Cl, R′ = Me, R″ = Pr^i) and N-p-*chlorophenyl*-N′-(NN-*diethylguanyl*)*urea* (III; R = Cl, R′ = R″ = Et).

The results of antimalarial tests, against *P. gallinaceum* in chicks, carried out with the guanylureas, of type (III) are shown in the table below. It will be seen that, whilst they all show some activity against the blood forms, the variations in activity in no way parallel those observed with the corresponding diguanides (cf. Part X, *J.*, 1946, 729). Further, the guanylureas, unlike the diguanides, exhibit no prophylactic activity even at maximum tolerated doses, and there can therefore be no question of the antimalarial activity of the diguanides being due to *in vivo* deamination to the corresponding guanylureas.

The only compound of the *N*-arylguanyl-*N′*-alkylurea series prepared was N-p-*chlorophenyl-guanyl*-N′-iso*propylurea* (II), which resulted from the interaction of *iso*propyl *iso*cyanate and *p*-chlorophenylguanidine, but this compound was devoid of antimalarial activity (see Table) and the type was not further investigated.

Antimalarial Activities.

The compounds were tested for antimalarial activity against the blood forms of *P. gallinaceum* in chicks using the method previously described (Davey, *Ann. Trop. Med. Parasit.*, 1946, **40**, 52). The results given below are expressed in the same way as in previous papers in this series.

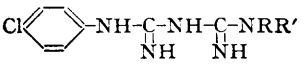
Ref. no.	Compound.	Dose, mg./kg.	Activity.
6354	*N-p*-Chlorophenyl-*N′*-methylguanylurea	80	++
		40	+
6615	*N-p*-Chlorophenyl-*N′*-ethylguanylurea	80	++
		40	+
		20	—
6045	*N-p*-Chlorophenyl-*N′-iso*propylguanylurea	80	+ to ++
		40	—
5964	*N-p*-Chlorophenyl-N′-*n*-butylguanylurea	160	++
		80	+
		40	—
5940	*N*-Phenyl-*N′*-(*NN*-dimethylguanyl)urea	80	—
5963	*N-p*-Chlorophenyl-*N′*-(*NN*-dimethylguanyl)urea	80	++
		40	+ to ++
		20	—
6661	*N-p*-Chlorophenyl-*N′*-(*N*-methyl-*N-iso*propylguanyl)urea	80	++
		40	+
		20	±
6814	*N-p*-Chlorophenyl-*N′*-(*NN*-diethylguanyl)urea	80	++
		40	++
6111	*N-p*-Chlorophenylguanyl-*N′-iso*propylurea	80	—
5965	1-Phenyl-5-*p*-chlorophenylbiuret	160	—
6031	1-*p*-Chlorophenyl-5-methylbiuret	80	—
6088	1-*p*-Chlorophenyl-5-ethylbiuret	40	—
6106	1-*p*-Chlorophenyl-4-methyl-5-*iso*propyl-4-*iso*biuret	80	—
6114	1-*p*-Chlorophenyl-5-*iso*propylbiuret	80	— (toxic)
		40	—
6178	1-*p*-Chlorophenyl-5-*n*-butylbiuret	40	—
6011	1-*p*-Chlorophenyl-4 : 5 : 5-trimethyl-4-*iso*biuret	80	—
6105	1-*p*-Chlorophenyl-4 : 5-dimethyl-5-*iso*propyl-4-*iso*biuret	80	—
6110	1-*p*-Chlorophenyl-5-methyl-5-*iso*propylbiuret	80	—
6078	1-*p*-Chlorophenyl-4-methyl-5 : 5-*cyclo*pentamethylene-4-*iso*biuret	Not tested	
6263	1-*p*-Chlorophenyl-5 : 5-*cyclo*pentamethylenebiuret	80	—

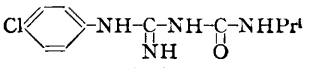
All the compounds were tested also for prophylactic activity against *P. gallinaceum* by the method described by one of us (Davey, *Ann. Trop. Med. Parasit.*, 1946, **40**, 453), in the majority of cases at the maximum tolerated dose (the highest dose quoted above) but at half this dose in the case of **5964**, **5965**, and **6114**, and at 120 mg./kg. in the case of **6661**. All were inactive. **6078** was tested at **160** mg./kg.

Despite the inactivity of (II) it seemed desirable to investigate some biurets analogous to the active diguanides (I; R = alkyl, R′ = H or alkyl), since it appeared conceivable that *in-vivo* deamination of the latter might proceed further than the guanylurea stages.

Several methods of preparing biuret derivatives have been described in the literature, and some have been reinvestigated with a view to the preparation of 1-*p*-chlorophenyl-5-alkyl- and 5 : 5-dialkyl-biurets (IV; R = alkyl, R′ = H or alkyl).

Kuhn and Henschel (*Ber.*, 1888, **21**, 504) have stated that, whereas the condensation of phenyl *iso*cyanate with *NN'*-diphenylurea gave rise to 1 : 3 : 5-triphenylbiuret as the sole product, with phenylurea there was formed a small quantity of a higher-melting by-product in addition to 1 : 5-diphenylbiuret. Similarly, it has now been found that condensation of phenyl *iso*cyanate with *p*-chlorophenylurea, and of *p*-chlorophenyl *iso*cyanate with phenylurea, gave rise to mixtures which could not be separated. Moreover, Biltz and Jeltsch (*Ber.*, **1923**, **56**, 1915) treated phenyl *iso*cyanate with methylurea at 120—130° in a closed vessel and obtained a product, m. p. 172—173°, which they claimed to be 1-phenyl-5-methylbiuret. Gatewood (*J. Amer. Chem. Soc.*, **1925**, **47**, 407) repeated this reaction at 80—90° and obtained a different product, m. p. 132—133°, which was shown to be authentic 1-phenyl-5-methylbiuret by its independent synthesis from *N*-carbethoxy-*N'*-phenylurea (ethyl N^{ω}-phenyl allophanate) and methylamine. In a later paper, Biltz and Beck (*Ber.*, 1925, **58**, 2187) acknowledged the difference in the products and repeated the reaction to give 1-phenyl-5-methylbiuret, m. p. 133°. With an excess of phenyl *iso*cyanate, however, another compound, m. p. 183°, was also formed which was found to be identical with the product obtained by Gatewood (*loc. cit.*) by the action of methyl sulphate on 1-phenylbiuret and considered to be 1-phenyl-3-methylbiuret. Although no attempt has been made to confirm this work it was taken to indicate the possibility of the formation of more than one product and the method, therefore, appeared unsuitable for our purpose.


(I.)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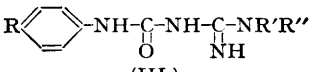
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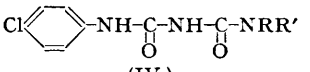
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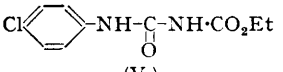
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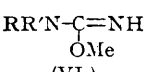
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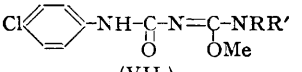
(VII.)

Another method for the preparation of biurets which, although not always successful, has been used by several previous workers (cf., *e.g.*, Biltz and Jeltsch, *loc. cit.*; Wertheim, *J. Amer. Chem. Soc.*, **1931**, **53**, 200; Chabrier de la Saulnière, *Ann. Chim.*, **1942**, **17**, 353; Gatewood, *loc. cit.*) is the reaction of allophanic esters with amines. By use of this method 1-p-*chlorophenyl*-5-*methyl*- (IV; R = H, R' = Me) and 1-p-*chlorophenyl*-5-*ethyl*-*biuret* (IV; R = H, R' = Et) were prepared by the action of methylamine and ethylamine respectively on N-*carbethoxy*-N'-p-*chlorophenylurea* (V), but it failed when applied to *iso*propylamine, *n*-butylamine, or dimethylamine, *p*-chlorophenylurea being the only isolable product.

The *N*-carbethoxy-*N'*-*p*-chlorophenylurea (V) required for this work was prepared by the action of ethyl carbonate on *p*-chlorophenylurea in alcoholic sodium ethoxide solution. This method was taken from D.R.-P. 427,417, which *inter alia* described the preparation of *N*-carbethoxy-*N'*-phenylurea from phenylurea and ethyl carbonate under these conditions. Other methods described in the literature for the preparation of *N*-carbethoxy-*N'*-phenylurea included the condensation of phenyl *iso*cyanate with urethane (Dains, Greider, and Kidwell, *J. Amer. Chem. Soc.*, 1919, **41**, 1004; cf. Folin, *Amer. Chem. J.*, 1897, **19**, 323) and the reaction of *N*-carbethoxyurea with aniline at 120—125° (Dains and Wertheim, *J. Amer. Chem. Soc.*, 1920, **42**, 2303), but these methods appeared too liable to be complicated by side-reactions and were therefore not seriously considered for the preparation of (V). The work of Biltz and Jeltsch (*loc. cit.*) who prepared *N*-carbethoxy-*N'*-methylurea from methylurea and ethyl chloroformate suggested a similar reaction with *p*-chlorophenylurea but an attempt to effect this failed.

Attention was then directed to the work of McKee (*Amer. Chem. J.*, 1901, **26**, 209) who prepared a number of *iso*biurets by condensation of phenyl *iso*cyanate with *O*-alkyl*iso*ureas and *N*-aryl-substituted derivatives thereof, and converted them into the corresponding biurets by spontaneous decomposition of the hydrochlorides in a vacuum (loss of alkyl chloride) or by boiling hydrochloric acid. We have verified the applicability of the method to the preparation of 1 : 5-diarylbiurets in the following way. *N*-Phenyl-*O*-methyl*iso*urea (McKee, *loc. cit.*) and the corresponding p-*chlorophenyl* derivative (prepared by the action of dry hydrogen chloride on *p*-chlorophenylcyanamide in methanol, followed by decomposition of the resulting hydrochloride with alkali) were condensed with *p*-chlorophenyl *iso*cyanate and phenyl *iso*cyanate respectively

to give 1-*phenyl*-5-p-*chlorophenyl*-4-*methyl*-4-iso*biuret* and 1-*phenyl*-5-p-*chlorophenyl*-2-*methyl*-2-iso*biuret* (VII; R = H, R′ = Ph), both of which in boiling 2N-hydrochloric acid afforded 1-*phenyl*-5-p-*chlorophenylbiuret* (IV; R = H, R′ = Ph). 1-p-*Chlorophenylbiuret* (IV; R = R′ = H) was prepared by condensing *p*-chlorophenyl *iso*cyanate with *O*-methyl*iso*urea to give 1-p-*chlorophenyl*-4-*methyl*-4-iso*biuret* (VII; R = R′ = H) which was boiled with hydrochloric acid, and the method was then extended, in the first instance, to the synthesis of a number of 1-*p*-chlorophenyl-5 : 5-dialkylbiurets. The preparation of various *O*-methyl- (and *O*-ethyl)-*NN*-dialkyl*iso*ureas from the corresponding dialkylcyanamides has been described by McKee (*ibid.*, 1909, **42**, 1), either through the hydrochlorides which were obtained by the action of dry hydrogen chloride in methanol, or preferably by the action of methanolic sodium methoxide (alcoholic sodium ethoxide for the *O*-ethyl compounds). The former method was used to prepare *ONN*-trimethyl*iso*urea (cf. McKee) and the latter for ON-*dimethyl*-N-iso*propyl*iso*urea* (VI; R = Me, R′ = Pr^i) and O-*methyl*-NN-cyclo*pentamethylene*iso*urea* (VI; R and R′ = $[CH_2]_5$). These *O*-methyl-*NN*-dialkyl*iso*ureas condensed with *p*-chlorophenyl *iso*cyanate in ether to give 1-*p*-chlorophenyl-4-methyl-5 : 5-dialkyl-4-*iso*biurets of type (VII) which were decomposed by boiling dilute hydrochloric acid to give the required 1-*p*-chlorophenyl-5 : 5-dialkylbiurets (IV; R and R′ = alkyl). Thus *p*-chlorophenyl *iso*cyanate and *ONN*-trimethyl*iso*urea gave 1-p-*chlorophenyl*-5 : 5-*dimethylbiuret* (IV; R = R′ = Me) by way of 1-p-*chlorophenyl*-4 : 5 : 5-*trimethyl*-4-iso*biuret* (VII; R = R′ = Me), and the corresponding 5-*methyl*-5-iso*propyl* (IV; R = Me, R′ = Pr^i) and 5 : 5-cyclo*pentamethylene* (IV; R and R′ = $[CH_2]_5$) compounds were prepared analogously.

For the preparation of 1-*p*-chlorophenyl-5-monoalkylbiurets by a similar method, *O*-alkyl-*N*-monoalkyl*iso*ureas were required. It has been found that the *O*-methyl*iso*ureas can be prepared by passing dry hydrogen chloride into a solution of the monoalkylcyanamide (prepared *in situ* from the amine and cyanogen bromide) and excess methanol in ether, followed by liberation of the base with sodium hydroxide. In this way *ON*-dimethyl*iso*urea (VI; R = H, R′ = Me) (not analysed) was made in small yield, and converted, by the action of *p*-chlorophenyl *iso*cyanate, into 1-p-*chlorophenyl*-4 : 5-*dimethyl*-4-iso*biuret* (VII; R = H, R′ = Me) which in boiling 2N-hydrochloric acid afforded 1-*p*-chlorophenyl-5-methylbiuret, identical with the product obtained from *N*-carbethoxy-*N′*-*p*-chlorophenylurea and methylamine (see above). This synthesis of the same biuret by two different methods was held to substantiate its structure and therefore that of the analogous compounds prepared by either method. The exact biuret analogue (IV; R = H, R′ = Pr^i) of " Paludrine " was then prepared by converting *iso*propyl-cyanamide into O-*methyl*-N-iso*propyl*iso*urea* (VI; R = H, R′ = Pr^i), condensing this with *p*-chlorophenyl *iso*cyanate, and decomposing the resulting 1-p-*chlorophenyl*-4-*methyl*-5-iso*propyl*-4-iso*biuret* (VII; R = H, R′ = Pr^i) with acid. 1-*p*-Chlorophenyl-5-*n*-butylbiuret (IV; R = H, R′ = Bu^n) was prepared analogously from *n*-butylcyanamide through (VI; R = H, R′ = Bu^n) and (VII; R = H, R′ = Bu^n).

Experimental.

Hydrolysis of " Paludrine " with Cold Hydrochloric Acid (Experiment by Mr. R. S. Neal).—*N*^{1}-*p*-Chlorophenyl-*N*^{5}-*iso*propyldiguanide (20 g.) was dissolved in 2N-hydrochloric acid (125 c.c.) and the solution set aside for 1 year. A crystalline solid was gradually deposited which was eventually collected and crystallised from water to give colourless flat prisms, m. p. 126—127°, which showed no depression when mixed with *N*-*p*-chlorophenyl-*N′*-*iso*propylguanylurea hydrochloride (see below). When this hydrochloride was dissolved in water and the solution made alkaline with ammonia, the corresponding base was obtained. It was collected, washed with water, dried, and crystallised from benzene; m. p. 133°, either alone or in admixture with *N*-*p*-chlorophenyl-*N′*-*iso*propylguanylurea made by the methods described below (Found: C, 51·6; H, 5·7; N, 22·0; Cl, 13·9, 14·2. $C_{11}H_{15}ON_4Cl$ requires C, 51·9; H, 5·9; N, 22·0; Cl, 13·9%).

N-p-*Chlorophenyl*-N′-*methylguanylurea* (III; R = Cl, R′ = H, R″ = Me).—Sodium (1·9 g.) was dissolved in acetone (100 c.c.) (previously dried over potassium carbonate and distilled over phosphoric oxide), and methylguanidine sulphate (11·5 g.) added. After the mixture had been stirred for 1 hour, phenyl *iso*cyanate (9·6 g.) in acetone (50 c.c.) was added, and the mixture stirred at 35—40° for 1½ hours and then poured into water. When kept, the precipitated oil gradually solidified and was collected, washed with water, and dried. Crystallisation from toluene gave N-p-*chlorophenyl*-N′-*methylguanylurea* as colourless prisms (8·5 g.), m. p. 130—132° (Found: C, 48·0; H, 5·1; N, 24·1. $C_9H_{11}ON_4Cl$ requires C, 47·7; H, 4·9; N, 24·7%) (6354).

N-p-*Chlorophenyl*-N′-*ethylguanylurea* (III; R = Cl, R′ = H, R″ = Et).—Prepared similarly from *p*-chlorophenyl *iso*cyanate and ethylguanidine sulphate, the *product* crystallised from benzene as colourless prisms, m. p. 142—144° (Found: C, 49·6; H, 5·4; N, 23·8. $C_{10}H_{13}ON_4Cl$ requires C, 49·9; H, 5·4; N, 23·3%) (6615).

N-*Phenyl*-N′-(NN-*dimethylguanyl*)*urea* (III; R = H, R′ = R″ = Me).—Prepared in an analogous manner from phenyl *iso*cyanate and *NN*-dimethylguanidine sulphate, this *compound* crystallised from

benzene as colourless elongated flat prisms, m. p. 130—132° (Found : C, 58·2; H, 6·9; N, 27·0. $C_{10}H_{14}ON_4$ requires C, 58·25; H, 6·8; N, 27·2%) (5940).

N-p-*Chlorophenyl*-N′-iso*propylguanylurea* (III; R = Cl, R′ = H, R″ = Pr^i).—(*a*) To a solution of sodium (1·9 g.) in dry acetone (100 c.c.) *iso*propylguanidine sulphate (14 g.) was added, and the mixture stirred for 1½ hours. A solution of *p*-chlorophenyl *iso*cyanate (9·6 g.) in acetone (50 c.c.) was then added, and the mixture stirred at 30—35° for 2 hours and poured into water. The sticky solid precipitated was collected and dissolved in hot 50% aqueous alcohol, which when cooled and set aside deposited a substance, m. p. 208—210°. This was removed by filtration and discarded. The mother-liquors were diluted with water to precipitate N-p-*chlorophenyl*-N′-iso*propylguanylurea* which was collected, dried, and crystallised from benzene; it formed colourless flat prisms, m. p. 131—133° (Found : C, 52·1; H, 5·7; N, 21·6. $C_{11}H_{15}ON_4Cl$ requires C, 51·9; H, 5·9; N, 22·0%) (6045).

(*b*) N^1-*p*-Chlorophenyl-N^5-*iso*propyldiguanide hydrochloride (2·53 g.) was dissolved in N-hydrochloric acid (100 c.c.), and sodium nitrite (5 g.) added gradually at room temperature. A solid soon separated and was collected and crystallised from water to give N-p-*chlorophenyl*-N′-iso*propylguanylurea hydrochloride* as clusters of colourless prisms, m. p. 126—127° (Found : C, 42·8; H, 5·8; N, 17·8. $C_{11}H_{15}ON_4Cl,HCl,H_2O$ requires C, 42·7; H, 5·8; N, 18·1%). Addition of ammonia to a solution of this hydrochloride in water precipitated the base which crystallised from benzene; m. p. 131—133°, undepressed in admixture with material made by method (*a*) (Found : C, 51·7; H, 5·8; N, 22·4%).

N-p-*Chlorophenyl*-N′-n-*butylguanylurea* (III; R = Cl, R′ = H, R″ = Bu^n).—Prepared from *p*-chlorophenyl *iso*cyanate and *n*-butylguanidine sulphate as described under (*a*) above, the crude product was obtained as an oil on pouring the reaction mixture into water. It was separated by decantation and dissolved in hot alcohol. A small amount of a high-melting insoluble by-product was removed by filtration at this stage and the alcoholic filtrate poured into water. The precipitated oil soon solidified and was then collected, dried, and crystallised from benzene–light petroleum (b. p. 60—80°) to give N-p-*chlorophenyl*-N′-n-*butylguanylurea* as colourless prisms, m. p. 108—110° (Found : C, 53·5; H, 6·5; N, 20·6; Cl, 13·4. $C_{12}H_{17}ON_4Cl$ requires C, 53·6; H, 6·3; N, 20·8; Cl, 13·2%) (5964).

N-p-*Chlorophenyl*-N′-(NN-*dimethylguanyl*)*urea* (III; R = Cl, R′ = R″ = Me).—(*a*) Prepared from *p*-chlorophenyl *iso*cyanate and *NN*-dimethylguanidine sulphate as described above, the *product* crystallised from benzene as colourless prisms, m. p. 151—153° (Found : C, 49·8; H, 5·1; N, 23·1; Cl, 14·6. $C_{10}H_{13}ON_4Cl$ requires C, 49·9; H, 5·4; N, 23·3; Cl, 14·8%) (5963).

(*b*) N^1-*p*-Chlorophenyl-N^5N^5-dimethyldiguanide (8·28 g.) was dissolved in a mixture of water (125 c.c.) and 10N-hydrochloric acid (46 c.c.). Sodium nitrite (18·2 g.) was gradually added and the mixture stirred for 1½ hours. The precipitated solid was filtered off and stirred with dilute sodium hydroxide solution. The resulting base was collected, washed with water, and dried to give the same material as in (*a*); m. p. and mixed m. p. 151—152°.

N-p-*Chlorophenyl*-N′-(N-*methyl*-N-iso*propylguanyl*)*urea* (III; R = Cl, R′ = Me, R″ = Pr^i).—N^1-*p*-Chlorophenyl-N^5-methyl-N^5-*iso*propyldiguanide (32·1 g.) was dissolved in a mixture of 10N-hydrochloric acid (186 c.c.) and water (500 c.c.), and sodium nitrite (64·2 g.) added with stirring. The mixture was stirred for 1½ hours whereupon an oil separated on the surface. The oil was separated, stirred with aqueous sodium hydroxide, and extracted with ether. Evaporation of the dried (K_2CO_3) extract gave N-p-*chlorophenyl*-N′-(N-*methyl*-N-iso*propylguanyl*)*urea* which crystallised from benzene–light petroleum (b. p. 60—80°) as colourless flat prisms (10·5 g.), m. p. 132—133° (Found : C, 53·5; H, 6·3; N, 21·2. $C_{12}H_{17}ON_4Cl$ requires C, 53·6; H, 6·3; N, 20·8%) (6661).

N-p-*Chlorophenyl*-N′-(NN-*diethylguanyl*)*urea* (III; R = Cl, R′ = R″ = Et), prepared similarly from N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide, crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 116—117° (Found : C, 53·5; H, 5·9; N, 20·7. $C_{12}H_{17}ON_4Cl$ requires C, 53·6; H, 6·3; N, 20·8%) (6814).

N-p-*Chlorophenylguanyl*-N′-iso*propylurea* (II).—*p*-Chlorophenylguanidine (8·48 g.) was dissolved in benzene (50 c.c.), and *iso*propyl *iso*cyanate (4·25 g.) (Hofmann, *Ber.*, 1882, **15**, 756) added. Heat was evolved and a solid separated. After the mixture had been kept overnight, the solid was collected and crystallised from chlorobenzene to give the *product* as colourless laminæ (11 g.), m. p. 172—174° (Found : C, 52·0; H, 5·8; N, 22·6. $C_{11}H_{15}ON_4Cl$ requires C, 51·9; H, 5·9; N, 22·0%) (6111). The hydrochloride had m. p. 160—162°.

N-*Carbethoxy*-N′-p-*chlorophenylurea* (V).—*p*-Chlorophenylurea (17 g.) and ethyl carbonate (12·5 g.) were added to a solution of sodium (2·3 g.) in dry alcohol (60 c.c.), and the mixture boiled under reflux for 1 hour. The precipitated solid was collected, suspended in water, and acidified with acetic acid. The resulting product was extracted with chloroform, and the extract dried and evaporated. Crystallisation of the residue from methanol gave N-*carbethoxy*-N′-p-*chlorophenylurea* as long colourless prisms (11·9 g.), m. p. 162° (Found : C, 49·3; H, 4·7; N, 11·5. $C_{10}H_{11}O_3N_2Cl$ requires C, 49·5; H, 4·5; N, 11·5%).

Condensation of N-*Carbethoxy*-N′-p-*chlorophenylurea with Methylamine.*—The above compound (4 g.) and 21% aqueous methylamine (50 c.c.) were heated together at 100° in a closed vessel for 1 hour. The crystalline product which separated on cooling was collected, washed with water, and dried. Crystallisation from methanol gave 1-p-*chlorophenyl*-5-*methylbiuret* as colourless thin prisms (2 g.), m. p. 182° (Found : C, 47·8; H, 4·3; N, 18·1. $C_9H_{10}O_2N_3Cl$ requires C, 47·5; H, 4·4; N, 18·5%) (6031). See also p. 1738.

Condensation of N-*Carbethoxy*-N′-p-*chlorophenylurea with Ethylamine.*— N-Carbethoxy-*N′-p*-chlorophenylurea (5 g.) and 33% aqueous ethylamine (50 c.c.) reacted as in the preceding experiment to give 1-p-*chlorophenyl*-5-*ethylbiuret* which crystallised from methanol as colourless prisms (4·1 g.), m. p. 180—182° (Found : C, 49·2; H, 4·8; N, 17·4. $C_{10}H_{12}O_2N_3Cl$ requires C, 48·7; H, 5·0; N, 17·4%) (6088).

Condensation of N-*Carbethoxy*-N′-p-*chlorophenylurea with* iso*Propylamine.*—*N′*-Carbethoxy-*N*-*p*-chlorophenylurea (4 g.), *iso*propylamine (18 c.c.), and water (22 c.c.) were heated at 100° in a closed vessel for 1 hour. After cooling, the reaction mixture was diluted with water, and the product collected. Crystallised from methanol it had m. p. 206—208°, either alone or in admixture with *p*-chlorophenylurea (Young and Dunstan, *J.*, 1908, **93**, 1058). Similar results were obtained using *n*-butylamine and dimethylamine.

N-p-*Chlorophenyl*-O-*methyl*iso*urea* (VI; R = H, R′ = *p*-C_6H_4Cl).—*p*-Chlorophenylcyanamide (15 g.) was dissolved in dry methanol (100 c.c.), and dry hydrogen chloride passed in until the gain in weight was 7 g. The solution was set aside for 2 days and then poured into excess of potassium hydroxide solution. The precipitated solid was extracted with ether and filtered from a little insoluble material (*p*-chlorophenylurea), and the solution dried (Na_2SO_4) and evaporated. Crystallisation of the residue from light petroleum (b. p. 60—80°) gave N-p-*chlorophenyl*-O-*methyl*iso*urea* as colourless laminæ, m. p. 62—63° (Found: C, 52·5; H, 4·6; N, 14·9. $C_8H_9ON_2Cl$ requires C, 52·0; H, 4·9; N, 15·2%).

1-*Phenyl*-5-p-*chlorophenyl*-2-*methyl*-2-iso*biuret* (VII; R = H, R′ = Ph).—*p*-Chlorophenyl *iso*cyanate (7·7 g.) in dry ether (20 c.c.) was added to a solution of *N*-phenyl-*O*-methyl*iso*urea (8·25 g.) (McKee, *Amer. Chem. J.*, 1901, **26**, 209) in the same solvent (20 c.c.). Heat was evolved. After 2 hours, light petroleum (b. p. 40—60°) was added to precipitate the *product* which was collected, washed, and crystallised from light petroleum (b. p. 80—100°), to give colourless long thin prisms, m. p. 106—108° (Found: C, 59·4; H, 4·6; N, 13·9. $C_{15}H_{14}O_2N_3Cl$ requires C, 59·3; H, 4·6; N, 13·8%).

1-*Phenyl*-5-p-*chlorophenyl*-4-*methyl*-4-iso*biuret*.—Prepared similarly from phenyl *iso*cyanate and *N*-*p*-chlorophenyl-*O*-methyl*iso*urea, this *compound* crystallised from light petroleum (b. p. 80—100°) as colourless long prisms, m. p. 92—94° (Found: C, 59·3; H, 4·7; N, 13·8; Cl, 12·1. $C_{15}H_{14}O_2N_3Cl$ requires C, 59·3; H, 4·6; N, 13·8; Cl, 11·7%).

1-*Phenyl*-5-p-*chlorophenylbiuret* (IV; R = H, R′ = Ph).—(*a*) 1-Phenyl-5-*p*-chlorophenyl-4-methyl-4-*iso*biuret (5 g.) and 2N-hydrochloric acid (50 c.c.) were boiled under reflux for 1½ hours. Methyl chloride was evolved. After the mixture had cooled, the solid reaction product was collected, dried, and washed with ether. Crystallisation from alcohol then gave 1-*phenyl*-5-p-*chlorophenylbiuret* as colourless long flat needles, m. p. 216—218° (Found: C, 58·5; H, 4·1; N, 14·5. $C_{14}H_{12}O_2N_3Cl$ requires C, 58·0; H, 4·1; N, 14·5%) (5965).

(*b*) 1-Phenyl-5-*p*-chlorophenyl-2-methyl-2-*iso*biuret (5 g.) was boiled under reflux with 2N-hydrochloric acid (50 c.c.) to give the same compound as in (*a*); m. p. and mixed m. p. 216—218°.

1-p-*Chlorophenyl*-4-*methyl*-4-iso*biuret* (VII; R = R′ = H).—*p*-Chlorophenyl *iso*cyanate (4·5 g.) in ether (25 c.c.) was added to *O*-methyl*iso*urea (2·4 g.) (McKee, *Amer. Chem. J.*, 1901, **26**, 247) in ether (25 c.c.). After a few minutes, the *product* was precipitated with light petroleum (b. p. 40—60°). Next day it was collected and crystallised from light petroleum (b. p. 100—120°); colourless elongated prisms (5·6 g.), m. p. 120° (Found: C, 47·8; H, 4·1; N, 18·0. $C_9H_{10}O_2N_3Cl$ requires C, 47·5; H, 4·4; N, 18·5%) (6179).

1-p-*Chlorophenylbiuret* (IV; R = R′ = H).—The preceding compound (2·5 g.) and 2N-hydrochloric acid (25 c.c.) were boiled under reflux for 1 hour, the mixture cooled, and the product collected and washed with water. Crystallisation from aqueous methanol gave 1-p-*chlorophenylbiuret* as colourless thick prisms, m. p. 182—184° (Found: C, 45·3; H, 3·9. $C_8H_8O_2N_3Cl$ requires C, 45·0; H, 3·7%).

ONN-*Trimethyl*iso*urea* (VI; R = R′ = Me).—Dimethylcyanamide (14·6 g.) was dissolved in dry methanol (100 c.c.), and dry hydrogen chloride passed in until the gain in weight was 8 g. After 8 days the solution was evaporated under diminished pressure at <35°. The white solid residue was kept overnight in a desiccator containing solid potassium hydroxide and concentrated sulphuric acid. It was then dissolved in water (20 c.c.), ether (100 c.c.) added, and the mixture cooled in solid carbon dioxide. Solid sodium hydroxide (60 g.) was carefully added, the ether decanted, and the residue washed twice with ether (100 c.c.). Evaporation of the combined, dried (Na_2SO_4), ethereal extracts and distillation of the residue gave *ONN*-trimethyl*iso*urea (7·35 g.), b. p. 80°/85 mm.

ON-*Dimethyl*-N-iso*propyl*iso*urea* (VI; R = Me, R′ = Pr^i).—Methyl*iso*propylcyanamide (12·1 g.) (Ainley, Curd, and Rose, this vol., p. 98) was added to a solution of sodium (3·2 g.) in methanol (50 c.c.), and the mixture stirred at 50—55° for 2 hours. After cooling, the solution was diluted with water, and hydrochloric acid added to render the solution just acid to Congo-red. It was then shaken with ether to remove any unchanged methyl*iso*propylcyanamide, made alkaline with sodium hydroxide, and again extracted with ether. Evaporation of the dried (Na_2SO_4) ether extract and distillation of the residue gave the *product* as a colourless oil (10·4 g.), b. p. 70°/12 mm. (Found: C, 55·2; H, 10·7. $C_6H_{14}ON_2$ requires C, 55·4; H, 10·8%).

O-*Methyl*-NN-cyclo*pentamethylene*iso*urea* (VI; R and R′ = <$[CH_2]_5$), prepared analogously from *cyclo*pentamethylenecyanamide, formed a colourless oil, b. p. 102—104°/14 mm. (Found: C, 58·5; H, 9·5; N, 19·7. $C_7H_{14}ON_2$ requires C, 59·1; H, 9·9; N, 19·7%).

1-p-*Chlorophenyl*-4 : 5 : 5-*trimethyl*-4-iso*biuret* (VII; R = R′ = Me).—A solution of *ONN*-trimethyl-*iso*urea (7·5 g.) in dry ether (30 c.c.) was added to one of *p*-chlorophenyl *iso*cyanate (10 g.) in dry ether (30 c.c.). Heat was evolved, and the *product* separated. After a few minutes it was collected, dried, and crystallised from benzene; colourless rods (10·25 g.), m. p. 129° (Found: C, 51·7; H, 5·5; N, 16·1. $C_{11}H_{14}O_2N_3Cl$ requires C, 51·7; H, 5·5; N, 16·4%) (6011).

1-p-*Chlorophenyl*-4 : 5-*dimethyl*-5-iso*propyl*-4-iso*biuret* (VII; R = Me, R′ = Pr^i).—Similarly prepared by use of *ON*-dimethyl-*N*-*iso*propyl*iso*urea and precipitated from the reaction mixture by the addition of light petroleum (b. p. 40—60°), this *compound* crystallised from light petroleum (b. p. 80—100°) as colourless elongated prisms, m. p. 104° (Found: C, 55·4; H, 6·4; N, 14·6. $C_{13}H_{18}O_2N_3Cl$ requires C, 55·0; H, 6·3; N, 14·8%) (6105).

1-p-*Chlorophenyl*-4-*methyl*-5 : 5-cyclo*pentamethylene*-4-iso*biuret* (VII; R and R′ = <$[CH_2]_5$).—Prepared in a corresponding manner from *O*-methyl-*NN*-*cyclo*pentamethylene*iso*urea, the *product* crystallised from light petroleum (b. p. 100—120°) as colourless thick prisms, m. p. 126° (Found: C, 57·2; H, 6·2; N, 14·2. $C_{14}H_{18}O_2N_3Cl$ requires C, 56·9; H, 6·1; N, 14·2%).

1-p-*Chlorophenyl*-5 : 5-*dimethylbiuret* (IV; R = R′ = Me).—1-*p*-Chlorophenyl-4 : 5 : 5-trimethyl-4-*iso*biuret (5 g.) was dissolved in 2N-hydrochloric acid (50 c.c.), and the solution boiled under reflux for 1 hour. Methyl chloride was evolved. The product which separated was collected, after cooling, and purified by crystallisation from methanol; colourless thick plates, m. p. 184—186° (Found: C, 51·1; H, 5·0. $C_{10}H_{12}O_2N_3Cl$ requires C, 49·7; H, 5·0%).

1-p-*Chlorophenyl*-5-*methyl*-5-iso*propylbiuret* (IV; R = Me, R′ = Pr^i).—Prepared similarly from the corresponding *O*-methyl*iso*biuret (VII; R = Me, R′ = Pr^i), this *biuret* crystallised from light petroleum

(b. p. 80—100°) as colourless, long, thin prisms, m. p. 142—144° (Found: C, 52·2; H, 5·8; N, 14·8. $C_{12}H_{16}O_2N_3Cl$, $0·5H_2O$ requires C, 51·7; H, 6·1; N, 15·1%) (6110).

1-p-*Chlorophenyl*-5 : 5-cyclo*pentamethylenebiuret* (IV; R and R′ = <[CH_2]$_5$), prepared similarly from (VII; R and R′ = <[CH_2]$_5$), crystallised from acetone as colourless long prisms, m. p. 194—196° (Found: C, 55·9; H, 5·7; N, 14·9. $C_{13}H_{16}O_2N_3Cl$ requires C, 55·4; H, 5·7; N, 14·9%).

ON-*Dimethyl*iso*urea* (VI; R = H, R′ = Me).—Gaseous methylamine (35 g.) was absorbed in dry ether (200 c.c.), and cyanogen bromide (68 g.) added slowly to the stirred solution cooled to −5° to −10°. The temperature was kept at or below −5°. When the addition was complete, the mixture was stirred for ½ hour, and the mixture filtered to remove methylamine hydrobromide. To the filtrate dry methanol (300 c.c.) was added, and dry hydrogen chloride passed in until the gain in weight was *ca.* 40 g. After 4 days the solution was evaporated under reduced pressure, and the residue dissolved in a small quantity of water. Ether was added, followed by sodium hydroxide to make the mixture strongly alkaline. The ethereal layer was separated, and the aqueous layer re-extracted twice with ether. Evaporation of the dried (Na_2SO_4) ethereal extracts gave *ON*-dimethyl*iso*urea, b. p. 68°/16 mm., in very small yield.

O-*Methyl*-N-iso*propyl*iso*urea* (VI; R = H, R′ = Pr^i), similarly prepared from *iso*propylamine, formed a colourless oil (yield, 22·7%), b. p. 77°/12 mm. (Found: C, 51·7; H, 10·3; N, 23·7. $C_5H_{12}ON_2$ requires C, 51·7; H, 10·3; N, 24·1%).

O-*Methyl*-N-n-*butyl*iso*urea* (VI; R = H, R′ = Bu^n), prepared analogously from *n*-butylamine, was obtained as a colourless oil (yield, 55%), b. p. 90°/10 mm. (Found: C, 55·7; H, 11·1; N, 21·5. $C_6H_{14}ON_2$ requires C, 55·4; H, 10·8; N, 21·5%).

1-p-*Chlorophenyl*-4 : 5-*dimethyl*-4-iso*biuret* (VII; R = H, R′ = Me).—*ON*-Dimethyl*iso*urea (0·8 g.) and *p*-chlorophenyl *iso*cyanate (1·3 g.) were allowed to react in ether (15 c.c.) and, after a few minutes, light petroleum (b. p. 40—60°) was added to precipitate the product. This was collected and crystallised from light petroleum (b. p. 100—120°) to give 1-p-*chlorophenyl*-4 : 5-*dimethyl*-4-iso*biuret* (1·45 g.), m. p. 135—137° (Found: C, 49·6, 49·7; H, 5·0, 5·0; N, 17·8. $C_{10}H_{12}O_2N_3Cl$ requires C, 49·7; H, 5·0; N, 17·4%).

1-p-*Chlorophenyl*-4-*methyl*-5-iso*propyl*-4-iso*biuret* (VII; R = H, R′ = Pr^i), prepared similarly from *O*-methyl-*N*-*iso*propyl*iso*urea, crystallised from light petroleum (b. p. 60—80°) as colourless flat needles, m. p. 82—84° (Found: C, 53·5; H, 6·0; N, 15·6. $C_{12}H_{16}O_2N_3Cl$ requires C, 53·4; H, 5·9; N, 15·6%) (6106).

1-p-*Chlorophenyl*-5-*methylbiuret* (IV; R = H, R′ = Me).—1-*p*-Chlorophenyl-4 : 5-dimethyl-4-*iso*biuret (1·2 g.) and 2N-hydrochloric acid (12 c.c.) were boiled under reflux for 1 hour, and the resulting precipitate filtered off, after cooling, washed with water, dried, and crystallised from methanol to give the product (0·8 g.), m. p. 182—184°, undepressed by admixture with material made by condensation of *N*-carbethoxy-*N*′-*p*-chlorophenylurea and methylamine (see above).

1-p-*Chlorophenyl*-5-iso*propylbiuret* (IV; R = H, R′ = Pr^i).—Similarly prepared by treatment of 1-*p*-chlorophenyl-4-methyl-5-*iso*propyl-4-*iso*biuret (5 g.) with boiling 2N-hydrochloric acid (50 c.c). for 1½ hours, this *compound* crystallised from aqueous methanol as colourless flat needles (yield, 3·9 g.), m. p. 184° (Found: C, 51·6; H, 5·4; N, 15·9. $C_{11}H_{14}O_2N_3Cl$ requires C, 51·7; H, 5·5; N, 16·4%) (6114).

1-p-*Chlorophenyl*-5-n-*butylbiuret* (IV; R = H, R′ = Bu^n).—*O*-Methyl-*N*-*n*-butyl*iso*urea (8·4 g.) in ether (20 c.c.) was treated with a solution of *p*-chlorophenyl *iso*cyanate (9 g.) in ether (50 c.c.). After the spontaneous reaction had subsided, the bulk of the solvent was evaporated, and light petroleum (b. p. 40—60°) added. After 48 hours a small amount of solid which had separated was removed by filtration. The filtrate was evaporated to leave 1-*p*-chlorophenyl-4-methyl-5-*n*-butyl-4-*iso*biuret which solidified slowly when kept but could not be recrystallised. The crude material (10 g.) was accordingly boiled with 2N-hydrochloric acid (100 c.c.) for 1 hour under reflux. The oily layer which formed solidified gradually and, after cooling, the solid was collected, washed with water, and dried. Crystallisation from aqueous methanol afforded 1-p-*chlorophenyl*-5-n-*butylbiuret* as colourless thick prisms, m. p. 141—143° (Found: C, 53·2; H, 5·9; N, 15·5. $C_{12}H_{16}O_2N_3Cl$ requires C, 53·4; H, 5·9; N, 15·6%) (6178).

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