372. *Synthetic Antimalarials. Part XLIII. Some Dithiobiurets and 1 : 2 : 4-Triazoles related to "Paludrine."*

By (the late) F. H. S. CURD, D. G. DAVEY, (Miss) D. N. RICHARDSON, and (in part) R. DE B. ASHWORTH.

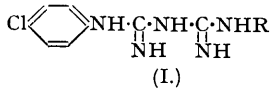
1-*p*-Chlorophenyl-5-*iso*propyldithiobiuret and a number of related substances of type (II) have been prepared by reaction of the corresponding 1-aryl-4-ethyl-5-alkyl-4-*iso*dithiobiurets (III) with sodium hydrogen sulphide, and examined for antimalarial activity. Unlike the analogous diguanides described in Part X (Curd and Rose, *J.*, 1946, 729), none exhibited any activity.

Using the 5-*iso*propyl compound as an example, it has been shown that the primary ethylation product of the 1-aryl-5-alkyldithiobiurets, like that of the 1-aryldithiobiurets (Johnson, *Amer. Chem. J.*, 1903, **30**, 167) is the 2-*S*-ethyl derivative (VI). Similarly, the 4-*S*-ethyl compounds (III) from which the normal dithiobiurets of type (II) were derived, and which were prepared by condensation of aryl *iso*thiocyanates with *S*-ethyl-*N*-alkyl*iso*thioureas, were further ethylated to give 2 : 4-di-*S*-ethyl derivatives (VII). By the action of hydrazine on this type of compound a number of 3-arylamino-5-alkylamino-1 : 2 : 4-triazoles (VIII) were prepared, but despite their obvious structural similarity to the diguanides (I) they were without antimalarial activity. This is discussed.

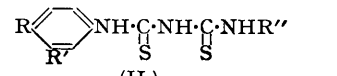
1-*p*-Chlorophenyl-5-*iso*propyldithiobiuret and its 2- and 4-*S*-ethyl derivatives were all converted into N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide by reaction with ammonia and mercuric oxide. The suggestion is made that such reactions proceed *via* intermediate carbodi-imide stages and must accordingly be stepwise.

The investigation also included some miscellaneous work on monothiobiurets, such as the preparation of 1-p-*chlorophenyl*-5-iso*propyl*-4-*thiobiuret* (X; R = Pr^i), and the corresponding 5-*ethyl* compound. Neither showed any antimalarial activity.

THE preceding paper described the synthesis, and examination for antimalarial activity, of a number of guanylurea and biuret analogues of the active N^1-aryl-N^5-alkyldiguanides such as "Paludrine" (I; R = Pr^i). In the present investigation this exploration of compounds related to the diguanides has been extended, in the first place to the analogous dithiobiurets (II). When our investigation was complete it came to our notice that a number of 1-aryldithiobiurets had been examined under the American wartime antimalarial programme (Wiselogle, "Survey of Antimalarial Drugs," 1941—1945, p. 656) without the disclosure of any marked antimalarial activity. More recently, the preparation of the exact dithiobiuret analogue (II; R = Cl, R′ = H, R″ = Pr^i) of "Paludrine" has been reported (Fullhart, *Iowa State College J. Sci.*, 1947, **22**, 27) but no detailed account has yet appeared and no results of antimalarial tests have so far been published. Dr. Fullhart has, however, kindly sent us details of his work. From this it appears that *iso*propyl *iso*thiocyanate was condensed with *N*-*p*-chloro-



(I.)



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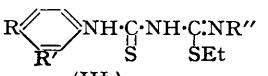


(III.)

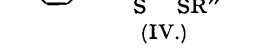
phenyl-*S*-methyl*iso*thiourea in aqueous alcoholic solution to give 1-*p*-chlorophenyl-2-methyl-5-*iso*propyl-2-*iso*dithiobiuret which, without purification, was thiohydrolysed with sodium hydrogen sulphide to give (II; R = Cl, R′ = H, R″ = Pr^i). One of our first approaches to this compound was by the same method, but since, in one experiment, we failed to effect the condensation of *iso*propyl *iso*thiocyanate with *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea in ethereal solution, we turned our attention to the condensation of *p*-chlorophenyl *iso*thiocyanate with *S*-ethyl-*N*-*iso*propyl*iso*thiourea. This was successfully effected in ether, but more conveniently in aqueous-alcoholic solution, to give 1-p-*chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret* (III; R = Cl, R′ = H, R″ = Pr^i), which was thiohydrolysed by boiling with alcoholic sodium hydrogen sulphide, saturated with hydrogen sulphide, to give 1-*p*-chlorophenyl-5-*iso*propyldithiobiuret.

Using similar procedures, the following dithiobiurets of type (II) were made: 1-p-*chlorophenyl*-5-*methyl*-, -5-*ethyl*-, -5-n-*propyl*-, -5-n-*butyl*-, 1-m-*chlorophenyl*-5-iso*propyl*-, 1-p-*bromophenyl*-5-iso*propyl*-, 1-p-*iodophenyl*-5-iso*propyl*-, and 1-3′ : 4′-*dichlorophenyl*-5-iso*propyl*-.

That the synthesis had indeed taken the expected course was proved by treating not only 1-*p*-chlorophenyl-5-*iso*propyldithiobiuret, but also the 4-*S*-ethyl compound (III; R = Cl, R′ = H, R″ = Pr^i) from which it was derived, with alcoholic ammonia in presence of mercuric oxide to give, in both cases, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide. In a similar manner, 1-*p*-chlorophenyl-5-methyldithiobiuret afforded N^1-*p*-chlorophenyl-N^5-methyldiguanide (I; R = Me).

In the conversion of 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret into N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide it seemed possible that the desulphurising agent was unnecessary for the replacement of the *S*-ethyl group by NH_2. This was supported by the observation that 1-*p*-chlorophenyl-4-methyl-4-*iso*dithiobiuret (IV; R = R′ = H, R″ = Me) reacted with *iso*propylamine, without the intervention of any desulphurising agent, to give *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylthiourea (V; X = S, R = Pr^i) identical with material prepared by condensation of *p*-chlorophenyl *iso*thiocyanate with *iso*propylguanidine (see Part XXIX, *J.*, 1948, 1636). Analogously (IV; R = R′ = H, R″ = Me) shaken with aqueous alcoholic methylamine gave N-p-*chlorophenyl*-N′-*methylguanylthiourea* (V; R = Me), and reacted with methanolic ammonia to give *N*-*p*-chlorophenyl-*N*′-guanylthiourea (Part XXXVII, this vol., p. 475).

Evidence has been adduced to support the belief that the conversion of *N*-aryl-*N*′-alkylguanylthioureas and *N*-arylguanyl-*N*′-alkylthioureas and their respective *S*-alkyl derivatives into N^1-aryl-N^5-alkyldiguanides, described in Parts XXIX and XXX (*J.*, 1948, 1636, 1645), proceeded *via* a carbodi-imide stage, and if the same mechanism operated in the analogous conversion of dithiobiurets of types (II) and (III) into diguanides the reaction must necessarily have been stepwise. Some support for this mechanism is provided by the Indian patent 37,045 which claims the conversion of 1-substituted dithiobiurets into dicyandiamides by reaction with ammonia in presence of a desulphurising agent, and by our failure to convert into diguanides *iso*dithiobiurets of the type (IV; R and R′ = alkyl) in which the necessary hydrogen atoms for carbodi-imide formation are not available. The compounds studied were 1-p-*chlorophenyl*-5 : 5-*dimethyl*-4-*ethyl*-4-iso*dithiobiuret* (IV; R = R′ = Me, R″ = Et) and 1-p-*chlorophenyl*-5-*methyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret* (IV; R = Me, R′ = Pr^i, R″ = Et) which were prepared by the action of *p*-chlorophenyl *iso*thiocyanate on *NN*-dimethyl-*S*-ethyl*iso*thiourea



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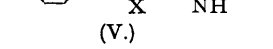

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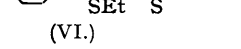


(VI.)

and *N*-methyl-*S*-ethyl-*N*-*iso*propyl*iso*thiourea respectively, with a view to the preparation of 1-*p*-chlorophenyl-5 : 5-dimethyl- and 1-*p*-chlorophenyl-5-methyl-5-*iso*propyl-dithiobiuret. However, attempts to effect the thiohydrolysis of (IV; R = R′ = Me, R″ = Et) and (IV; R = Me, R′ = Pr^i, R″ = Et) were unsuccessful, apparently because of breakdown of the molecule, since neither starting material nor dithiobiuret could be isolated.

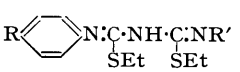
This was unfortunate because we were particularly anxious, as a means of throwing further light on the reaction mechanism discussed above, to study the action of ammonia and a desulphurising agent on 1-*p*-chlorophenyl-5 : 5-dimethyl- and 1-*p*-chlorophenyl-5-methyl-5-*iso*propyl-dithiobiuret. It seemed possible that, in contrast to the corresponding 4-*iso*dithiobiurets, replacement of the 2-sulphur atom might occur to give the corresponding *N*-*p*-chlorophenylguanyl-*N*′*N*′-dimethyl- and *N*′-methyl-*N*′-*iso*propyl-thioureas, but that the reactions would not proceed further to give diguanides because of the absence, in either case, of a hydrogen atom on the nitrogen atom carrying the alkyl groups.

The methods used by Fullhart and ourselves for the preparation of 1-aryl-5-monoalkyldithiobiurets were based on the earlier syntheses of 1-aryl- and 1 : 5-diaryl-dithiobiurets by the condensation of aryl *iso*thiocyanates with *S*-alkyl*iso*thioureas and *N*-aryl-*S*-alkyl*iso*thioureas, respectively (cf. Johnson, *Amer. Chem. J.*, 1903, **30**, 167), followed by thiohydrolysis of the resulting 1-aryl- and 1 : 5-diaryl-4-alkyl-4-*iso*dithiobiurets (cf. Underwood and Dains, *Kansas Univ. Sci. Bull.*, 1937, **24**, 5). The reaction of arylamines with perthiocyanic acid (xanthan hydride) to give 1-aryldithiobiurets (for references see Part XXX, *loc. cit.*) cannot be modified to give the 5-alkyl compounds.

Previously, abortive attempts had been made to prepare 1-*p*-chlorophenyl-5-*iso*propyl-dithiobiuret by the direct interaction of *p*-chlorophenyl *iso*thiocyanate with *iso*propylthiourea, but no condensation occurred when the reactants were heated together in boiling xylene for ¾ hour, in pyridine at 120°, or on fusion together at 170°. Likewise, the reaction of *iso*propyl *iso*thiocyanate with *p*-chlorophenylthiourea could not be effected.

Tursini (*Ber.*, 1884, **17**, 584) observed that 1-phenyldithiobiuret was alkylated with ethyl iodide in alcohol in presence of ammonia, and Johnson (*loc. cit.*) concluded that the product was 1-phenyl-2-ethyl-2-*iso*dithiobiuret (VI; R = R′ = H) since it was not identical with the 4-*S*-ethyl compound (III; R = R′ = R″ = H) prepared by interaction of phenyl *iso*thiocyanate with *S*-ethyl*iso*thiourea. Further proof has now been provided that alkylation of 1-aryldithiobiurets occurs first in the 2-position by the observation that 1-*p*-chlorophenyl-5-*iso*propyldithio-

biuret on treatment with ethyl iodide under Tursini's conditions must have given 1-p-*chlorophenyl*-2-*ethyl*-5-iso*propyl*-2-iso*dithiobiuret* (VI; R = Cl, R′ = Pr^i), since it was not only different from the 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret described above, but also gave N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide on treatment with alcoholic ammonia in presence of mercuric oxide.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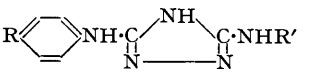
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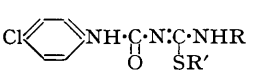
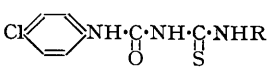
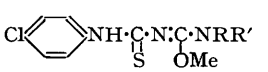

(IX.)

Johnson (*loc. cit.*) has shown that 1 : 5-diaryl-4-alkyl-4-*iso*dithiobiurets are further alkylated with methyl iodide to give 2 : 4-di-*S*-alkyl derivatives, *i.e.*, 1 : 5-diaryl-2 : 4-dialkyl-2 : 4-di*iso*dithiobiurets. Analogously, further alkylation of the 1-aryl-5-alkyl-4-*S*-ethyl*iso*dithiobiurets of type (III) with ethyl iodide in alcoholic solution in the cold led to compounds of the type (VII), from which we were able to prepare a number of 3-arylamino-5-alkylamino-1 : 2 : 4-triazoles of type (VIII) by reaction with hydrazine (cf. the preparation of 3-amino-5-arylamino-1 : 2 : 4-triazoles from 1-aryl-2 : 4-dialkyl-2 : 4-di*iso*dithiobiurets; Underwood and Dains, *loc. cit.*). In general, the intermediate 1-aryl-2 : 4 : 5-trialkyl-2 : 4-di*iso*dithiobiurets were obtained as oils, or low-melting solids, which were difficult to crystallise, although in one case, that of 1-*p*-chlorophenyl-5-*iso*propyl-2 : 4-diethyl-2 : 4-di*iso*dithiobiuret, the compound was isolated as its *hydriodide*. Usually, therefore, the crude compounds of type (VII) were caused to react directly with hydrazine in alcoholic solution. The compounds of type (VIII) prepared included 3-p-*chloroanilino*-5-iso*propylamino*-, -5-*methylamino*-, -5-*ethylamino*-, and -5-n-*butylamino*-1 : 2 : 4-*triazoles* and 3-p-*bromoanilino*-5-iso*propylamino*-1 : 2 : 4-*triazole*, but none showed any antimalarial activity when tested against *P. gallinaceum* in chicks, despite their apparent close similarity to the diguanides.

In the course of the investigations described in this series of papers we have continually attempted to relate antimalarial activity with chemical structure. Thus in Part XII (*J.*, 1947, 154) the suggestion was made that in the diguanides (I), and in the earlier pyrimidine types from which they were evolved, the possession of antimalarial activity was to be associated with the contribution to a resonance hybrid of the polarised form in which a conjugated path could be traced through alternate carbon and nitrogen atoms from the anilino-nitrogen to the nitrogen atom carrying the terminal alkyl- or dialkylaminoalkyl-group. On this basis the triazoles of type (VIII) might have been expected to exhibit activity.

Another suggestion which has been made (Curd and Rose, *Nature*, 1946, **158**, 707) to explain the antimalarial activity of the diguanide (I; R = Pr^i) was that it might be capable of interfering with a porphyrin-containing enzyme system essential to the malaria parasites, because of a similarity between the copper complex of the drug (containing two molecules of diguanide to one atom of copper, and assuming the symmetrical disposition of the diguanide molecules in a planar structure) and the metal protoporphyrins. Manifestly the triazoles (VIII) cannot form similarly constituted copper complexes, nor can they, through hydrogen-bond resonance such as is possible in the case of the diguanides (cf. Gage, Part XXXIV, this vol., p. 221), give a structure simulating a portion of the metal protoporphyrins.

(X.) 


(XI.)

The investigation was terminated with some miscellaneous experiments on monothiobiurets. It has been recorded in the preceding paper that *p*-chlorophenyl *iso*cyanate reacted with *ON*-dialkyl*iso*ureas to give 1-*p*-chlorophenyl-4 : 5-dialkyl-4-*iso*biurets which were hydrolysed to 1-*p*-chlorophenyl-5-alkylbiurets. Analogously, the same *iso*cyanate reacted with *NS*-dialkyl-*iso*thioureas, for instance with *NS*-diethyl*iso*thiourea and with *S*-ethyl-*N*-*iso*propyl*iso*thiourea, to give respectively 1-p-*chlorophenyl*-4 : 5-*diethyl*-4-iso*thiobiuret* (IX; R = R′ = Et) and 1-p-*chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*thiobiuret* (IX; R = Pr^i, R′ = Et), which on treatment with a boiling alcoholic solution of sodium hydrogen sulphide afforded the corresponding monothiobiurets, 1-p-*chlorophenyl*-5-*ethyl*- (X; R = Et) and -5-iso*propyl*-4-*thiobiuret* (X; R = Pr^i). Neither of these compounds exhibited any activity when tested against *P. gallinaceum* in chicks. Their constitution followed from the method of synthesis, but additional proof was provided by reaction of (X; R = Pr^i) with ammonia in presence of mercuric oxide whereby it was converted into *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylurea (V; X = O,

R = Pr^{i}), identical with the compound made by condensation of *p*-chlorophenyl *iso*cyanate with *iso*propylguanidine (preceding paper).

It has been reported (Lakra and Dains, *J. Amer. Chem. Soc.*, 1929, **51**, 220) that 1-phenyl-4-thiobiuret was converted into 1-phenylbiuret by the action of lead monoxide in alcohol, but when 1-*p*-chlorophenyl-5-*iso*propyl-4-thiobiuret was treated with mercuric oxide in methanol it was converted into 1-*p*-chlorophenyl-4-methyl-5-*iso*propyl-4-*iso*biuret described in the preceding paper. To account for this it is suggested that desulphurisation to give a carbodiimide first occurs, which then adds on the elements of methanol.

Just as phenyl *iso*cyanate was condensed with *N*-*p*-chlorophenyl-*O*-methyl*iso*urea to give 1-phenyl-5-*p*-chlorophenyl-4-methyl-4-*iso*biuret (Part XLII, *loc. cit.*), *p*-chlorophenyl *iso*thiocyanate was condensed with the same compound to give 1 : 5-*di*-p-*chlorophenyl*-4-*methyl*-4-iso-2-*thiobiuret* (XI; R = H, R′ = C_6H_4Cl-*p*) and with the appropriate *O*-methyl-*N*-alkyl- or *NN*-dialkyl-*iso*ureas to give 1-p-*chlorophenyl*-4 : 5-*dimethyl*-5-iso*propyl*-, -4-*methyl*-5 : 5-*di*-n-*butyl*-, and -4-*methyl*-5-n-*butyl*-4-iso-2-*thiobiuret* (XI; R = H, R′ = Bu^{n}). None of these compounds was hydrolysed to the corresponding monothiobiuret in view of the inactivity of the compounds of type (X), but it was also shown that *p*-chlorophenyl *iso*cyanate condensed with *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea to give 1 : 5-*di*-p-*chlorophenyl*-4-*methyl*-4-iso-4-*thiobiuret* (IX; R = C_6H_4Cl-*p*, R′ = Me). Fullhart (*loc. cit.*) has reported the analogous condensation of phenyl *iso*cyanate with *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea and thiohydrolysis of the resulting 1-phenyl-5-*p*-chlorophenyl-4-methyl-4-*iso*-4-thiobiuret to give 1-phenyl-5-*p*-chlorophenyl-4-thiobiuret.

Experimental.

1-p-*Chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*thiobiuret* (III; R = Cl, R′ = H, R″ = Pr^{i}).—*S*-Ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide (22·8 g.) (Part XXXVII, *loc. cit.*) was dissolved in a solution of potassium hydroxide (5·6 g.) in water (50 c.c.), and a solution of *p*-chlorophenyl *iso*thiocyanate (16·8 g.) in alcohol (50 c.c.) added. The mixture was stirred for 20 hours. The oil first formed gradually solidified. The product was then collected, dried, and crystallised from light petroleum (b. p. 100—120°) to give 1-p-*chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret* (6281) as colourless prisms, m. p. 122—124° (Found : C, 49·8; H, 6·1; N, 13·3; S, 20·8. $C_{13}H_{18}N_3ClS_2$ requires C, 49·4; H, 5·7; N, 13·3; S, 20·3%).

1-p-*Chlorophenyl*-5-*methyl*-4-*ethyl*-4-iso*dithiobiuret*.—*N*-Methylthiourea (16·5 g.) was dissolved in alcohol (100 c.c.), ethyl bromide (22 g.) added, and the solution boiled under reflux for 20 hours. The reaction mixture was evaporated to dryness under reduced pressure and the residue stirred with ethyl acetate. The resulting crystalline *N*-methyl *S*-ethyl*iso*thiourea hydrobromide was collected and dried in a vacuum (yield, 31·35 g.). Because of its hygroscopic nature it was used directly, without further purification or analysis, for reaction with *p*-chlorophenyl *iso*thiocyanate, as described above, to give 1-p-*chlorophenyl*-5-*methyl*-4-*ethyl*-4-iso*dithiobiuret* as colourless flat prisms, m. p. 104—105° (Found : C, 46·0; H, 5·0; N, 14·7. $C_{11}H_{14}N_3ClS_2$ requires C, 45·9; H, 4·9; N, 14·6%) (6355).

1-p-*Chlorophenyl*-4 : 5-*diethyl*-4-iso*dithiobiuret*.—Prepared similarly from *NS*-diethyl*iso*thiourea hydrobromide (Part XXXVII, *loc. cit.*) and *p*-chlorophenyl *iso*thiocyanate, this *biuret* crystallised from light petroleum (b. p. 80—100°) as colourless prisms, m. p. 110—112° (Found : C, 47·7; H, 5·4; N, 13·7; S, 22·0. $C_{12}H_{16}N_3ClS_2$ requires C, 47·8; H, 5·3; N, 13·9; S, 21·3%) (6356).

1-p-*Chlorophenyl*-4-*ethyl*-5-n-*butyl*-4-iso*thiobiuret*.—*N*-*n*-Butylthiourea was treated with ethyl bromide as described above for *N*-methylthiourea. The resulting crude *S*-ethyl-*N*-*n*-butyl*iso*thiourea hydrobromide (12·1 g.) was dissolved in a solution of potassium hydroxide (2·8 g.) in water (50 c.c.), and a solution of *p*-chlorophenyl *iso*thiocyanate (8·5 g.) in alcohol (50 c.c.) added. The mixture was stirred at room temperature for 4 hours during which the oil first precipitated gradually solidified. The product was collected, washed with water, and dried in a vacuum. Crystallisation from light petroleum (b. p. 80—100°) gave 1-p-*chlorophenyl*-4-*ethyl*-5-n-*butyl*-4-iso*dithiobiuret* as colourless rhombs, m. p. 77—79° (Found : C, 51·2; H, 5·9; N, 12·3. $C_{14}H_{20}N_3ClS_2$ requires C, 51·0; H, 6·1; N, 12·7%) (6569).

1-m-*Chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret*, similarly prepared from *m*-chlorophenyl *iso*thiocyanate (Hofmann, *Ber.*, 1880, **13**, 14) and *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, crystallised from light petroleum (b. p. 60—80°) as colourless prisms, m. p. 80—81° (Found : C, 48·9; H, 5·5; N, 13·8. $C_{13}H_{18}N_3ClS_2$ requires C, 49·4; H, 5·7; N, 13·3%) (6459).

1-p-*Bromophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret*, prepared analogously but from *p*-bromophenyl *iso*thiocyanate, crystallised from light petroleum (b. p. 100—120°) as colourless elongated prisms, m. p. 129—130° (Found : C, 43·2; H, 5·0; N, 11·6. $C_{13}H_{18}N_3BrS_2$ requires C, 43·3; H, 5·0; N, 11·7%).

1-p-*Iodophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret*, prepared similarly from *p*-iodophenyl *iso*thiocyanate (see Part XXIX, *loc. cit.*) and *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, crystallised from light petroleum (b. p. 100—120°) as colourless parallelepipeds, m. p. 124—125° (Found : C, 38·7; H, 5·0; N, 10·5. $C_{13}H_{18}N_3IS_2$ requires C, 38·3; H, 4·5; N, 10·3%) (6492).

1-3′ : 4′-*Dichlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret*, prepared in a similar manner from 3 : 4-dichlorophenyl *iso*thiocyanate (Dyson, George, and Hunter, *J.*, 1926, 3041), separated from light petroleum (b. p. 80—100°) as colourless laminæ, m. p. 104° (Found : C, 44·7; H, 4·9; N, 11·7. $C_{13}H_{17}N_3Cl_2S_2$ requires C, 44·55; H, 4·9; N, 12·0%).

1 : 5-*Di*-p-*chlorophenyl*-4-*methyl*-4-iso*dithiobiuret* (IV; R = H, R′ = C_6H_4Cl-*p*, R″ = Me).—*N*-*p*-Chlorophenyl-*S*-methyl*iso*thiourea (6·68 g.) (Part XXV, Crowther, Curd, and Rose, *J.*, 1948, 586) was dissolved in dry ether (50 c.c.), and a solution of *p*-chlorophenyl *iso*thiocyanate (5·65 g.) in dry ether

(50 c.c.) added. After standing for 3 days the solvent was evaporated and the residue crystallised first from chlorobenzene and then from 2-ethoxyethanol to give the product as colourless flat prisms, m. p. 158—160° (Found : C, 48·5; H, 3·6; N, 11·6; S, 17·8. Calc. for $C_{15}H_{13}N_3Cl_2S_2$: C, 48·6; H, 3·5; N, 11·3; S, 17·3%) (6254) (Fullhart, *loc. cit.*, gives m. p. 154—155°).

1-p-*Chlorophenyl*-5-iso*propyldithiobiuret* (II; R = Cl, R′ = H, R″ = Pr^i).—Sodium (0·92 g.) was dissolved in alcohol (25 c.c.), and hydrogen sulphide passed into the solution until the gain in weight was 1·36 g. This solution was added to a solution of 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret (6·3 g.) in alcohol (50 c.c.), and the mixture boiled under reflux for 1 hour while hydrogen sulphide passed through it. The hot reaction mixture was then carbon-treated, filtered, and acidified with acetic acid. On cooling, the product crystallised and was collected and recrystallised from light petroleum (b. p. 100—120°); colourless, long, flat prisms, m. p. 148° (Found : C, 45·8; H, 5·0; N, 14·4; S, 22·4. Calc. for $C_{11}H_{14}N_3ClS_2$: C, 45·9; H, 4·9; N, 14·6; S, 22·3%) (6337) (Fullhart, *loc. cit.*, quotes m. p. 135—137°).

1-p-*Chlorophenyl*-5-*methyldithiobiuret*, prepared similarly by thiohydrolysis of 1-*p*-chlorophenyl-5-methyl-4-ethyl-4-*iso*dithiobiuret, crystallised from toluene as colourless plates, m. p. 164—166° (Found : C, 42·0; H, 4·1; N, 16·1; S, 25·0. $C_9H_{10}N_3ClS_2$ requires C, 41·6; H, 3·9; N, 16·2; S, 24·7%) (6406).

1-p-*Chlorophenyl*-5-*ethyldithiobiuret*, similarly prepared from 1-*p*-chlorophenyl-4 : 5-diethyl-4-*iso*-dithiobiuret, crystallised from benzene as colourless minute prisms, m. p. 158—160° (Found : C, 43·8; H, 4·5; N, 15·4. $C_{10}H_{12}N_3ClS_2$ requires C, 43·85; H, 4·4; N, 15·3%) (6587).

1-p-*Chlorophenyl*-5-n-*propyldithiobiuret*.—*N*-*n*-Propylthiourea (18·9 g.) (Hecht, *Ber.*, 1890, **23**, 283) in alcohol (200 c.c.) was heated under reflux with ethyl bromide (20 g.) overnight, and the reaction mixture evaporated to dryness under reduced pressure. Without further purification the resulting *S*-ethyl-*N*-*n*-propyl*iso*thiourea hydrobromide was treated with potassium hydroxide to liberate the base, which was brought into reaction with *p*-chlorophenyl *iso*thiocyanate in aqueous-alcoholic solution, as described above in similar cases, to give 1-*p*-chlorophenyl-4-ethyl-5-*n*-propyl-4-*iso*dithiobiuret. Complete purification of this substance was difficult and so the crude material was thiohydrolysed in the usual way to give 1-p-*chlorophenyl*-5-n-*propyldithiobiuret*, which crystallised from light petroleum (b. p. 100—120°) as a colourless microcrystalline powder, m. p. 140—141° (Found : C, 46·3; H, 4·5; N, 14·7. $C_{11}H_{14}N_3ClS_2$ requires C, 45·9; H, 4·9; N, 14·6%) (6813).

1-p-*Chlorophenyl*-5-n-*butyldithiobiuret*, prepared as described for the corresponding 5-*iso*propyl compound but from 1-*p*-chlorophenyl-4-ethyl-5-*n*-butyl-4-*iso*dithiobiuret, crystallised from light petroleum (b. p. 100—120°) as colourless needles, m. p. 132—133° (Found : C, 47·7; H, 5·2; N, 13·8. $C_{12}H_{16}N_3ClS_2$ requires C, 47·8; H, 5·3; N, 13·9%) (6589).

1-m-*Chlorophenyl*-5-iso*propyldithiobiuret*, similarly prepared from 1-*m*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret, crystallised from benzene–light petroleum (b. p. 60—80°) as colourless laminæ, m. p. 128—129° (Found : C, 46·0; H, 5·5; N, 15·0. $C_{11}H_{14}N_3ClS_2$ requires C, 45·9; H, 4·9; N, 14·6%) (6491).

1-p-*Bromophenyl*-5-iso*propyldithiobiuret*, prepared, as described for 6337, from the corresponding 4-*S*-ethyl compound, separated from benzene–light petroleum (b. p. 60—80°) as colourless flat prisms, m. p. 150—152° (Found : C, 39·8; H, 4·3; N, 12·4. $C_{11}H_{14}N_3BrS_2$ requires C, 39·8; H, 4·2; N, 12·6%) (6493).

1-p-*Iodophenyl*-5-iso*propyldithiobiuret*, prepared similarly from 1-*p*-iodophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret, crystallised from benzene–light petroleum (b. p. 60—80°) as colourless elongated prisms, m. p. 136—138° (Found : C, 34·9; H, 3·9; N, 11·1. $C_{11}H_{14}N_3IS_2$ requires C, 34·8; H, 3·7; N, 11·1%) (6568).

1-3′ : 4′-*Dichlorophenyl*-5-iso*propyldithiobiuret*, prepared in an analogous manner from 1-3′ : 4′-dichlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret, crystallised from benzene as colourless felted needles, m. p. 158° (Found : C, 41·4; H, 4·1; N, 12·8. $C_{11}H_{13}N_3Cl_2S_2$ requires C, 41·0; H, 4·1; N, 13·0%).

Reaction of 1-p-*Chlorophenyl*-5-iso*propyldithiobiuret with Ammonia and Mercuric Oxide*.—1-*p*-Chlorophenyl-5-*iso*propyldithiobiuret (2·85 g.), mercuric oxide (8·68 g.), and saturated alcoholic ammonia (100 c.c.) were stirred together at room temperature for 20 hours. The reaction mixture was then filtered and evaporated to dryness under diminished pressure. The residue was dissolved in acetone, and the solution made acid to litmus with acetic acid. The crystalline material precipitated was collected and crystallised from alcohol–acetone to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. and mixed m. p. 184—185°.

Reaction of 1-p-*Chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret with Ammonia and Mercuric Oxide*.—1-*p*-Chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret (3·15 g.), mercuric oxide (8·68 g.), and saturated alcoholic ammonia (50 c.c.) were stirred together at 30—35° for 20 hours, and the mixture filtered and evaporated to dryness under reduced pressure. The residue was extracted with warm 2N-hydrochloric acid, the extract carbon-treated, filtered, and made just alkaline to brilliant-yellow with ammonia. The precipitated solid was collected and crystallised from water to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride, m. p. 243—244°, undepressed in admixture with an authentic specimen.

Reaction of 1-p-*Chlorophenyl*-5-*methyldithiobiuret with Ammonia and Mercuric Oxide*.—The dithiobiuret (2·6 g.), mercuric oxide (8·68 g.), and saturated alcoholic ammonia (100 c.c.) were stirred at 30—35° for 20 hours and the mixture worked up as in the preceding experiment to give N^1-*p*-chlorophenyl-N^5-methyldiguanide hydrochloride, m. p. 227—228° either alone or in admixture with authentic material.

Reaction of 1-p-*Chlorophenyl*-4-*methyl*-4-iso*dithiobiuret with* iso*Propylamine*.—1-*p*-Chlorophenyl-4-methyl-4-*iso*dithiobiuret (1 g.) (Part XXX, *loc. cit.*) and *iso*propylamine (5 c.c.) were heated together at 60° for 2 hours. The mixture was then poured into water and kept until the product solidified. Collected and crystallised from benzene, it formed colourless small flat prisms, m. p. 143°, undepressed in admixture with *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylthiourea prepared as described in Part XXIX (*loc. cit.*).

Reaction of 1-p-*Chlorophenyl*-4-*methyl*-4-iso*dithiobiuret with Methylamine*.—The dithiobiuret (6 g.), methylamine (20 c.c. of 21% aqueous solution), and alcohol (10 c.c.) were shaken together overnight at room temperature. The starting material gradually dissolved and was replaced by a granular product.

This was collected, washed with water, dried, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°) to give N-p-*chlorophenyl*-N′-*methylguanylthiourea* as colourless rhombic crystals, m. p. 130—132° (Found: C, 44·3; H, 4·3; S, 13·2. $C_9H_{11}N_4ClS$ requires C, 44·5; H, 4·6; S, 13·2%).

Reaction of 1-p-*Chlorophenyl*-4-*methyl*-4-iso*dithiobiuret with Ammonia.*—1-*p*-Chlorophenyl-4-methyl-4-*iso*dithiobiuret (2 g.) and saturated methanolic ammonia (20 c.c.) were heated at 50—60° for 10 hours. The mixture was then filtered and the filtrate poured into water. The precipitated crystalline material was collected, dried, and crystallised first from benzene–alcohol and then from xylene–butanol to give *N*-*p*-chlorophenyl-*N*′-guanylthiourea, m. p. 195°, either alone or in admixture with material prepared as in Part XXXVII (*loc. cit.*).

1-p-*Chlorophenyl*-5: 5-*dimethyl*-4-*ethyl*-4-iso*dithiobiuret* (IV; R = R′ = Me, R″ = Et).—*NN*-Dimethylthiourea (5·2 g.) (Wallach, *Ber.*, 1899, **32**, 1874), alcohol (150 c.c.), and ethyl bromide (12 g.) were allowed to stand together for 3 days and the solution then evaporated to dryness under reduced pressure. The residual oil readily solidified and consisted substantially of NN-*dimethyl*-S-*ethyl*iso*thiourea hydrobromide.* A sample crystallised from alcohol–ethyl acetate had m. p. 142—143° (Found: C, 27·6; H, 6·0; S, 15·1. $C_5H_{12}N_2S,HBr$ requires C, 28·1; H, 6·1; S, 15·0%). 6·89 G. of this were added to a solution of potassium hydroxide (1·68 g.) in water (50 c.c.), followed by a solution of *p*-chlorophenyl *iso*thiocyanate (5·05 g.) in alcohol (50 c.c.). The precipitated product was collected and crystallised, first from alcohol and then from benzene, to give 1-p-*chlorophenyl*-5: 5-*dimethyl*-4-*ethyl*-4-iso*dithiobiuret* as colourless prisms, m. p. 172—174° (Found: C, 47·8; H, 4·8. $C_{12}H_{16}N_3ClS_2$ requires C, 47·8; H, 5·3%).

N-*Methyl*-N-iso*propylthiourea.*—Hydrogen sulphide was passed into a solution of methyl*iso*propylcyanamide (20 g.) (Part XXXIII, Ainley, Curd, and Rose, this vol., p. 98) in alcohol (50 c.c.) saturated with ammonia. When precipitation had visibly ceased, the reaction mixture was kept for 3 days and then evaporated to dryness under reduced pressure. The residual solid crystallised from water to give N-*methyl*-N-iso*propylthiourea* as colourless leaves, m. p. 100—102° (Found: C, 44·9; H, 8·9; N, 20·7. $C_5H_{12}N_2S$ requires C, 45·4; H, 9·2; N, 21·2%).

Ethyl bromide (6·0 g.) was added to a solution of *N*-methyl-*N*-*iso*propylthiourea (6·6 g.) in dry alcohol (50 c.c.), and the mixture kept overnight. After evaporation under reduced pressure, the residue was stirred with ethyl acetate and filtered to give *N*-methyl-*S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, m. p. 130—132° (not analysed).

1-p-*Chlorophenyl*-5-*methyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret* (IV; R = Me, R′ = Pr^i, R″ = Et).—Prepared from *p*-chlorophenyl *iso*thiocyanate and *N*-methyl-*S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, as described above in similar cases, this *biuret* crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 126° (Found: C, 51·2; H, 6·1; N, 12·7. $C_{14}H_{20}N_3ClS_2$ requires C, 51·0; H, 6·1; N, 12·7%).

1-p-*Chlorophenyl*-2-*ethyl*-5-iso*propyl*-2-iso*dithiobiuret* (VI; R = Cl, R′ = Pr^i).—1-*p*-Chlorophenyl-5-*iso*propyldithiobiuret (8·61 g.), ethyl iodide (5·15 g.), alcohol (150 c.c.), and ammonia (3 c.c.) were mixed and kept for 3 days. Evaporation of the solution under diminished pressure and crystallisation of the residue from alcohol gave the *product*, which was recrystallised from light petroleum (b. p. 60—80°); clusters of colourless prisms, m. p. 82—84° (Found: C, 49·3; H, 5·6; N, 13·7. $C_{13}H_{18}N_3ClS$ requires C, 49·4; H, 5·7; N, 13·3%).

Reaction of 1-p-*Chlorophenyl*-2-*ethyl*-5-iso*propyl*-2-iso*dithiobiuret with Ammonia and Mercuric Oxide.*—The preceding compound (2·55 g.), mercuric oxide (7·1 g.), and saturated alcoholic ammonia (50 c.c.) were stirred together at 30—35° for 20 hours. The mixture was then filtered and evaporated to dryness under diminished pressure. The residue was extracted with hot 2N-hydrochloric acid, and the extract filtered from a little insoluble matter and made faintly alkaline to brilliant-yellow with ammonia. Addition of a little salt induced separation of the product, which was collected, crystallised from water, and identified as N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride, m. p. and mixed m. p. 243—244°.

1-p-*Chlorophenyl*-2: 4-*diethyl*-5-iso*propyl*-2: 4-*di*iso*dithiobiuret* (VII; R = Cl, R′ = Pr^i).—A solution of 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret (6·3 g.) in alcohol (75 c.c.) was treated with ethyl iodide (6·24 g.) and the mixture kept for 4 days. It was then warmed until homogeneous, more ethyl iodide (6·24 g.) and alcohol (25 c.c.) added, and the whole set aside for a further 24 hours and then evaporated to dryness under diminished pressure. The residue solidified on standing overnight and was crystallised from alcohol–ether to give 1-p-*chlorophenyl*-2: 4-*diethyl*-5-iso*propyl*-2: 4-*di*iso*dithiobiuret hydriodide* as colourless prisms, m. p. 134—136° (Found: C, 37·9; H, 4·5; N, 9·4. $C_{15}H_{22}N_3ClS,HI$ requires C, 38·2; H, 4·9; N, 8·9%) (6595).

The corresponding base liberated from the hydriodide by stirring with sodium carbonate solution and isolated by extraction with ether formed a low-melting (*ca.* 40°) solid.

3-p-*Chloroanilino*-5-iso*propylamino*-1: 2: 4-*triazole* (VIII; R = Cl, R′ = Pr^i).—The above base (2·75 g.) was dissolved in alcohol (20 c.c.), hydrazine hydrate (2·2 c.c.) added, and the mixture heated under reflux for 4 hours. The *triazole* which separated on cooling and dilution with water was collected and crystallised from benzene; colourless laminæ, m. p. 162—164° (Found: C, 52·5; H, 5·5; N, 27·4. $C_{11}H_{14}N_5Cl$ requires C, 52·5; H, 5·6; N, 27·8%) (6488).

3-p-*Chloroanilino*-5-*methylamino*-1: 2: 4-*triazole.*—1-*p*-Chlorophenyl-5-methyl-4-ethyl-4-*iso*dithiobiuret was treated with ethyl iodide in alcohol as described above to give 1-*p*-chlorophenyl-5-methyl-2: 4-diethyl-2: 4-di*iso*dithiobiuret as an oil. This oil (8·58 g.) was boiled under reflux for 4 hours with alcohol (50 c.c.) containing hydrazine hydrate (7·9 c.c. of 35%). The product, which separated on cooling, was collected and crystallised from aqueous 2-ethoxyethanol to give the *triazole* as colourless elongated prisms, m. p. 261—263° (Found: C, 48·4; H, 4·6; N, 30·9. $C_9H_{10}N_5Cl$ requires C, 48·3; H, 4·5; N, 31·3%) (6442).

3-p-*Chloroanilino*-5-*ethylamino*-1: 2: 4-*triazole*, prepared similarly from 1-*p*-chlorophenyl-4: 5-diethyl-4-*iso*dithiobiuret by *S*-ethylation followed by reaction with hydrazine, crystallised from aqueous 2-ethoxyethanol as colourless elongated flat prisms, m. p. 228—230° (Found: C, 50·5; H, 4·7; N, 29·2. $C_{10}H_{12}N_5Cl$ requires C, 50·5; H, 5·1; N, 29·5%) (6588).

3-p-*Chloroanilino*-5-n-*butylamino*-1: 2: 4-*triazole*, similarly prepared from 1-*p*-chlorophenyl-4-ethyl-

5-*n*-butyl-4-*iso*dithiobiuret, separated from alcohol in the form of elongated flat prisms, m. p. 196—198° (Found : C, 54·1; H, 5·7; N, 26·7. $C_{12}H_{16}N_5Cl$ requires C, 54·2; H, 6·1; N, 26·4%) (6614).

3-p-*Bromoanilino*-5-iso*propylamino*-1 : 2 : 4-*triazole*, likewise synthesised from 1-*p*-bromophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret, crystallised from chlorobenzene as colourless prisms, m. p. 154—156° (Found : C, 45·0; H, 4·7; N, 23·4. $C_{11}H_{14}N_5Br$ requires C, 44·6; H, 4·8; N, 23·6%) (6626).

1-p-*Chlorophenyl*-4 : 5-*diethyl*-4-iso*thiobiuret* (IX; R = R′ = Et).—A solution of potassium hydroxide (3·7 g.) in water (20 c.c.) was added to a solution of *NS*-diethyl*iso*thiourea hydrobromide (15·16 g.) in water (80 c.c.), and the mixture extracted with ether. To the dried ethereal solution a solution of *p*-chlorophenyl *iso*cyanate (9·2 g.) in ether (50 c.c.) was added. When the ensuing reaction was complete the solvent was evaporated off, and the residue crystallised from light petroleum (b. p. 80—100°) to give the *thiobiuret* as colourless elongated prisms, m. p. 122—124° (Found : C, 50·2; H, 5·4; N, 15·3. $C_{12}H_{16}ON_3ClS$ requires C, 50·4; H, 5·6; N, 14·7%) (6427).

The 4-*ethyl*-5-iso*propyl* analogue, prepared similarly from *p*-chlorophenyl *iso*cyanate and *S*-ethyl-*N*-iso*propyliso*thiourea hydrobromide, separated from light petroleum (b. p. 80—100°) as colourless thin prisms, m. p. 132° (Found : C, 51·5; H, 5·8; N, 13·9. $C_{13}H_{18}ON_3ClS$ requires C, 52·1; H, 6·0; N, 14·0%) (6408).

1-p-*Chlorophenyl*-5-*ethyl*-4-*thiobiuret* (X; R = Et).—Sodium (0·9 g.) was dissolved in alcohol (50 c.c.), and hydrogen sulphide passed through the mixture until the gain in weight was 1·4 g. The resulting solution was added to a suspension of (IX; R = R′ = Et) (6 g.) in alcohol (50 c.c.), and the mixture boiled under reflux for 1 hour with the passage of hydrogen sulphide. The resulting solution was carbon-treated, filtered, and acidified with acetic acid. Addition of water precipitated the *thiobiuret*, which was collected, washed with water, dried, and crystallised from chlorobenzene; colourless flat needles, m. p. 184° (efferv.) (Found, in material dried in a vacuum at 80° : C, 46·3; H, 4·8; N, 16·3. $C_{10}H_{12}ON_3ClS$ requires C, 46·6; H, 4·7; N, 16·3%) (6949).

1-p-*Chlorophenyl*-5-iso*propyl*-4-*thiobiuret*, similarly prepared from (IX; R = Pr^i, R′ = Et (by thiohydrolysis, separated from benzene as colourless flat needles, m. p. 176—178° (Found : N, 15·5. $C_{11}H_{14}ON_3ClS$ requires N, 15·5%) (8607).

Reaction of 1-p-*Chlorophenyl*-5-iso*propyl*-4-*thiobiuret with Ammonia and Mercuric Oxide*.—The preceding compound (1·36 g.), mercuric oxide (4·3 g.), and saturated alcoholic ammonia (100 c.c.) were stirred together at 30—35° for 2 hours. After standing overnight, the mixture was filtered and evaporated to dryness. The solid residue crystallised from benzene to give *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylurea, m. p. 130—132° undepressed in admixture with material prepared as described in the preceding paper.

Reaction of 1-p-*Chlorophenyl*-5-iso*propyl*-4-*thiobiuret with Methanol and Mercuric Oxide*.—A mixture of (X; R = Pr^i) (1·2 g.), mercuric oxide (2·1 g.), and methanol (100 c.c.) was boiled under reflux for 1 hour, then filtered hot, and the filtrate evaporated to dryness. The residue crystallised from aqueous methanol to give 1-*p*-chlorophenyl-4-methyl-5-*iso*propyl-4-*iso*biuret, m. p. 82—84° undepressed in admixture with authentic material (Part XLII).

1 : 5-*Di*-p-*chlorophenyl*-4-*methyl*-4-iso-2-*thiobiuret* (XI; R = H, R′ = C_6H_4Cl-*p*).—*p*-Chlorophenyl-*iso*thiocyanate (5·1 g.), dissolved in ether (25 c.c.), was added to a solution of *N*-*p*-chlorophenyl-*O*-methyl*iso*urea (5·5 g.) in ether (25 c.c.), and the whole kept for 3 days; light petroleum (b. p. 40—60°) was then added, and the precipitated solid filtered off. The mother-liquors were evaporated to dryness, leaving a solid residue. The combined solids were crystallised from benzene–light petroleum (b. p. 60—80°) to give the *thiobiuret* as colourless prisms, m. p. 143—145° (Found : C, 51·1; H, 3·6; N, 12·0. $C_{15}H_{13}ON_3Cl_2S$ requires C, 50·85; H, 3·7; N, 11·9%) (6441).

1-p-*Chlorophenyl*-4 : 5-*dimethyl*-5-iso*propyl*-4-iso-2-*thiobiuret*.—p-Chlorophenyl *iso*thiocyanate (5·1 g.), *ON*-dimethyl-*N*-*iso*propyl*iso*urea (3·9 g.), and water (25 c.c.) were mixed and warmed on the steam-bath for 10 minutes. After standing overnight, the solid product was collected, washed with water, and dried. Crystallisation from benzene gave the *thiobiuret* as minute colourless prisms, m. p. 147° (Found : C, 52·3; H, 6·1; N, 14·4. $C_{13}H_{18}ON_3ClS$ requires C, 52·1; H, 6·0; N, 14·0%) (6374).

O-*Methyl*-NN-*di*-n-*butyliso*urea.—Sodium (8·5 g.) was dissolved in dry methanol (125 c.c.), di-*n*-butylcyanamide (52 g.) added, and the mixture stirred at 50—60° for 2 hours. After cooling and dilution with water, hydrochloric acid was added to render the solution just acid, and the mixture extracted with ether. The aqueous layer was made alkaline with sodium hydroxide, and the precipitated product extracted with benzene. Evaporation of the dried (K_2CO_3) benzene extract then gave O-*methyl*-NN-*di*-n-*butyliso*urea as a colourless oil, b. p. 122°/18 mm. (Found : N, 15·2. $C_{10}H_{22}ON_2$ requires N, 15·0%).

1-p-*Chlorophenyl*-4-*methyl*-5 : 5-*di*-n-*butyl*-4-iso-2-*thiobiuret* (XI; R = R′ = Bu^n), prepared as described for 6374 from *p*-chlorophenyl *iso*thiocyanate and *O*-methyl-*NN*-di-*n*-butyl*iso*urea, crystallised from alcohol as colourless parallelepipeds, m. p. 124—126° (Found : C, 57·4; H, 7·3; N, 12·1. $C_{17}H_{26}ON_3ClS$ requires C, 57·4; H, 7·4; N, 11·8%) (6314).

The *monobutyl* analogue, prepared similarly from *p*-chlorophenyl *iso*thiocyanate and *O*-methyl-*N*-*n*-butyl*iso*urea, crystallised from light petroleum (b. p. 80—100°) as colourless prisms, m. p. 94—96° (Found : C, 52·4; H, 6·1; N, 14·0. $C_{13}H_{18}ON_3ClS$ requires C, 52·1; H, 6·0; N, 14·0%) (6357).

1 : 5-*Di*-p-*chlorophenyl*-4-*methyl*-4-iso*thiobiuret* (IX; R = C_6H_4Cl-*p*, R′ = Me).—*p*-Chlorophenyl *iso*cyanate (7·67 g.), dissolved in ether (25 c.c.), was added to a solution of *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (10·02 g.) in ether (20 c.c.). Heat was evolved, and on standing a crystalline product separated. Collected and crystallised from benzene, this *thiobiuret* formed colourless thin prisms, m. p. 139—140° (Found : C, 50·7; H, 3·6; N, 11·8. $C_{15}H_{13}ON_3Cl_2S$ requires C, 50·85; H, 3·7; N, 11·9%) (6409).

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