617. *Dithiobiurets. Part III.*[1] 1,1-*Disubstituted Derivatives.*

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Methods for the preparation of 1,1-disubstituted dithiobiurets, particularly 1,1-diaryl derivatives, are described.

SINCE 1-alkyl-1-aryl derivatives were the most effective of the dithiobiurets tested by Woolfe[2] against *Trypanosoma congolense* in mice, a more extensive examination of this type was considered desirable. A particular objective was the synthesis of 1,1-diaryldithiobiurets, since it had been observed that 5-benzoyl-1,1-diphenyldithiobiuret was considerably more active than 5-benzoyl-1-methyl-1-phenyldithiobiuret. It therefore appeared possible that 1,1-diphenyldithiobiuret would be correspondingly more active than 1-methyl-1-phenyldithiobiuret.

A number of 1-alkyl-1-aryldithiobiurets and a few 1-aryldithiobiurets were prepared by fusion of the corresponding arylamine with 3-imino-5-thiono-1,2,4-dithiazolidine (" isoperthiocyanic acid ").[3] Where applicable, the method provided easy access to the required compounds but yields were generally low and variable and the method failed altogether with weakly basic amines including diphenylamine. More general methods were therefore sought.

By heating cyanoiminobismethylthiomethane (I) with anilines Nirenburg and his co-workers[4] obtained *N*-aryl-*N'*-cyano-*S*-methylisothioureas (II), thiohydrolysis of which should afford the dithiobiuret. An investigation of this reaction showed that, where applicable, it provided a simple synthesis of 1-aryldithiobiurets but that it was even less general than the isoperthiocyanic acid route, failing completely with secondary amines.

(I) $(MeS)_2C{:}N{\cdot}CN$ $\quad$ $Ar{\cdot}NH{\cdot}C(SMe){:}N{\cdot}CN$ (II)

The method of Wunderlich[5] and Hecht,[6] involving isothiocyanates and sodium

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[1] Part II, Fairfull and Peak, *J.*, 1955, 803.
[2] Woolfe, *Brit. J. Pharmacol.*, 1953, **8**, 420.
[3] Fairfull and Peak, *J.*, 1955, 796.
[4] Nirenburg, Postovskii, and Cherkasov, *J. Gen. Chem. U.S.S.R.*, 1958, **28**, 198.
[5] Wunderlich, *Ber.*, 1886, **19**, 448.
[6] Hecht, *Ber.*, 1892, **25**, 749.

cyanamide, leads only to 1-monosubstituted dithiobiurets. Adaptation of this to the preparation of 1,1-disubstituted dithiobiurets was sought by the use of *NN*-disubstituted thiocarbamoyl chlorides instead of isothiocyanates. Even in the presence of a considerable excess of sodium cyanamide, two molecules of the thiocarbamoyl chloride invariably condensed with one molecule of cyanamide. Thiohydrolysis of the product under mild conditions resulted in the loss of one thiocarbamoyl residue and the formation of the required 1,1-disubstituted dithiobiuret. Although spectroscopic evidence of the

(III) RR′N·C(S·CS·NRR′):N·CN $\qquad$ $(RR'N{\cdot}CS)_2N{\cdot}CN$ (IV)

structure of the intermediate product was inconclusive, the ready fission of the thiocarbamoyl residue is regarded as favouring structure (III) rather than (IV). Fair yields of dithiobiuret were obtained in certain cases but in others thiuram sulphides were obtained as major, or even exclusive, products and the method was abandoned in favour of the more consistent method described below.

Benzoyl isothiocyanate has been used extensively for the preparation of thioureas from amines[7] and this type of synthesis has now been extended to *NN*-disubstituted isothioureas. Thus, benzoyl isothiocyanate was condensed with *NS*-dimethyl-*N*-phenylisothiourea to give 5-benzoyl-1,2-dimethyl-1-phenyl-2-isodithiobiuret, thiohydrolysis of which afforded 5-benzoyl-1-methyl-1-phenyldithiobiuret. Some difficulty was experienced in removal of the benzoyl radicle without rupture of the dithiobiuret chain but brief heating with aqueous alkali was found to be effective. 3-Benzoylimino-5-(*N*-methyl-*N*-phenylimino)-1,2,4-dithiazole is formed as a by-product during the thiohydrolysis stage. Its identity was proved by its preparation (*a*) by oxidation of 5-benzoyl-1-methyl-1-phenyldithiobiuret with iodine and (*b*) by benzoylation of 3-amino-5-(*N*-methylanilino)-1,2,4-dithiazole.[8]

The method appears to be general for 1-alkyl-1-aryl- or 1,1-diaryldithiobiurets. It fails with 1-monosubstituted dithiobiurets since the intermediate benzoylisodithiobiuret cyclises to a triazine with elimination of water.[9]

Acetyl isothiocyanate can be used instead of benzoyl isothiocyanate but offers no advantage.

None of the dithiobiurets, including the 1,1-diaryl derivatives, had greater biological activity than analogues known before. Further substitution by aryl or alkyl in the 5-position had no beneficial effect.

EXPERIMENTAL

Syntheses from Amines and Isoperthiocyanic Acid.—The following *dithiobiurets* were prepared by the procedure described by Fairfull and Peak [3] (times of heating and yields in parentheses), and crystallised from ethanol: 1-(2,6-*dimethylphenyl*)- (2·5 hr., 10%), prisms, m. p. 179—180° (Found: C, 50·1; H, 5·4. $C_{10}H_{13}N_3S_2$ requires C, 50·2; H, 5·45%); 1-(2,5-*dimethoxyphenyl*)- (1 hr., 40%), prisms, m. p. 145—146° (Found: C, 44·6; H, 4·9. $C_{10}H_{13}N_3O_2S_2$ requires C, 44·3; H, 4·8%); 1-*methyl*-1-p-*tolyl*- (1 hr., 22%), prisms, m. p. 157—158° * (Found: C, 50·2; H, 5·6; N, 17·6; S, 26·4. $C_{10}H_{13}N_3S_2$ requires C, 50·2; H, 5·45; N, 17·6; S, 26·7%); 1-*ethyl*-1-p-*tolyl*- (1·5 hr., 32%), prisms, m. p. 156—157° (Found: C, 52·1; H, 5·9. $C_{11}H_{15}N_3S_2$ requires C, 52·2; H, 5·9%); 1-*benzyl*-1-p-*tolyl*- (2 hr., 5%), fine needles, m. p. 140—141° (Found: C, 60·9; H, 5·2. $C_{16}H_{17}N_3S_2$ requires C, 60·8; H, 5·4%); 1-*ethyl*-1-o-*tolyl*- (2 hr., 24%), prisms, m. p. 147—148° (Found: C, 52·6; H, 5·8; S, 25·0. $C_{11}H_{15}N_3S_2$ requires C, 52·2; H, 5·9; S, 25·3%); 1-p-*hydroxyphenyl*-1-*methyl*- (45 min., 41%), prisms, m. p. 174—175° (Found: C, 45·3; H, 4·3; S, 26·3. $C_9H_{11}N_3OS_2$ requires C, 44·8; H, 4·6; S, 26·6%); 1-p-*methoxyphenyl*-1-*methyl*- (45 min., 58%), prisms, m. p. 141—142° (Found: C, 47·6; H, 5·0; N, 16·7.

* This result was confirmed by a preparation by a different method (see below) and the assignment of this structure by Underwood and Dains [10] to their compound, m. p. 236°, must be incorrect.

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[7] Douglass and Dains, *J. Amer. Chem. Soc.*, 1934, **56**, 1408.

[8] Fromm and Junius, *Ber.*, 1895, **28**, 1096.

[9] Douglass and Dains, *J. Amer. Chem. Soc.*, 1934, **56**, 719.

[10] Underwood and Dains, *J. Amer. Chem. Soc.*, 1935, **57**, 1768.

$C_{10}H_{13}N_3OS_2$ requires C, 47·1; H, 5·1; N, 16·5%); 1-o-*methoxyphenyl*-1-*methyl*- (5 hr., 0·6%), prisms, m. p. 153—154° (Found: N, 16·4%); 1-(2,5-*dimethoxyphenyl*)-1-*methyl*- (1·5 hr., 6%), prisms, m. p. 137—138° (Found: C, 46·4; H, 5·2. $C_{11}H_{15}N_3O_2S_2$ requires C, 46·3; H, 5·3%); 1-p-*dimethylaminophenyl*-1-*methyl*- (15 min., 28%), prisms, m. p. 156° (Found: C, 49·6; H, 6·3; N, 21·1; S, 23·8. $C_{11}H_{16}N_4S_2$ requires C, 49·2; H, 6·0; N, 20·9; S, 23·9%).

Many amines, notably *N*-methyl-*p*-nitroaniline, *N*-methyl-*m*-trifluoromethylaniline, and diphenylamine failed to yield any dithiobiuret.

N′-*Cyano*-S-*methylisothioureas from Amines and Cyanoiminobismethylthiomethane*.—Equivalent amounts of the amine and cyanoiminobismethylthiomethane were heated on the steam-bath for 20—30 min. with some ethanol. Crystals of the product were obtained on cooling and purified by recrystallisation from ethanol. In this way the following *N*′-cyano-*S*-methylisothioureas were prepared (yields in parentheses): *N*-phenyl- (55%), prisms, m. p. 191—192°; *N*-*p*-tolyl- (60%), prisms, m. p. 150—151°; *N*-*p*-methoxyphenyl- (70%), prisms, m. p. 184—185°; N-m-*chlorophenyl*- (18%), prisms, m. p. 173—174° (Found: N, 18·5; S, 14·3. $C_9H_8ClN_3S$ requires N, 18·6; S, 14·2%); N-(2,5-*dimethoxyphenyl*)- (47%), prisms, m. p. 165—166° (Found: S, 12·7. $C_{11}H_{13}N_3O_2S_2$ requires S, 12·7%).

p-Nitroaniline, *m*-trifluoromethylaniline, 2,6-dibromoaniline, methylaniline, and diphenylamine failed to react.

In the one case tried, thiohydrolysis of *N*-cyano-*S*-methyl-*N*′-*p*-tolyl-isothiourea gave a 77% yield of 1-p-tolyldithiobiuret, identified by m. p. and mixed m. p.

Syntheses from Thiocarbamoyl Chlorides and Sodium Cyanamide.—The thiocarbamoyl chlorides were prepared as described by von Braun [11] and Cambron.[12]

A suspension of *N*-ethyl-*N*-phenylthiocarbamoyl chloride (5 g.) in methanol (25 ml.) was added to a solution of sodium cyanamide, prepared by adding cyanamide (1·2 g.) to a cold solution from sodium (0·6 g.) in methanol (20 ml.), and the mixture was shaken for a few minutes. The thiocarbamoyl chloride dissolved, the solution became yellow, and a solid began to separate. Next day the product, N-*cyano*-N′-*ethyl*-S-(N-*ethyl*-N-*phenylthiocarbamoyl*)-N′-*phenylisothiourea*, was filtered off, washed with water to remove salt, and dried (3·53 g., 80%; m. p. 159—160°). Recrystallisation from ethanol gave yellow prisms, m. p. 161° (Found: C, 61·9; H, 5·3; N, 15·0; S, 17·5. $C_{19}H_{20}N_4S_2$ requires C, 62·0; H, 5·4; N, 15·2; S, 17·4%).

This compound (4 g.) was dissolved in pyridine (40 ml.) and triethylamine (8 ml.) and treated with hydrogen sulphide overnight. Dilution with ice-water (500 ml.) gave 1-ethyl-1-phenyldithiobiuret (2·0 g., 77%), m. p. 124—125°. Recrystallisation from ethanol afforded needles, m. p. 128—129° (Found: N, 17·9. Calc. for $C_{10}H_{13}N_3S_2$: N, 17·6%). Identity was confirmed by mixed m. p. and by comparison of infrared spectra.

Similarly, *N*-methyl-*N*-phenylthiocarbamoyl chloride and sodium cyanamide yielded N-*cyano*-N′-*methyl*-S-(N-*methyl*-N-*phenylthiocarbamoyl*)-N-*phenylisothiourea*. In this case the product (52%) was precipitated from the methanol solution by ether (2 vol.). Recrystallisation from ethanol gave yellow prisms, m. p. 161—162° (Found: C, 60·3; H, 5·0; N, 16·4. $C_{17}H_{16}N_4S_2$ requires C, 60·0; H, 4·7; N, 16·5%). Thiohydrolysis in pyridine–triethylamine gave 1-methyl-1-phenyldithiobiuret (80%).

Dilution of the reaction mixture of *N*-ethyl-*N*-*o*-tolylthiocarbamoyl chloride and sodium cyanamide with water gave N-*cyano*-N′-*ethyl*-S-(N-*ethyl*-N-o-*tolylthiocarbamoyl*)-N′-o-*tolylisothiourea* as an oil which crystallised from toluene–light petroleum as prisms, m. p. 116—117° (Found: C, 63·4; H, 6·0. $C_{21}H_{24}N_4S_2$ requires C, 63·6; H, 6·1%). Thiohydrolysis of the crude oil gave 1-ethyl-1-*o*-tolyldithiobiuret (70% overall yield), prisms (from ethanol), m. p. and mixed m. p. 147—148°.

N-Methyl-*N*-*p*-tolylthiocarbamoyl chloride in the same way gave N-*cyano*-N′-*methyl*-S-(N-*methyl*-N-p-*tolylthiocarbamoyl*)-N′-p-*tolylisothiourea* as an oil which crystallised from toluene–light petroleum in needles, m. p. 138—139° (Found: C, 61·7; H, 5·2. $C_{19}H_{20}N_4S_2$ requires C, 62·0; H, 5·4%). Thiohydrolysis of the crude oil gave 1-methyl-1-*p*-tolyldithiobiuret, prisms, m. p. and mixed m. p. 157—158°. A by-product which separated from the original reaction mixture proved to be *NN*′-dimethyl-*NN*′-di-*p*-tolylthiuram sulphide, yellow prisms, m. p. 147—148° after crystallisation first from toluene–light petroleum and then from ethanol (Found: C, 60·3; H, 5·7. Calc. for $C_{18}H_{20}N_2S_3$: C, 60·0; H, 5·6%). Cambron [12] records m. p. 144°.

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[11] von Braun, *Ber.*, 1903, **36**, 2259.
[12] Cambron, *Canad. J. Res.*, 1930, **2**, 341.

In the case of *N*-methyl-*N*-*p*-nitrophenylthiocarbamoyl chloride the solid (m. p. *ca.* 184°) which separated from the reaction mixture was thiohydrolysed without purification. Crystallisation of the resulting yellow solid from ethanol yielded needles, m. p. 151—152°, identified as *N*-methyl-*p*-nitroaniline. Dilution of the ethanolic mother-liquor with sodium hydroxide solution and precipitation with hydrogen sulphide gave 1-p-*aminophenyl*-1-*methyldithiobiuret*, prisms (from ethanol), m. p. 166—167° (Found: C, 44·9; H, 5·1; N, 23·5. $C_9H_{12}N_4S_2$ requires C, 45·0; H, 5·0; N, 23·3%).

With *N*-*p*-chlorophenyl-*N*-methylthiocarbamoyl chloride the solid which separated from the reaction mixture proved to be NN′-*di*-p-*chlorophenyl*-NN′-*dimethylthiuram sulphide*, yellow needles (from ethanol), m. p. 171° (Found: S, 23·7. $C_{16}H_{14}Cl_2N_2S_3$ requires S, 23·9%). The oil obtained on dilution of the methanolic filtrate failed to give any dithiobiuret after thiohydrolysis.

Syntheses from Benzoyl Isothiocyanate and Isothioureas.—1-*Methyl*-1-*phenyldithiobiuret.* *S*-Ethyl-*N*-methyl-*N*-phenylthiouronium iodide (25 g.), m. p. 138°, from *N*-methyl-*N*-phenylthiourea and ethyl iodide, was covered with ether, and then an excess of potassium carbonate solution was added. The ether layer was washed with water and dried (Na_2SO_4), and benzoyl isothiocyanate (12·5 g.) was added. Next day, the 5-*benzoyl*-2-*ethyl*-1-*methyl*-1-*phenyl*-2-*isodithiobiuret* (24 g., 86%) which had separated as yellow prisms, m. p. 107—108°, was filtered off. Recrystallisation from chloroform–ether did not raise the m. p. (Found: C, 60·7; H, 5·4; N, 11·8. $C_{18}H_{19}N_3OS_2$ requires C, 60·5; H, 5·3; N, 11·8%).

A solution of the isodithiobiuret (15·3 g.) in pyridine (85 ml.) and triethylamine (8·5 ml.) was treated with hydrogen sulphide overnight, then poured into water (2 l.), and the solid product (10 g., 71%) was collected. Crystallisation from chloroform–ether gave 5-*benzoyl*-1-*methyl*-1-*phenyldithiobiuret* as yellow prisms, m. p. 133° (Found: C, 58·6; H, 4·8; N, 12·9. $C_{16}H_{15}N_3OS_2$ requires C, 58·4; H, 4·6; N, 12·8%). Evaporation of the mother-liquor and recrystallisation of the residue from methanol yielded 3-*benzoylimino*-5-*methylphenylamino*-1,2,4-*dithiazole* (2·7 g.) as colourless needles, m. p. 213—214° (Found: C, 59·2; H, 4·0; N, 13·1; S, 19·6. $C_{16}H_{13}N_3OS_2$ requires C, 58·7; H, 4·0; N, 12·9; S, 19·6%).

The dithiazole was also obtained when 5-benzoyl-1-methyl-1-phenyldithiobiuret (3·3 g.) in hot ethanol (150 ml.) was treated with an excess of iodine (2·6 g.). Precipitation with water and recrystallisation from ethanol gave the dithiazole (2·3 g.) as needles, m. p. 213—214° (Found: C, 58·5; H, 4·2; S, 19·6%).

Alternatively, 3-imino-5-methylphenylamino-1,2,4-dithiazole hydriodide[8] (0·406 g.) in pyridine (3 ml.) was treated with benzoyl chloride (0·285 g.). Next day ethanol (25 ml.) was added, the mixture heated to the b. p., filtered, and cooled. 3-Benzoylimino-5-methylphenylamino-1,2,4-dithiazole (0·3 g.), m. p. 213—214°, separated.

5-Benzoyl-1-methyl-1-phenyldithiobiuret (4·9 g.) was boiled for 5 min. with 10% sodium hydroxide solution (35 ml.), and the mixture was cooled, neutralised with 6N-hydrochloric acid, and made slightly alkaline with ammonia. The product (2·5 g., 75%), m. p. 147—148°, recrystallised from ethanol, afforded 1-methyl-1-phenyldithiobiuret as needles, m. p. 156—157°. The infrared spectrum confirmed its identity.

5-Benzoyl-1-methyl-1-phenyldithiobiuret was alternatively obtained by conversion of *NS*-dimethyl-*N*-phenylthiouronium iodide (75 g.) into the free base and condensation with benzoyl isothiocyanate (34·5 g.) in acetone (350 ml.) overnight. Next morning the precipitated 5-*benzoyl*-1,2-*dimethyl*-1-*phenyl*-2-*isodithiobiuret* (48 g., 66%; m. p. 120—126°) was collected. A portion of the product was crystallised from chloroform–ether, separating as pale yellow prisms, m. p. 124—125° (Found: C, 59·6; H, 5·3; N, 12·5. $C_{17}H_{17}N_3OS_2$ requires C, 59·5; H, 5·0; N, 12·2%). Thiohydrolysis of the crude isodithiobiuret (25 g.) afforded 5-benzoyl-1-methyl-1-phenyldithiobiuret (14·9 g., 62%), m. p. and mixed m. p. 133—134°.

1,1-*Diphenyldithiobiuret.* *NN*-Diphenylthiourea was converted into *S*-methyl-*NN*-diphenylthiouronium iodide, m. p. 166° (from ethanol–ether) (Found: I, 34·3. Calc. for $C_{14}H_{15}IN_2S$: I, 34·3%). Beals and Brown[13] record m. p. 159—160°. The iodide (17 g.) was converted into the free base and condensed with benzoyl isothiocyanate as previously, affording 5-*benzoyl*-2-*methyl*-1,1-*diphenyl*-2-*isodithiobiuret* (17·35 g., 93%), yellow prisms (from chloroform–ether), m. p. 153° (Found: C, 65·4; H, 5·1; N, 10·4. $C_{22}H_{19}N_3OS_2$ requires C, 65·1; H, 4·7; N, 10·4%). Thiohydrolysis of the foregoing (10 g.) and crystallisation from chloroform–ether gave 5-*benzoyl*-1,1-*diphenyldithiobiuret* (3·5 g., 36%), m. p. 141° raised to

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[13] Beals and Brown, *Canad. J. Chem.*, 1956, **34**, 1408.

144—145° by recrystallisation from methanol (Found: C, 64·8; H, 4·5. $C_{21}H_{17}N_3S_2$ requires C, 64·4; H, 4·4%).

The residues from the chloroform–ether mother-liquor crystallised from methanol to give 3-*benzoylimino*-5-*diphenylamino*-1,2,4-*dithiazole* as colourless prisms, m. p. 229—230° (Found: C, 64·8; H, 4·0; N, 11·1. $C_{21}H_{15}N_3OS_2$ requires C, 64·8; H, 3·9; N, 10·8%).

5-Benzoyl-1,1-diphenyldithiobiuret (2 g.) was boiled for 2 min. with 10% sodium hydroxide solution (40 ml.), cooled, and diluted to 200 ml., and the solution was filtered through Celite. Hydrogen sulphide precipitated 1,1-*diphenyldithiobiuret* (1·06 g., 70%), colourless prisms (from ethanol), m. p. 157—158° (Found: C, 58·5; H, 4·3; N, 14·6; S, 22·0. $C_{14}H_{13}N_3S_2$ requires C, 58·5; H, 4·5; N, 14·6; S, 22·3%).

1-o-*Methoxyphenyl*-1-*phenyldithiobiuret*. Benzoyl isothiocyanate (25·6 g.) and 2-methoxydiphenylamine (31·4 g.) in benzene (150 ml.) yielded N′-*benzoyl*-N-o-*methoxyphenyl*-N-*phenylthiourea* as yellow prisms (82%), m. p. 134° (from ethanol) (Found: N, 7·9; S, 9·0. $C_{21}H_{18}N_2O_2S$ requires N, 7·7; S, 8·8%). Heating under reflux with a solution of sodium hydroxide (6 g.) in ethanol (150 ml.) for 4 hr., dilution with water, and recrystallisation of the product from ethanol gave N-o-*methoxyphenyl*-N-*phenylthiourea* (75%) as colourless needles, m. p. 185° (Found: N, 11·1. $C_{14}H_{14}N_2OS$ requires N, 10·85%).

The thiourea (18·7 g.) in acetone (125 ml.) was heated under reflux with methyl iodide (10 ml.) for 4 hr. On cooling, N-o-*methoxyphenyl*-S-*methyl*-N-*phenylthiouronium iodide* (27·6 g., 95%; m. p. 195—208°) separated. A portion crystallised from ethanol–ether had m. p. 208—209° (Found: I, 31·9. $C_{15}H_{17}IN_2OS$ requires I, 31·75%).

The iodide (26·25 g.) was converted into the free base in the usual way and condensed with benzoyl isothiocyanate (10·5 g.) in ether (400 ml.). The 5-*benzoyl*-1-o-*methoxyphenyl*-2-*methyl*-1-*phenyl*-2-*isodithiobiuret* which separated (27·4 g., 96%) recrystallised from methanol in pale yellow needles, m. p. 102—103° (Found: N, 9·7. $C_{23}H_{21}N_3O_2S_2$ requires N, 9·65%).

Thiohydrolysis of the foregoing material (20 g.) and recrystallisation of the crude product from chloroform–ether afforded 5-*benzoyl*-1-o-*methoxyphenyl*-1-*phenyldithiobiuret* (9·8 g., 51%) as yellow prisms, m. p. 141—142° raised by further recrystallisation to 144—145° (Found: C, 63·0; H, 4·3; N, 10·4; S, 14·7. $C_{22}H_{19}N_3O_2S_2$ requires C, 62·7; H, 4·5; N, 10·0; S, 15·2%). The residue from the chloroform–ether mother-liquor crystallised from toluene, affording 3-*benzoylimino*-5-o-*methoxyphenylamino*-1,2,4-*dithiazole* as colourless prisms, m. p. 190—191° (Found: C, 63·5; H, 4·1. $C_{22}H_{17}N_3O_2S_2$ requires C, 63·0; H, 4·1%).

Hydrolysis of the benzoyldithiobiuret with boiling 10% sodium hydroxide solution for 2·5 min. and precipitation of the product with hydrogen sulphide gave 1-o-*methoxyphenyl*-1-*phenyldithiobiuret* (42%), colourless prisms (from ethanol), m. p. 148—149° (Found: C, 56·9; H, 4·7; N, 13·3; S, 20·2. $C_{15}H_{15}N_3OS_2$ required C, 56·8; H, 4·7; N, 13·25; S, 20·2%).

1-p-*Methoxyphenyl*-1-*phenyldithiobiuret*. In the same way 4-methoxydiphenylamine was converted into N′-*benzoyl*-N-p-*methoxyphenyl*-N-*phenylthiourea*, m. p. 149—150° (Found: N, 7·9. $C_{21}H_{18}N_2O_2S$ requires N, 7·7%), and thence into N-p-*methoxyphenyl*-N-*phenylthiourea*, colourless needles (from ethanol), m. p. 179—180° (Found: N, 11·2; S, 12·4. $C_{14}H_{14}N_2OS$ requires N, 10·85; S, 12·4%). The derived thiouronium iodide was converted, without purification, into the free base and condensed in ether with benzoyl isothiocyanate, to give 5-*benzoyl*-1-p-*methoxyphenyl*-2-*methyl*-1-*phenyl*-2-*isodithiobiuret* (80% from the thiourea), pale yellow prisms (from chloroform–ether), m. p. 144—145° (Found: C, 63·5; H, 5·0. $C_{23}H_{21}N_3O_2S_2$ requires C, 63·4; H, 4·8%).

A solution of the foregoing (10 g.) in pyridine (50 ml.) and triethylamine (10 ml.) was treated overnight with hydrogen sulphide. Half the mixture was poured into boiling 10% sodium hydroxide solution (120 ml.), boiled for 5 min., diluted with ice–water (1 l.), and filtered through Celite. Precipitation with hydrogen sulphide gave 1-p-*methoxyphenyl*-1-*phenyldithiobiuret* (1·15 g., 32%; m. p. 145—147°). Two recrystallisations from ethanol gave colourless prisms, m. p. 156—157° (Found: C, 57·2; H, 5·1; N, 13·4; S, 19·9. $C_{15}H_{15}N_3OS_2$ requires C, 56·8; H, 4·7; N, 13·25; S, 20·2%).

The other half of the mixture was poured into water, and the oily solid crystallised from chloroform–ether. The product (2·35 g., 49%; m. p. 207—211°) was recrystallised from ethanol, affording 3-*benzoylimino*-5-(p-*methoxydiphenylamino*)-1,2,4-*dithiazole* as colourless prisms, m. p. 213—214° (Found: C, 63·0; H, 4·0; N, 10·0. $C_{22}H_{17}N_3O_2S_2$ requires C, 63·0; H, 4·1; N, 10·0%).

1-p-*Isopropoxyphenyl*-1-*phenyldithiobiuret*. 4-Isopropoxydiphenylamine was converted into

1-p-*isopropoxyphenyl*-1-*phenylthiourea*, needles, m. p. 178—179° (Found: N, 9·9; S, 10·7. $C_{16}H_{18}N_2OS$ requires N, 9·8; S, 11·2%) and thence into N-*isopropoxyphenyl*-S-*methyl*-N-*phenylthiouronium iodide*, m. p. 174° (Found: I, 29·8. $C_{17}H_{21}IN_2OS$ requires I, 29·7%). The free base in ether with benzoyl isothiocyanate afforded 5-*benzoyl*-1-p-*isopropoxyphenyl*-2-*methyl*-1-*phenyl*-2-*isodithiobiuret* (92%), yellow prisms, m. p. 151° unchanged by recrystallisation from methanol (Found: C, 64·7; H, 5·5; S, 13·6. $C_{25}H_{25}N_3O_2S_2$ requires C, 64·7; H, 5·4; S, 13·8%), and this was thiohydrolysed as in the previous experiment. Alkaline hydrolysis of half the mixture afforded 1-p-*isopropoxyphenyl*-1-*phenyldithiobiuret*, colourless prisms (from ethanol), m. p. 146—147° (Found: C, 59·1; H, 5·8; S, 18·5. $C_{17}H_{19}N_3OS_2$ requires C, 59·1; H, 5·5; S, 18·55%).

The other half of the mixture was poured into dilute hydrochloric acid, and the product recrystallised from chloroform–ether. 5-*Benzoyl*-1-p-*isopropoxyphenyl*-1-*phenyldithiobiuret* (42%) separated as yellow prisms, m. p. 141°, raised to 143—144° by a further recrystallisation (Found: C, 63·9; H, 5·0; S, 14·3. $C_{24}H_{23}N_3O_2S_2$ requires C, 64·1; H, 5·1; S, 14·25%). The residue from the chloroform–ether mother-liquor was recrystallised from toluene, affording 3-*benzoylimino*-5-(p-*isopropoxydiphenylamino*)-1,2,4-*dithiazole* as colourless prisms, m. p. 215° (Found: C, 65·1; H, 4·9; S, 13·9. $C_{24}H_{21}N_3O_2S_2$ requires C, 64·5; H, 4·9; S, 14·3%).

1,1-*Di*-p-*ethoxyphenyldithiobiuret*. *pp′*-Diethoxydiphenylamine, plates, m. p. 95—96° (from light petroleum), was obtained from *p*-bromophenetole and phenacetin by the method of Goldberg [14] as modified by Smith [15] (Found: N, 5·45. Calc. for $C_{16}H_{19}NO_2$: N, 5·45%). It was converted into NN-*di*-p-*ethoxyphenylthiourea*, colourless needles (from ethanol), m. p. 144° (Found: S, 9·8. $C_{17}H_{20}N_2O_2S$ requires S, 10·1%) and thence in the usual manner into 5-*benzoyl*-1,1-*di*-p-*ethoxyphenyl*-2-*methyl*-2-*isodithiobiuret* (80%), yellow needles, m. p. 128° unchanged by recrystallisation from chloroform–ether (Found: S, 12·9. $C_{26}H_{27}N_3O_3S_2$ requires S, 13·0%). Thiohydrolysis followed by alkaline hydrolysis gave 1,1-*di*-p-*ethoxyphenyldithiobiuret* (39%), colourless prisms (from ethanol), m. p. 145° (Found: C, 57·9; H, 5·8. $C_{18}H_{21}N_3O_2S_2$ requires C, 57·6; H, 5·6%).

1-*Methyl*-1-m-*trifluoromethylphenyldithiobiuret*. *N*-Methyl-*m*-trifluoromethylaniline treated with hydrochloric acid and then potassium thiocyanate yielded N-*methyl*-N-m-*trifluoromethylphenylthiourea*, colourless needles (from ethanol), m. p. 121° (Found: N, 11·9; S, 14·2. $C_9H_9F_3N_2S$ requires N, 12·0; S, 13·7%). This was converted by the usual procedure, without purification of intermediates, into 1-*methyl*-1-m-*trifluoromethylphenyldithiobiuret* (39%), colourless plates (from ethanol), m. p. 156—157° (Found: N, 13·9; S, 21·8. $C_{10}H_{10}F_3N_3S_2$ requires N, 14·3; S, 21·8%).

Syntheses from Acetyl Isothiocyanate and Isothioureas.—(*a*) Acetyl chloride (7·2 ml.) in benzene (50 ml.) was refluxed for 2 hr. over lead thiocyanate (18 g.). The mixture was then filtered and the filtrate (30 ml.) added to a solution of *S*-methyl-*NN*-diphenylisothiourea (12 g.) in benzene (30 ml.). Some heat was evolved. On cooling, a solid (17 g.) separated. Recrystallisation from toluene (200 ml.) gave 5-*acetyl*-2-*methyl*-1,1-*diphenyl*-2-*isodithiobiuret* (5·6 g., 33%) as yellow needles, m. p. 134—135° (Found: C, 59·4; H, 5·1; N, 12·6; S, 18·7. $C_{17}H_{17}N_3OS_2$ requires C, 59·5; H, 5·0; N, 12·2; S, 18·65%). From the mother-liquor colourless crystals of S-*methyl*-NN-*diphenylthiouronium thiocyanate*, m. p. 143—144°, were obtained (Found: C, 61·1; H, 5·0; N, 14·0. $C_{15}H_{15}N_3S_2$ requires C, 59·8; H, 5·0; N, 14·0%); this gave the expected blood-red colour with aqueous ferric sulphate solution.

(*b*) Acetyl isothiocyanate [16] (25 g.) in ether (50 ml.) was added to a solution of *NS*-dimethyl-*N*-phenylisothiourea (45 g.) in ether (150 ml.). An oil separated which soon solidified. Crystallisation from toluene gave 5-*acetyl*-1,2-*dimethyl*-1-*phenyl*-2-*isodithiobiuret* (54 g., 76%) as yellow prisms, m. p. 135—136°, raised to 138—139° by recrystallisation from methanol (Found: C, 51·0; H, 5·3; N, 15·1. $C_{12}H_{15}N_3OS_2$ requires C, 51·3; H, 5·3; N, 14·9%). A by-product (0·67 g.), m. p. 174°, probably *NS*-dimethyl-*N*-phenylthiouronium thiocyanate, was also isolated.

A solution of the isodithiobiuret (5 g.) in pyridine (50 ml.) and triethylamine (15 ml.) was treated with hydrogen sulphide overnight, poured into boiling 10% sodium hydroxide solution (100 ml.), boiled for 4 min., diluted with ice–water, and filtered through Celite; the product was precipitated with hydrogen sulphide. Recrystallisation from ethanol yielded 1-methyl-1-phenyldithiobiuret (1·76 g., 44%), m. p. and mixed m. p. 155°.

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[14] Goldberg, *Ber.*, 1907, **40**, 4541.

[15] Smith, *J. Org. Chem.*, 1950, **15**, 1125.

[16] Miquel, *Ann. Chim.* (*France*), 1877, **11**, 295.

1,1,5-*Trisubstituted Dithiobiurets from Isothioureas and Isothiocyanates.*—An ethereal solution of *S*-methyl-*NN*-diphenylisothiourea, prepared from *S*-methyl-*NN*-diphenylthiouronium iodide and potassium carbonate solution, was caused to react with methyl, ethyl, and phenyl isothiocyanate, and the products were thiohydrolysed in pyridine–triethylamine. In this manner were prepared: 2,5-*dimethyl*-1,1-*diphenyl*-2-*isodithiobiuret*, prisms (from benzene–light petroleum), m. p. 97—98° (Found: S, 19·5. $C_{16}H_{17}N_3S_2$ requires S, 20·3%); 5-*methyl*-1,1-*diphenyldithiobiuret*, prisms (from benzene–light petroleum), m. p. 131° (Found: C, 60·1; H, 5·5; S, 21·4. $C_{15}H_{15}N_3S_2$ requires C, 59·8; H, 5·0; S, 21·25%); 5-*ethyl*-2-*methyl*-1,1-*diphenyl*-2-*isodithiobiuret*, prisms (from benzene–light petroleum), m. p. 110° (Found: S, 19·4. $C_{17}H_{19}N_3S_2$ requires S, 19·45%); 5-*ethyl*-1,1-*diphenyldithiobiuret*, prisms (from benzene–light petroleum), m. p. 127° (Found: N, 13·7; S, 20·5. $C_{16}H_{17}N_3S_2$ requires N, 13·3; S, 20·3%); 2-*methyl*-1,1,5-*triphenyl*-2-*isodithiobiuret*, prisms (from toluene), m. p. 155° (Found: S, 16·8. $C_{21}H_{19}N_3S_2$ requires S, 17·0%); 1,1,5-*triphenyldithiobiuret* (from ethanol), m. p. 124—125° (Found: N, 11·5; S, 17·3. $C_{20}H_{17}N_3S_2$ requires N, 11·6; S, 17·6%).

The authors thank Mr. J. L. Lowe for helpful discussions, Miss R. M. Tancock and Mr. E. C. Wilmshurst for the biological tests, and Mr. A. Sweeney for technical assistance.

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[*Received, January* 31*st*, 1963.]