Dithiobiurets. Part I. Some 1- and 1 : 5-Substituted Derivatives.

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Numerous 1- and 1 : 5-substituted dithiobiurets have been prepared for test as trypanocidal agents. A new method for the preparation of 1-monosubstituted dithiobiurets from alkyl dithiocarbamates has been developed.

THE observation of low but well-defined activity against *Trypanosoma congolense* in mice among a number of simple 1-aryldithiobiurets (Woolfe, *Brit. J. Pharmacol.*, 1953, **8**, 420) prompted us to extend our examination of this type of compound. This and the following paper describe the preparation for this purpose of a wide variety of dithiobiurets.

1-Substituted dithiobiurets were prepared for the most part by standard procedures. The first of these was by fusion of arylamines with 3-imino-5-thio-1 : 2 : 4-dithiazolidine (" perthiocyanic acid "), a method due to Glutz (*Annalen*, 1870, **154**, 44) and later developed by Tursini (*Ber.*, 1884, **17**, 584) and Fromm (*Annalen*, 1893, **275**, 20, and other papers). Crude products prepared by this method are frequently contaminated by sulphur which is difficult to eliminate by direct crystallisation. Precipitation from dilute sodium hydroxide solution with hydrogen sulphide was found to effect rapid purification, often with improved yields. Weakly basic amines either fail to react or, in certain cases, afford the amine thiocyanate as sole product.

The second method was that due to Wunderlich (*Ber.*, 1886, **19**, 452) and Hecht (*Ber.*, 1892, **25**, 749) whereby *iso*thiocyanates are condensed with sodium cyanamide to give *N*-cyanothioureas to which hydrogen sulphide is then added.

A third method was developed which may be regarded as a modification of the second. It was particularly useful since it avoids the preparation of the *iso*thiocyanate. It is known that dithiocarbamates of the type, $RNH{\cdot}CS_2R'$, decompose to RNCS and R'SH on gentle heating (von Braun, *Ber.*, 1902, **35**, 3368; Delépine, *Bull. Soc. chim.*, 1902, **27**, 809). It was therefore thought possible that alkyl dithiocarbamates might condense directly with sodium cyanamide to yield *N*-cyanothioureas. Such condensation does, in fact, occur in refluxing methanol or ethanol—whether directly or through the intermediate formation of the *iso*thiocyanate is not known—and further processing according to Hecht's method affords satisfactory yields of dithiobiurets.

By these methods dithiobiurets were prepared variously substituted in the 1-position with alkyl, aryl, substituted aryl, and heterocyclic radicals. Three bisdithiobiurets were also prepared.

1 : 5-Disubstituted dithiobiurets were prepared by condensation of the appropriate

*iso*thiocyanates and *S*-ethyl*iso*thioureas (cf. Curd, Davey, Richardson, and Ashworth, *J.*, 1949, 1739) and thiohydrolysis of the resulting 2-ethyl-2-*iso*dithiobiurets.

Since trypanocidal activity is frequently dependent on the presence of a quaternary ammonium grouping in the molecule, it was thought of interest to prepare a number of dithiobiurets possessing this feature. These were prepared by two methods. In the first, an *iso*thiocyanato-substituted base was quaternised and then converted by the cyanamide route into the corresponding dithiobiuret. Alternatively, the dithiobiuret residue of the unquaternised compound was first protected by conversion into its 2 : 4-dimethyl-2 : 4-di*iso*-derivative. The basic centre could then be quaternised and the protecting groups removed by thiohydrolysis. Neither these compounds nor the others described in this paper showed any significantly higher level of trypanocidal activity than that originally observed in 1-phenyldithiobiuret (Woolfe, *loc. cit.*).

EXPERIMENTAL

M. p.s vary with rate of heating and were therefore taken under standard conditions by placing the tube in the bath at 10° below the m. p. and raising the temperature by 2° per minute.

1-*Substituted dithiobiurets.*

(a) *From Amines and Perthiocyanic Acid.*—A mixture of the amine (0·2 mol.) and perthiocyanic acid (0·1 mol.) was heated in a steam-bath until either the yellow colour disappeared and a white solid product was obtained, or until the perthiocyanic acid had dissolved to give a clear solution (5 min. to 5 hr.). The mixture was then warmed with ethanol (30 c.c.), the suspension cooled, and N-hydrochloric acid (120 c.c.) added. The resulting precipitate was filtered off, washed with water, and triturated with 5N-sodium hydroxide. The suspension was diluted to 750 c.c. and filtered through kieselguhr, and the product precipitated with hydrogen sulphide and crystallised.

In this manner the following new dithiobiurets were prepared (time of heating and yield in parentheses) : 1-m-*methoxyphenyl*- (35 min., 50%), felted needles (from ethanol), m. p. 173—174° (Found : N, 17·1. $C_9H_{11}ON_3S_2$ requires N, 17·0%) ; 1-p-*butoxyphenyl*- (30 min., 43%), plates (from ethanol), m. p. 161—162° (Found : N, 14·7. $C_{12}H_{17}ON_3S_2$ requires N, 14·8%) ; 1-*phenyl*-1-*propyl*- (5 hr., 37·5%), needles (from ethanol), m. p. 141—142° (Found : N, 16·4. $C_{11}H_{15}N_3S_2$ requires N, 16·6%) ; and 1-*butyl*-1-*phenyl*- (5 hr., 41%), plates (from ethanol), m. p. 136—137° (Found : N, 15·8. $C_{12}H_{17}N_3S_2$ requires N, 15·7%).

The following known dithiobiurets were prepared by the same method : 1-phenyl- (4 min., 43%), m. p. 183—184° (Fromm, *loc. cit.*, records m. p. 184°); 1-*o*-methoxyphenyl- (40 min., 37%), needles (from benzene) or plates (from aqueous methanol), m. p. 143—144° (Found : C, 44·8; H, 4·4; N, 17·0. Calc. for $C_9H_{11}ON_3S_2$: C, 44·8; H, 4·6; N, 17·4%) (Fromm, Brück, Runkel, and Mayer, *Annalen*, 1924, **437**, 106, record m. p. 148°) ; 1-*p*-methoxyphenyl- (25 min., 42% ; prepared by Dr. P. E. Macey), plates (from ethanol), m. p. 173—174° (Swaminathan and Guha, *J. Indian Chem. Soc.*, 1946, **42**, 3350, record m. p. 165°) ; 1-*p*-ethoxyphenyl- (30 min., 40%), plates (from ethanol), m. p. 171—172° (Found : N, 16·6. Calc. for $C_{10}H_{13}ON_3S_2$: N, 16·5%) (Fromm and Vetter, *Annalen*, 1907, **356**, 178, record m. p. 178°) ; 1-*p*-tolyl- (10 min., 55%), m. p. 173—174° (Fromm and Schneider, *Annalen*, 1906, **348**, 161, record m. p. 173·5°) ; 1-*p*-chlorophenyl- (40 min., 40%), m. p. 179—180° (Fairfull, Lowe, and Peak, *J.*, 1952, 742, record m. p. 179—180°) ; 1-*p*-dimethylaminophenyl- (25 min., 39%), m. p. 159—160° (Found : N, 21·8; S, 25·6. Calc. for $C_{10}H_{14}N_4S_2$: N, 22·0; S, 25·2%) (Fromm and Weller, *Annalen*, 1908, **361**, 345, record m. p. 168—169°) ; 1-α-naphthyl- (1 hr., 44%), m. p. 194—195° (Found : C, 55·5; H, 4·0; N, 15·8. Calc. for $C_{12}H_{11}N_3S_2$: C, 55·2; H, 4·2; N, 16·0%) (Swaminathan and Guha, *loc. cit.*, record m. p. 246°) ; 1-β-naphthyl- (1·5 hr., 36%), m. p. 244—245° (*idem, ibid.*, record m. p. 245°) ; 1-methyl-1-phenyl- (1·5 hr., 55%), m. p. 156—157° (Fromm and Junius, *Ber.*, 1895, **28**, 1096, record m. p. 157°) ; and 1-ethyl-1-phenyl-, m. p. 128—129° (Found : N, 17·3. Calc. for $C_{10}H_{13}N_3S_2$: N, 17·6%) (Fromm and Baumhauer, *Annalen*, 1908, **361**, 319, record m. p. 119·5°).

p-Ethylsulphonylaniline, *p*-aminoacetanilide, *p*-aminoformanilide, *p*-phenylenediamine, *p*-nitroaniline, *p*-aminobenzonitrile, and ethyl *p*-aminobenzoate all failed to react with perthiocyanic acid.

2-Aminopyridine afforded 2-*aminopyridine thiocyanate*, needles (from *n*-hexanol), m. p· 116—119° (Found : C, 47·4; H, 4·6. $C_6H_7N_3S$ requires C, 47·1; H, 4·6%), also prepared by evaporating a solution of 2-aminopyridine and ammonium thiocyanate in methanol. Similarly, 3-aminopyridine afforded *3-aminopyridine thiocyanate*, m. p. 138—140° after repeated crystallisation from *iso*propanol (Found: N, 27·0. $C_6H_7N_3S$ requires N, 27·4%). *N*-(2-Diethylaminoethyl)aniline afforded an oily thiocyanate which regenerated the parent base when treated with aqueous sodium hydroxide.

(b) *From* iso*Thiocyanates and Sodium Cyanamide*.—(1) *Preparation of new* iso*thiocyanates.*

2-Pyridyl iso*thiocyanate*. (i) From ammonium *N*-2-pyridyldithiocarbamate. Finely powdered 2-aminopyridine (225·6 g., 2·4 mols.) was added slowly to a mixture of concentrated aqueous ammonia (340 c.c., 5·2 mols.) and carbon disulphide (216 g., 2·84 mols.) at 0°. The turbid solution, which began to deposit yellow prisms after 2 hr., was stirred overnight at room temperature and the solid filtered off and washed with a little methanol and then with acetone. Evaporation of the mother-liquors yielded only 2-aminopyridine thiocyanate (154 g.), identified by mixed m. p. The yellow solid [61 g.; m. p. 96—97° (decomp.)] was unstable, decomposing on exposure to moist air or in a desiccator over sulphuric acid but it could be preserved in a stoppered bottle. It decomposed on attempted recrystallisation from methanol or aqueous ethanol with evolution of ammonia. It crystallised from dilute aqueous ammonia but its analysis (Found: N, 21·85. $C_6H_9N_3S_2$ requires N, 22·4%) indicated some loss of ammonia. Its identity as *ammonium* N-*2-pyridyldithiocarbamate* was confirmed by its acid hydrolysis to carbon disulphide, ammonia, and 2-aminopyridine, identified as its picrate, m. p. 221—222°.

The crude salt (25 g.) was suspended in dry toluene (200 c.c.) and a solution of carbonyl chloride (15·5 g., 1 mol.) in toluene (100 c.c.) added dropwise with stirring during 1·5 hr. at 0°, the colour of the solid progressively deepening. After being stirred overnight at room temperature, the solid was filtered off, washed with benzene, air-dried, and triturated with water (200 c.c.). The residue was filtered off and washed with water and finally with acetone (50 c.c.), affording *2-pyridyl* iso*thiocyanate* as a brick-red solid (15·4 g., 75%), m. p. 106—108°, raised to 110—111° by crystallisation from a large volume of acetone (Found: N, 20·4. $C_6H_4N_2S$ requires N, 20·6%). With aniline at 100° it afforded *N*-phenyl-*N'*-2-pyridylthiourea, m. p. and mixed m. p. 167—168°.

(ii) From triethylammonium *N*-2-pyridyldithiocarbamate. A mixture of 2-aminopyridine (6·27 g.), carbon disulphide (6 g., 1·2 mols.), triethylamine (111 g., 1·1 mols.), and absolute ethanol (5 c.c.) was kept for 2 days. The product which had separated was filtered off and washed with a little ethanol and with acetone, affording *triethylammonium* N-*2-pyridyldithiocarbamate* as yellow prisms (14·8 g.; 82%), m. p. 88—89° (decomp.) unchanged on recrystallisation from water containing a little triethylamine (Found: N, 15·5. $C_{12}H_{21}N_3S_2$ requires N, 15·5%).

Treatment of this salt with carbonyl chloride (1 mol.) as described above afforded 2-pyridyl *iso*thiocyanate (63·5%), m. p. 109—110°. Excess of carbonyl chloride gave *NN'*-di-2-pyridylthiourea as sole product.

3-Pyridyl iso*thiocyanate*. *Ammonium* N-*3-pyridyldithiocarbamate* was obtained as a pale yellow solid, m. p. 108° (Found: N, 22·1. $C_6H_9N_3S_2$ requires N, 22·4%), in 61% yield by the method described above for the 2-aminopyridine analogue. Treatment with carbonyl chloride (1 mol.) afforded a colourless precipitate and, by concentration of the toluene mother-liquor, a small quantity of an oil, b. p. 75—85°/2 mm. Redistillation at atmospheric pressure gave *3-pyridyl* iso*thiocyanate* (10%) as a pungent, colourless oil, b. p. 231—233° (Found: N, 19·8. $C_6H_4N_2S$ requires N, 20·6%). Its identity was confirmed by its condensation with aniline to give *N*-phenyl-*N'*-3-pyridylthiourea, m. p. 161—163° raised by admixture with authentic material of m. p. 163—164° (Camp, *Arch. Pharm.*, 1902, **240**, 356).

The colourless precipitate, after being washed with acetone, had m. p. 173—176°, not depressed by an authentic sample of NN'-*di-3-pyridylthiourea*, prisms (from ethanol), m. p. 178—179° (Found: N, 24·1. $C_{11}H_{10}N_4S$ requires N, 24·3%), prepared by condensing 3-pyridyl *iso*thiocyanate with 3-aminopyridine.

Triethylammonium N-*3-pyridyldithiocarbamate*, prisms (from acetone or ethanol–ether), m. p. 85—86° (Found: N, 15·2. $C_{12}H_{21}N_3S_2$ requires N, 15·5%), prepared in 92% yield as for the 2-aminopyridyl analogue, gave *NN'*-di-3-pyridylthiourea as the only isolatable product.

*9-Phenyl-2 : 7-di*iso*thiocyanatophenanthridine*. A solution of 2 : 7-diamino-9-phenylphenanthridine (14·25 g.) in N-hydrochloric acid (100 c.c.) was vigorously stirred with a solution of thiocarbonyl chloride (10 c.c., 2·4 mols.) in chloroform (100 c.c.) while N-sodium hydroxide (200 c.c.) was added during 1 hr. The pale brown solid which separated was dissolved by the addition of further chloroform (600 c.c.), and the chloroform layer was dried ($MgSO_4$) and evaporated. The residual solid was extracted with hot benzene (100 c.c.), affording a residue of

9-*phenyl*-2 : 7-*di*iso*thiocyanatophenanthridine* (13·7 g.) as pale brown needles, m. p. 235—236° unchanged by crystallisation from a large volume of benzene (Found : N, 11·4. $C_{21}H_{11}N_3S_2$ requires N, 11·4%). A further crop (1·1 g.; m. p. 235—236°) was deposited by the hot benzene extract on cooling.

(2) *Preparation of dithiobiurets.* The following dithiobiurets were obtained by Hecht's method (*Ber.*, 1892, **25**, 749); 1-methyl- (33%), m. p. 157—158° (Hecht, *loc. cit.*, records m. p. 153°); 1-ethyl- (38%), m. p. 178—179° (*idem, ibid.*, records m. p. 175°); 1-n-*butyl*- (34%), plates (from aqueous methanol), m. p. 115—116° (Found: N, 21·8. $C_6H_{13}N_3S_2$ requires N, 22·0%); 1-2′-*pyridyl*- (22%), needles (from ethanol), m. p. 189—190° (Found : C, 39·5; H, 3·7; N, 26·2. $C_7H_8N_4S_2$ requires C, 39·6; H, 3·8; N, 26·4%); 1-3′-*pyridyl*- (35%), needles (from ethanol), m. p. 164—165° (Found : C, 39·8; H, 3·4; N, 26·4. $C_7H_8N_4S_2$ requires C, 39·6; H, 3·8; N, 26·4%); and 1-6′-*quinolyl*- (35%), needles (from aqueous ethanol), m. p. 180—181° (Found : C, 50·5; H, 3·9; N, 21·3. $C_{11}H_{10}N_4S_2$ requires C, 50·4; H, 3·8; N, 21·4%).

p-Ethoxycarbonylphenyl *iso*thiocyanate (Dyson, George, and Hunter, *J.*, 1927, 436) afforded a crude product which was purified by solution in dilute aqueous sodium hydroxide. Precipitation with hydrogen sulphide gave 1-(p-*ethoxycarbonylphenyl*)*dithiobiuret* (17·5%), m. p. 171—172° unchanged by crystallisation from aqueous ethanol (Found : N, 14·9. $C_{11}H_{13}O_2N_3S_2$ requires N, 14·85%). Acidification of the mother-liquor with acetic acid gave 1-p-*carboxyphenyldithiobiuret* (17%), m. p. 197—198° after crystallisation from aqueous ethanol (Found : N, 16·1. $C_9H_9O_2N_3S_2$ requires N, 16·5%). In one experiment, where the precipitate was left in contact with dilute hydrochloric acid overnight, the product was 3-p-*carboxyphenylimino*-5-*imino*-1 : 2 : 4-*dithiazolidine hydrochloride monohydrate* (12%), m. p. 237—238° after crystallisation from aqueous ethanol (Found : C, 35·0; H, 3·4; N, 13·3. $C_9H_5O_2N_3S_2,HCl,H_2O$ requires C, 35·1; H, 3·25; N, 13·6%). The same compound was prepared by oxidation of 1-*p*-carboxyphenyldithiobiuret with aqueous alcoholic ferric chloride.

1 : 4-Di*iso*thiocyanatobenzene (Billeter and Steiner, *Ber.*, 1887, **20**, 228) similarly afforded 1 : 4-*di*-(3-*thiocarbamoylthioureido*)*benzene* (37%), m. p. 192—193° (Found : N, 24·4. $C_{10}H_{12}N_6S_4$ requires N, 24·4%). 4 : 4′-Di*iso*thiocyanatodiphenyl (*idem, ibid.*) afforded 4 : 4′-*di*-(3-*thiocarbamoylthioureido*)*diphenyl* (47%), m. p. 256—257° (Found : C, 45·9; H, 3·8. $C_{16}H_{16}N_6S_4$ requires C, 45·7; H, 3·8%). 9-Phenyl-2 : 7-di*iso*thiocyanatophenanthridine afforded 9-*phenyl*-2 : 7-*di*-(3-*thiocarbamoylthioureido*)*phenanthridine monohydrate* (75%), m. p. 222—223° (Found : C, 51·5; H, 3·5; N, 18·1. $C_{23}H_{19}N_7S_4,H_2O$ requires C, 51·2; H, 3·9; N, 18·2%). All three bisdithiobiurets separated from aqueous pyridine as microcrystalline powders.

Ammonium and methyl dithiocarbamates, R·NH·CS·SR′.

R	R′	Yield (%)	M. p.	Formula	N (%) Found	N (%) Reqd.
2-Pyridyl-	NHEt$_3$			See p. 799		
2-*Pyridyl*-	Me	90	88—89°	$C_7H_8N_2S_2$	15·2	15·2
3-Pyridyl-	NH$_4$			See p. 799		
3-*Pyridyl*-	Me	96	133—135	$C_7H_8N_2S_2$	15·1	15·2
4-*iso*Quinolyl-	NH$_4$	80	119—120	$C_{10}H_{11}N_3S_2$	Not analysed	
4-iso*Quinolyl*-	Me	66	139—140	$C_{11}H_{10}N_2S_2$	11·9	12·0
5-*Quinolyl*-	NH$_4$	55	98—99	$C_{10}H_{11}N_3S_2$	17·5	17·7
5-*Quinolyl*-	Me	86	147—148	$C_{11}H_{10}N_2S_2$	12·1	12·0
6-*Quinolyl*-	NH$_4$	90	111—112	$C_{10}H_{11}N_3S_2$	17·5	17·7
6-*Quinolyl*-	Me	92	160—161	$C_{11}H_{10}N_2S_2$	12·0	12·0
8-*Quinolyl*-	NH$_4$	70	86—87	$C_{10}H_{11}N_3S_2$	17·8	17·7
8-*Quinolyl*-	Me	91	100—101	$C_{11}H_{10}N_2S_2$	12·0	12·0
p-*Acetamidophenyl*-	NH$_4$	73	212—220	$C_9H_{13}ON_3S_2$	17·0	17·3
p-*Acetamidophenyl*-	Me	93	139—140	$C_{10}H_{12}ON_2S_2$	11·8	11·7
p-*Propylphenyl*-	NHEt$_3$	83	92—93	$C_{16}H_{28}N_2S_2$	9·1	9·0
p-*Propylphenyl*-	Me	91	68—69	$C_{11}H_{15}NS_2$	6·4	6·2
p-*Butylphenyl*-	NHEt$_3$	83	91—92	$C_{17}H_{30}N_2S_2$	8·4	8·6
p-*Butylphenyl*-	Me	90	70—71	$C_{12}H_{17}NS_2$	6·0	5·9
2-*Thiazolyl*- *	NHEt$_3$	60	141—142	$C_{10}H_{19}N_3S_3$	14·9	15·2
2-*Thiazolyl*-	Me	83	184—185	$C_5H_6N_2S_3$	15·0	14·7

* Preparation carried out in acetone.

(c) *From Methyl Dithiocarbamates and Sodium Cyanamide.*—The required ammonium dithiocarbamates and methyl dithiocarbamates were made by conventional procedures and are listed in the Table. The only starting materials requiring comment are *p*-propyl- and *p*-butyl-aniline. These were prepared more conveniently than by recorded methods by the modified Wolff–

Kishner reduction (Herr, Whitmore, and Scheissler, *J. Amer. Chem. Soc.*, **1945**, **67**, 2061) of *p*-amino-propiophenone and -butyrophenone (Kunckell, *Ber.*, 1900, **33**, 2641) in 58% and 83% yield respectively.

The following is a typical preparation of a dithiobiuret by this route. Methyl *N*-4-*iso*quinolyldithiocarbamate (14·2 g.) was heated under reflux for 24 hr. with a solution of sodium cyanamide, prepared by adding cyanamide (3·0 g.) to a solution of sodium (1·5 g.) in methanol (100 c.c.). (Longer heating is necessary if thiol evolution is sluggish.) The reaction mixture was evaporated to dryness on the steam-bath and the residual solid dissolved in water (100 c.c.) and filtered through kieselguhr. Ammonium chloride (3·6 g.) and concentrated ammonia solution (12 c.c.) were added and the solution was heated on the steam-bath in a stream of hydrogen sulphide. The solid which separated was filtered off at intervals and the filtrate re-treated until no further solid separated, affording a total of 14·0 g. (82%) of 1-4′-iso*quinolyldithiobiuret*, m. p. 184—185° (decomp.), unchanged by recrystallisation from a large volume of ethanol (Found: C, 50·6; H, 4·4; N, 21·5. $C_{11}H_{10}N_4S_2$ requires C, 50·4; H, 3·8; N, 21·4%).

The following dithiobiurets were obtained in a similar manner and crystallised from ethanol: 1-3′-pyridyl- (38%), m. p. and mixed m. p. 164—165°; 1-5′-*quinolyl-* (51%), m. p. 167—168° (Found: C, 50·0; H, 4·4. $C_{11}H_{10}N_4S_2$ requires C, 50·4; H, 3·8%); 1-p-*acetamidophenyl-* (71%), m. p. 190—191° (Found: C, 44·5; H, 4·5; N, 20·7. $C_{10}H_{12}ON_4S_2$ requires C, 44·8; H, 4·5; N, 20·8%); 1-p-*propylphenyl-* (63%), m. p. 160—161° (Found: C, 52·4; H, 5·9; N, 16·3. $C_{11}H_{15}N_3S_2$ requires C, 52·2; H, 5·9; N, 16·6%); and 1-p-*butylphenyl-* (35%), m. p. 158—159° (Found: N, 15·6. $C_{12}H_{17}N_3S_2$ requires N, 15·7%).

In two cases the intermediate *N*-cyanothiourea was isolated. Addition of ammonium chloride to the aqueous solution of the crude reaction product of the dithiocarbamate and sodium cyanamide afforded N-*cyano*-N′-2-*pyridylthiourea* (70%) as a yellow solid, m. p. 202—203° unchanged by recrystallisation from ethanol (Found: C, 47·2; H, 3·5; N, 31·0. $C_7H_6N_4S$ requires C, 47·2; H, 3·4; N, 31·4%). Methyl *N*-6-quinolyldithiocarbamate afforded in the same manner the cyano-derivative as its colourless *ammonium salt*, prisms (from dilute aqueous ammonia), m. p. 185—186° (Found: N, 28·3. $C_{11}H_{11}N_5S$ requires N, 28·6%), converted quantitatively into the yellow N-*cyano*-N′-6-*quinolylthiourea*, m. p. 180—181° (Found: N, 24·6. $C_{11}H_8N_4S$ requires N, 24·6%), by acidification of its aqueous solution with acetic acid. These cyano-derivatives were converted into the corresponding dithiobiurets in 82% and 72·5% yield respectively by addition of hydrogen sulphide in pyridine–triethylamine solution (Fairfull *et al.*, *loc. cit.*).

Methyl *N*-8-quinolyldithiocarbamate behaved abnormally, much decomposition occurring during the cyanamide condensation, and no dithiobiuret could be obtained. Methyl *N*-2-thiazolyldithiocarbamate afforded an unidentified yellow solid, m. p. 164—170°, also formed in the absence of cyanamide.

1 : 5-*Disubstituted dithiobiurets.*

The required thioureas were prepared (1) from the *iso*thiocyanate and ammonia or the appropriate amine or (2) from benzoyl *iso*thiocyanate and amine with subsequent hydrolysis of the *N*-benzoylthiourea (*Org. Synth.*, **28**, 89). The following new thioureas were obtained by the latter method: N′-*benzoyl*-N-2-*pyridyl-*, needles (from ethanol), m. p. 143—144° (Found: N, 16·4. $C_{13}H_{11}ON_3S$ requires N, 16·35%); N-2-*pyridyl-*, prisms (from ethanol), m. p. 147—148° (Found: N, 27·6. $C_6H_7N_3S$ requires N, 27·5%); N′-*benzoyl*-N-*methyl*-N-*phenyl-*, plates (from ethanol), m. p. 136—137° (Found: N, 10·4. $C_{15}H_{14}ON_2S$ requires N, 10·4%); N′-*benzoyl*-N-*phenyl*-N-*propyl-*, prisms (from ethanol), m. p. 126—127° (Found: N, 9·7. $C_{17}H_{18}ON_2S$ requires N, 9·4%); and N-*phenyl*-N-*propyl-*, plates (from benzene–light petroleum), m. p. 105° (Found: N, 14·5. $C_{10}H_{14}N_2S$ requires N, 14·4%). The last two *N*-benzoyl derivatives were resistant to hydrolysis and required heating under reflux for 2 hr.

By following the procedure of Curd *et al.* (*J.*, 1949, 1739), the thioureas were converted into the *S*-ethyl*iso*thioureas and the latter, with or without intermediate isolation as their hydriodides, were condensed with the appropriate *iso*thiocyanate, and the resulting 2-ethyl-2-*iso*dithiobiurets were thiohydrolysed with ethanolic sodium hydrogen sulphide to the dithiobiurets. In this manner *NS*-diethyl*iso*thiourea and phenyl *iso*thiocyanate afforded 1 : 2-*diethyl*-5-*phenyl*-2-iso*dithiobiuret* (57%), prisms (from light petroleum), m. p. 93—94° (Found: N, 15·4. $C_{12}H_{17}N_3S_2$ requires N, 15·7%), and thence 1-*ethyl*-5-*phenyldithiobiuret* (87%), needles (from light petroleum–benzene), m. p. 131—132° (Found: N, 17·4. $C_{10}H_{13}N_3S_2$ requires N, 17·6%).

N-Butyl-*S*-ethyl*iso*thiourea and phenyl *iso*thiocyanate similarly afforded 1-butyl-2-ethyl-5-phenyl-2-*iso*dithiobiuret as an uncrystallisable oil, thiohydrolysed directly to 1-*butyl*-5-*phenyl-*

dithiobiuret (39%), needles (from light petroleum), m. p. 96—97° (Found : N, 15·4. $C_{12}H_{17}N_3S_2$ requires N, 15·7%).

S-Ethyl-*N*-phenyl*iso*thiourea and *p*-methoxyphenyl *iso*thiocyanate afforded *2-ethyl-5-*p*-methoxyphenyl-1-phenyl-2-*iso*dithiobiuret* (54%), prisms (from light petroleum), m. p. 106—107° (Found : N, 12·3. $C_{17}H_{19}ON_3S_2$ requires N, 12·2%), thiohydrolysed to *5-*p*-methoxyphenyl-1-phenyldithiobiuret* (53%), needles (from benzene–light petroleum), m. p. 138—139° (Found : N, 13·2. $C_{15}H_{15}ON_3S_2$ requires N, 13·2%).

*S-Ethyl-*N*-*p*-methoxyphenyl*iso*thiourea hydriodide*, needles (from *iso*propanol–ether), m. p. 131—132° (Found : N, 8·3. $C_{10}H_{15}ON_2IS$ requires N, 8·3%), and *p*-methoxyphenyl *iso*thiocyanate afforded *2-ethyl-1 : 5-di-*p*-methoxyphenyl-2-*iso*dithiobiuret* (75%), prisms (from ethanol), m. p. 138—139° (Found : N, 11·2. $C_{18}H_{21}O_2N_3S_2$ requires N, 11·2%), thiohydrolysed to *1 : 5-di-*p*-methoxyphenyldithiobiuret* (51%), needles (from benzene–light petroleum), m. p. 131—132° (Found : N, 11·9. $C_{16}H_{17}O_2N_3S_2$ requires N, 12·1%).

*S-Ethyl-*N*-phenyl-*N*-propyl*iso*thiourea hydriodide*, plates (from *iso*propanol), m. p. 153—154° (Found : N, 8·2. $C_{12}H_{19}N_2IS$ requires N, 8·0%), and ethyl *iso*thiocyanate afforded *2 : 5-diethyl-1-phenyl-1-propyl-2-*iso*dithiobiuret* (51%), needles (from light petroleum–benzene), m. p. 100—101° (Found : C, 57·9; H, 6·9; N, 13·9. $C_{15}H_{23}N_3S_2$ requires C, 58·3; H, 7·4; N, 13·6%). Thiohydrolysis (in pyridine–triethylamine) gave *5-ethyl-1-phenyl-1-propyldithiobiuret* (88%), needles (from light petroleum), m. p. 97—98° (Found : C, 55·4; H, 7·0; N, 14·8. $C_{13}H_{19}N_3S_2$ requires C, 55·5; H, 6·8; N, 15·0%).

*S-Ethyl-*N*-methyl-*N*-phenyl*iso*thiourea hydriodide*, needles (from ethanol–ether), m. p. 137—138° (Found : N, 8·9. $C_{10}H_{15}N_2IS$ requires N, 8·7%), and ethyl *iso*thiocyanate afforded *2 : 5-diethyl-1-methyl-1-phenyl-2-*iso*dithiobiuret* (44%), prisms (from light petroleum–benzene), m. p. 81—82° (Found : C, 55·1; H, 6·7; N, 14·7. $C_{13}H_{19}N_3S_2$ requires C, 55·5; H, 6·8; N, 14·9%). Thiohydrolysis (in pyridine–triethylamine) gave *5-ethyl-1-methyl-1-phenyldithiobiuret* (87%), prisms (from light petroleum–benzene), m. p. 87—88° (Found : C, 51·9; H, 5·7; N, 16·5. $C_{11}H_{15}N_3S_2$ requires C, 52·1; H, 6·0; N, 16·6%).

Quaternary N-derivatives.

*1-*p*-Dimethylaminophenyldithiobiuret Methochloride.*—(i) *p*-Dimethylaminophenyl *iso*thiocyanate was prepared in improved yield (47% instead of 13%) by a modification of the Organic Syntheses' method (Coll. Vol. I, 1st Edn., 447). Instead of steam-distillation of the product, the reaction mixture was filtered and the *iso*thiocyanate extracted from the cake with hot acetone (3 × 300 c.c. on 0·2-molar scale). The combined extracts were evaporated under reduced pressure. The resulting colourless solid, after being pressed on a filter and washed with water, had m. p. 68—70°.

A solution of the *iso*thiocyanate (16·5 g.) in dry acetone (30 c.c.) and methyl iodide (10 c.c.) was kept at 0°. Over a period of 17 days, successive crops (26·1 g.) of *N-trimethyl-*p*-*iso*thiocyanatoanilinium iodide* were obtained, having m. p. 190° (decomp.) (Found : N, 8·9. $C_{10}H_{13}N_2IS$ requires N, 8·8%). Condensation of this in the usual manner with sodium cyanamide and thiohydration of the product afforded a precipitate of the crude dithiobiuret. This dissolved in warm dilute hydrochloric acid, the solution soon depositing *1-*p*-dimethylaminophenyldithiobiuret methochloride* (10·5%) as needles, m. p. 192° (decomp.) after recrystallisation from water (Found : C, 43·7; H, 5·3; N, 18·4. $C_{11}H_{17}N_4ClS_2$ requires C, 43·4; H, 5·6; N, 18·4%).

(ii) *1-*p*-Dimethylaminophenyl-2 : 4-dimethyldi*iso*dithiobiuret* was obtained in 46% yield by shaking a solution of the dithiobiuret in N-sodium hydroxide (2 equivs.) with methyl iodide (2 mols.) for 30 min. It crystallised from ethanol in needles, m. p. 105—106° (Found : C, 51·4; H, 6·9; N, 19·7. $C_{12}H_{18}N_4S_2$ requires C, 51·1; H, 6·4; N, 19·8%).

When this compound was kept for 2 days in acetone solution containing methyl iodide (1 mol.), the *methiodide* (80%) was obtained as a colourless solid, m. p. 185—186° (Found : C, 36·7; H, 5·0; N, 12·9. $C_{13}H_{21}N_4IS_2$ requires C, 36·8; H, 5·0; N, 13·2%).

The methiodide (0·51 g.) was heated under reflux for 1½ hr. in a stream of hydrogen sulphide with ethanolic sodium hydrogen sulphide, prepared by saturating a solution of sodium (0·08 g.) in ethanol (20 c.c.). The white precipitate which formed was isolated and dissolved in N-hydrochloric acid (10 c.c.), from which the dithiobiuret methochloride (0·25 g.) crystallised in needles, m. p. (after recrystallisation from dilute ammonium chloride solution) 192° (decomp.) undepressed by the material described above.

1-6′-Quinolyldithiobiuret 1′-Methochloride.—(i) 6-*iso*Thiocyanatoquinoline (Gulland and

Macey, *J.*, **1949**, 1249) similarly afforded 1-*methyl*-6-iso*thiocyanotoquinolinium iodide* (82%) as red needles, m. p. 237—238° (Found : N, 8·3. $C_{11}H_9N_2IS$ requires N, 8·5%).

Condensation with sodium cyanamide and thiohydrolysis gave a product from which 1-6′-*quinolyldithiobiuret* 1′-*methochloride* (17%) was obtained on treatment with dilute hydrochloric acid as buff plates, m. p. 219—220° (Found : C, 46·1; H, 4·4; N, 17·6. $C_{12}H_{13}N_4ClS_2$ requires C, 46·1; H, 4·2; N, 17·9%).

(ii) 1-6′-Quinolyldithiobiuret was converted into 2 : 4-*dimethyl*-1-6′-*quinolyldi*iso*dithiobiuret* (54%), plates (from aqueous ethanol), m. p. 152—153° (Found : N, 19·2. $C_{13}H_{14}N_4S_2$ requires N, 19·3%). Quaternisation in acetophenone at 70° afforded the *methiodide* (80%), m. p. 174° (Found : N, 13·1. $C_{14}H_{17}N_4IS_2$ requires N, 13·0%). Thiohydrolysis in pyridine–triethylamine and treatment with hydrochloric acid gave 1-6′-quinolyldithiobiuret 1′-methochloride (12%), identical in m. p. and mixed m. p. with the above compound.

(iii) *N*-Cyano-*N*′-6-quinolylthiourea was methylated as usual to give N-*cyano*-S-*methyl*-N′-6-*quinolyl*iso*thiourea* (80%), plates (from ethanol), m. p. 205—206° (Found : N, 22·9. $C_{12}H_{10}N_4S$ requires N, 23·1%). Quaternisation of this in acetophenone at 70° furnished the *methiodide* (89%), m. p. 218—219° (Found : N, 14·3. $C_{13}H_{13}N_4IS$ requires N, 14·6%). Thiohydrolysis as in (ii) and treatment with hydrochloric acid afforded the same compound in 8% yield.

1-3′-*Pyridyldithiobiuret* 1′-*Methochloride*.—1-3′-Pyridyldithiobiuret afforded 2 : 4-*dimethyl*-1-3′-*pyridyldi*iso*dithiobiuret* (51%), m. p. 126—127° (Found : C, 45·1; H, 5·1; N, 23·4. $C_9H_{12}N_4S_2$ requires C, 45·0; H, 5·0; N, 23·3%). Quaternisation in acetone gave the *methiodide* (90%), m. p. 192—193° (Found : C, 31·4; H, 4·0; N, 14·7. $C_{10}H_{15}N_4IS_2$ requires C, 31·4; H, 3·9; N, 14·7%). Thiohydrolysis with ethanolic sodium hydrogen sulphide and treatment with hydrochloric acid gave 1-3′-*pyridyldithiobiuret methochloride monohydrate* (65%), needles (from dilute hydrochloric acid), m. p. 181—182° (Found : C, 34·2; H, 4·5; N, 20·0. $C_8H_{11}N_4ClS_2,H_2O$ requires C, 34·2; H, 4·6; N, 20·0%). If its aqueous solution (pH 4) was adjusted to *ca.* pH 7, *anhydro*-1-3′-*pyridyldithiobiuret methohydroxide* separated as prisms, m. p. 193—194° (Found : C, 42·9; H, 4·2; N, 24·6. $C_8H_{10}N_4S_2$ requires C, 42·5; H, 4·4; N, 24·8%).

1-4′-iso*Quinolyldithiobiuret* 2′-*Methochloride*.—1-4′-*iso*Quinolyldithiobiuret afforded 2 : 4-*dimethyl*-1-4′-iso*quinolyldi*iso*dithiobiuret* (82%), prisms (from ethanol), m. p. 194—195° (Found : N, 19·3. $C_{13}H_{14}N_4S_2$ requires N, 19·3%). Quaternisation in acetophenone at 70° gave the *methiodide* (85%), m. p. 199—200° (Found : N, 12·9. $C_{14}H_{17}N_4IS_2$ requires N, 13·0%). Thiohydrolysis in ethanolic sodium hydrogen sulphide or pyridine–triethylamine suspension for 4 hr. gave the starting material as its *methochloride*, m. p. 195—196° (Found : N, 16·8. $C_{14}H_{17}N_4ClS_2$ requires N, 16·5%), identified by reconversion with aqueous sodium iodide into the methiodide, m. p. and mixed m. p. 198—200°. Thiohydrolysis by the latter method for 40 hr. and treatment of the product with aqueous hydrochloric acid gave 1-4′-iso*quinolyldithiobiuret methochloride* (73%), needles (from water), m. p. 194—195° (Found : C, 46·1; H, 4·3; N, 17·7. $C_{12}H_{13}N_4ClS_2$ requires C, 46·2; H, 4·2; N, 17·9%).

Attempted Preparation of 1-2′-*Pyridyldithiobiuret* 1′-*Methochloride*.—2-Pyridyl *iso*thiocyanate reacted readily with methyl iodide in acetone solution to give a *compound* of unknown structure as orange needles, m. p. 175° (decomp.) (Found : C, 37·8; H, 2·75; N, 13·5. $C_{13}H_{11}N_4IS_2$ requires C, 37·7; H, 2·7; N, 13·5%), evidently formed by the combination of two molecules of the *iso*thiocyanate with one of methyl iodide.

Attempted dimethylation of 1-2′-pyridyldithiobiuret under the usual conditions afforded, with loss of methanethiol, N-*cyano*-S-*methyl*-N′-2-*pyridyl*iso*thiourea hydriodide* (72%), needles (from ethanol), m. p. 237° (decomp.) (Found : C, 30·0; H, 2·9; N, 17·5. $C_8H_9N_4IS$ requires C, 30·0; H, 2·8; N, 17·5%). Its identity was confirmed by the methylation of *N*-cyano-*N*′-2-pyridylthiourea to give N-*cyano*-S-*methyl*-N′-2-*pyridyl*iso*thiourea* (80%), pale yellow needles (from light petroleum), m. p. 127—128° (Found : C, 50·4; H, 4·25; N, 28·8. $C_8H_8N_4S$ requires C, 50·0; H, 4·2; N, 29·2%), which afforded the above hydriodide when hydriodic acid was added to its solution in methanol.

Attempted Preparation of 1-5′-*Quinolyldithiobiuret Methochloride*.—1-5′-Quinolyldithiobiuret afforded 2 : 4-*dimethyl*-1-5′-*quinolyldi*iso*dithiobiuret*, prisms (from ethanol), m. p. 181—182° (Found : N, 19·1. $C_{13}H_{14}N_4S_2$ requires N, 19·3%). Attempted quaternisation failed under a variety of conditions.

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