Dithiobiurets. Part II. Some Cyclic Derivatives.*

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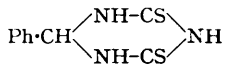
A number of cyclic dithiobiuret derivatives have been prepared for test as trypanocidal agents. The condensation products of dithiobiurets with aldehydes or ketones have been shown to be triazine derivatives, and not diaza*cyclo*butane derivatives as postulated by Fromm and his collaborators.

In continuation of our examination of dithiobiurets as potential trypanocidal compounds (see Part I *) we prepared a number of cyclic derivatives obtained by the condensation of dithiobiurets with aldehydes or ketones. This reaction was first observed by Fromm (*Annalen*, 1893, **275**, 20) who showed that under the influence of dry hydrogen chloride 1-phenyldithiobiuret condensed with acetone or benzaldehyde, with the elimination of water, to give compounds which he generically called "keturets" and "aldurets" respectively. Brodski (*Monatsh.*, 1887, **8**, 27) had earlier prepared a compound of this type indirectly by fusion of a mixture of benzaldehyde and ammonium thiocyanate and had ascribed to it the structure (I). A repetition of Brodski's work showed that the condensation product of dithiobiuret and benzaldehyde was in fact identical with his product. It was also identical with the product obtained by Foye and Hefferren (*J. Amer. Pharm. Assoc.*, 1953, **42**, 31) by heating dithiobiuret and benzaldehyde in acetic acid. These authors assumed the structure (II) without evidence.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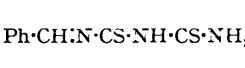
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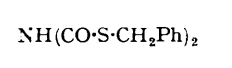
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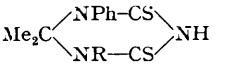
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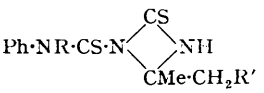
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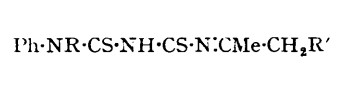
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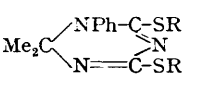
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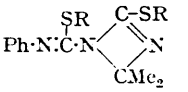
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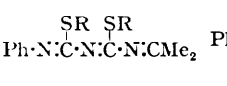
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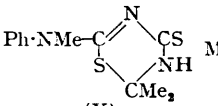
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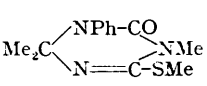
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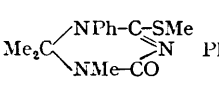
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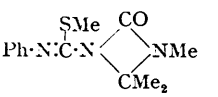
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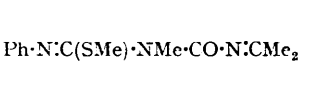
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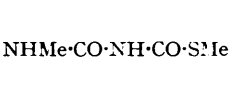
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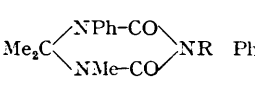
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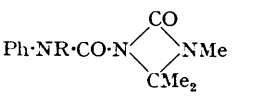
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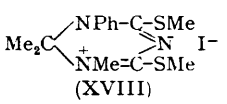
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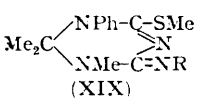
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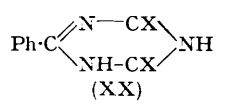
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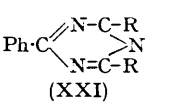

(XXI)

Compounds of this type seemed of potential interest since they could conceivably be formed *in vivo* from dithiobiurets and natural carbonyl constituents of the host, and might constitute the actual therapeutic agents. A number of such compounds were therefore prepared (see Table in Experimental) from dithiobiurets and a variety of carbonyl compounds. For reasons which appear below, they are formulated as hexahydrotriazine derivatives, a structure originally considered but rejected by Fromm (*loc. cit.*). Fromm's method of preparation proved generally satisfactory provided some ethanol was added as

* Part I, preceding paper.

a flux. Boron trifluoride–acetic acid complex was also found to be a satisfactory condensing agent.

The structure of the " aldurets " and " keturets " has not been rigidly proved. Fromm (*loc. cit.*) showed that benzylation of the condensation product of 1-phenyldithiobiuret and acetone gave a di-*S*-benzyl derivative since acid hydrolysis afforded dibenzyl iminodithiolcarboxylate (III). The thiocarbonyl groups are therefore not involved in the condensation and the possible structures are reduced to (IV, V, or VI; R = R′ = H), the alternative four-membered ring structure involving $N_{(1)}$ and $N_{(3)}$ being excluded by the formation of the di-*S*-benzyl derivative. Fromm regarded the second of these as the most probable for the following reasons. Of the corresponding structures (VII, VIII, and IX; R = CH_2Ph) for the dibenzyl derivative, Fromm regarded only (VIII; R = CH_2Ph) as likely to give rise to (III) because of the disposition of the carboimide linkages. The formation from 1-methyl-1-phenyldithiobiuret and acetone of an apparently similar " keturet " (Fromm and Junius, *Ber.*, 1895, **28**, 1096, 1102) was regarded as definitely excluding structure (IV; R = H) since such a structure is impossible where, as in this case, the phenylimino-group is blocked. Further evidence against structure (VI; R = R′ = H) was later provided by the observation (Fromm and Philippe, *Ber.*, 1899, **32**, 835) that the " keturet " from 1-phenyldithiobiuret and ethyl acetoacetate could be hydrolysed to the corresponding acid which showed no tendency to cyclodehydration. This was regarded as improbable for the structure (VI; R = H, R′ = CO_2H) but not unlikely for the structure (V; R = H, R′ = CO_2H).

This evidence appeared to us to be inconclusive and it seemed improbable for steric reasons that a diaz*ocyclo*butane ring would be formed in preference to a six-membered ring. There is no evidence for the structure (V; R = Me, R′ = H) for the " keturet " from 1-methyl-1-phenyldithiobiuret, and alternative formulæ such as (VI; R = Me, R′ = H), dimeric structures, or even (X), might be postulated where triazine ring formation is blocked. We have now obtained evidence that the condensation product of 1-phenyldithiobiuret and acetone has the structure (IV; R = H) and it appears reasonable to assume that other such compounds have the six-membered ring structure wherever this is possible.

The dimethyl derivative (VII, VIII, or IX; R = Me) readily afforded a monomethiodide. With one equivalent of alkali this was transformed with the loss of methanethiol into an *N*-methylamide, a sequence of reactions obviously involving one of the thioimidic groups :

$$\cdot C(SMe){:}N\cdot \xrightarrow{MeI^-} \cdot C(SMe){:}\overset{+}{N}Me\cdot\}I^- \xrightarrow{NaOH^-} \cdot CO\cdot NMe\cdot + NaI + MeSH$$

Acid hydrolysis of the *N*-methylamide afforded aniline and not *N*-methylaniline, showing that the *N*-phenyl group was not involved. The four possible structures for the *N*-methylamide are therefore (XI)—(XIV). A second major product of acid hydrolysis of the *N*-methylamide was a compound, $C_4H_8O_2N_2S$, which was identified as *N*-methyl-*N*′-methylthiocarbonylurea (XV) by conversion with hot aniline into 1 : 5-diphenylbiuret. This reaction presumably proceeds *via* the intermediate 1-methyl-5-phenylbiuret which is known to yield 1 : 5-diphenylbiuret under the same conditions (Gatewood, *J. Amer. Chem. Soc.*, 1925, **47**, 411). The formation of this fission product eliminates structures (XI) and (XIV), thereby also eliminating formula (VI; R = R′ = H) from consideration for the structure of the parent compound.

A choice between structures (XII) and (XIII) was possible from the following considerations. The *N*-methylamide (XII or XIII) afforded a methiodide, although with difficulty and in poor yield, quaternisation evidently involving the second thioimidic group since with alkali the quaternary system underwent the same transformation as in the previous case to an *N*-methylamide grouping to give (XVI or XVII; R = Me). The same compound was obtained more readily by oxidation of the *N*-methylamide (XII or XIII) with hydrogen peroxide, whereby the methylthio-group was eliminated to give the compound (XVI or XVII; R = H). Methylation of the latter with sodium hydroxide and methyl iodide gave (XVI or XVII; R = Me). That this compound was an *N*- and not an *O*-methyl derivative was confirmed by its low methoxyl content by Zeisel determination. Both the methiodide and the compound (XVI or XVII; R = Me) gave aniline

and not *N*-methylaniline on acid hydrolysis. Structures (XVII; R = Me) and hence (XIII) are therefore eliminated. These observations also provide additional evidence against structure (XIV).

The parent compound can therefore unequivocally be assigned the hexahydrotriazine structure (IV; R = H) (or one of its tautomeric equivalents). The methiodide of the di-*S*-methyl derivative (VII; R = Me) is therefore (XVIII). In addition to its behaviour with alkali, it undergoes the expected reactions (cf. Peak and Stansfield, *J.*, 1952, 4067) with ammonia, aniline, and thiosemicarbazide to give respectively the imino-derivative (XIX; R = H), the phenylimino-derivative (XIX; R = Ph), and the thiosemicarbazono-derivative (XIX; R = ·NH·CS·NH_2), and it can be thiohydrolysed to (IV; R = Me).

As a further type of cyclic dithiobiuret, the tetrahydrotriazine (XX; X = S) was prepared. 2 : 4-Dihydroxy-6-phenyl-1 : 3 : 5-triazine (XXI; R = OH) [or its tautomeride (XX; X = O)] (Adams, Ragg, Peters, Kaiser, Sperry, and Thurston, *J. Org. Chem.*, 1952, **17**, 1145) was converted with phosphorus oxychloride into the dichlorotriazine (XXI; R = Cl), a compound previously obtained by Ostrogovich (*Chem. Ztg.*, 1912, **36**, 739) by the action of phenylmagnesium bromide on cyanuric chloride. Treatment of this compound with potassium hydrogen sulphide afforded the required compound (XX; X = S). The same compound could also be obtained by the successive action of benzoyl chloride and pyridine on dithiobiuret, presumably through the intermediate formation of 1-benzoyldithiobiuret. Unsuccessful methods tried were the fusion of benzamidine with perthiocyanic acid which afforded benzamidinium thiocyanate as sole product, and condensation of dithiobiuret with orthocarboxylic esters which afforded only alkyl*iso*dithiobiurets.

The majority of the compounds described were tested for trypanocidal activity with negative results.

Experimental

Preparation of Hexahydro-4 : 6-thiono-1 : 3 : 5-triazines.—A mixture of the dithiobiuret and the aldehyde or ketone (10% excess) was suspended in ethanol (5 parts) and saturated with dry hydrogen chloride. The solid usually dissolved completely, more ethanol being used if this did not occur. After 30 min., the mixture was poured into an excess of N-sodium hydroxide, warmed to 50°, filtered, and acidified with acetic acid. The solid was collected and crystallised from a suitable solvent.

Alternatively, a mixture of equimolecular quantities of the dithiobiuret, aldehyde (or ketone), and boron fluoride–acetic acid complex was heated on the steam-bath for 15 min. and worked up as above.

The compounds so prepared are listed in the accompanying Table. No condensation products could be obtained from phenyldithiobiuret and pyruvic acid, crotonaldehyde, or benzoquinone.

1 : 2-Dihydro-2 : 2-dimethyl-4 : 6-dimethylthio-1 : 3 : 5-triazine 3-Methiodide (XVIII).—1 : 2-Dihydro-2 : 2-dimethyl-4 : 6-dimethylthio-1 : 3 : 5-triazine (23 g.) (Underwood and Dains, *Univ. Kansas Sci. Bull.*, 1936, **24**, 5) was heated under reflux overnight with acetone (100 c.c.) and methyl iodide (16 c.c.). On cooling and seeding, the *methiodide* (32 g.) crystallised in needles, m. p. 184—186° (decomp.), unchanged by recrystallisation from methanol–ether (Found: N, 10·1. $C_{14}H_{20}N_3IS_2$ requires N, 10·0%).

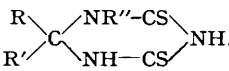
Reactions of the Methiodide.—(a) *With hydrogen sulphide.* A solution of the methiodide (5·25 g.) in pyridine (50 c.c.) and triethylamine (5·1 g.) was saturated with dry hydrogen sulphide for 2 hr. The mixture was poured into water and the solid (3·17 g.) collected. Crystallisation from butanol or pyridine afforded *hexahydro-2 : 2 : 3-trimethyl-1-phenyl-4 : 6-thiono-1 : 3 : 5-triazine* (IV; R = Me) as plates, m. p. 244—245° (Found: C, 54·2; H, 6·1; N, 15·9. $C_{12}H_{15}N_3S_2$ requires C, 54·3; H, 5·6; N, 15·8%).

(b) *With thiosemicarbazide.* The methiodide (1·05 g.) was shaken with thiosemicarbazide (0·23 g.), pyridine (5 c.c.), and diethylamine (1 c.c.). There was an immediate smell of thiol, and dissolution was complete in a few minutes. The product, *tetrahydro-2 : 2 : 3-trimethyl-6-methylthio-1-phenyl-4-thiosemicarbazono-1 : 3 : 5-triazine* (XIX; R = NH·CS·NH_2), obtained by pouring the mixture into water was a colourless solid (0·65 g.), m. p. 191—192° unchanged by recrystallisation from ethanol (Found: N, 24·8. $C_{14}H_{20}N_6S_2$ requires N, 25·0%).

(c) *With ammonia.* The methiodide (0·5 g.) was shaken with ethanolic ammonia (4 c.c. of 2·4N) until dissolution was complete and then kept for 4 hr. The ethanol was then removed in

a current of air and the residue triturated with water (3 c.c.). The product, tetrahydro-4-imino-2 : 2 : 3-trimethyl-6-methylthio-1-phenyl-1 : 3 : 5-triazine (XIX; R = H), separated as its *hydriodide monohydrate* (0·33 g.), m. p. 110—112° raised to 112—114° by recrystallisation from water (Found : C, 38·4; H, 5·0; N, 13·7. $C_{13}H_{19}N_4IS,H_2O$ requires C, 38·2; H, 5·15; N, 13·7%). A solution of this (0·5 g.) in hot water (5 c.c.) treated with N-sodium hydroxide (1 equiv.) deposited, on cooling, a colourless oil which solidified. This proved to be unchanged material.

(d) *With aniline.* A mixture of methiodide (5·0 g.), pyridine (12 c.c.), aniline (1·09 c.c.; 1 mol.), and diethylamine (1·38 c.c.; 1·1 mol.) was kept for 60 hr., dissolution then being

Hexahydro-4 : 6-thiono-1 : 3 : 5-triazines, 

Compound	R	R′	R″	Solvent [a]	M. p.	Formula	N (%) Found	N (%) Reqd.
(1) 2 : 2-*Dimethyl-* ...	Me	Me	H	A	282—283°	$C_5H_9N_3S_2$	24·35	24·0
(2) 2-Phenyl-[b]	Ph	H	H	B	243—244	$C_9H_9N_3S_2$	18·95	18·8
(3) 2-*p*-Methoxyphenyl-[c]	*p*-MeO·C_6H_4	H	H	B	236—237	$C_{10}H_{11}ON_3S_2$	16·55	16·6
(4) 2-*p*-Acetamidophenyl-[d]	*p*-NHAc·C_6H_4	H	H	C	252—253	$C_{11}H_{12}ON_4S_2$	20·1	20·0
(5) 2-*Methyl*-2-*phenyl-*	Ph	Me	H	C	281—282	$C_{10}H_{11}N_3S_2$	17·4	17·7
(6) 2-p-*Chlorophenyl*-1-*phenyl-*	*p*-C_6H_4Cl	H	Ph	B	215—216	$C_{15}H_{12}N_3ClS_2$	12·5	12·6
(7) 2-p-*Methoxyphenyl*-1-*phenyl-* ...	*p*-C_6H_4·OMe	H	Ph	D	197—198	$C_{16}H_{15}ON_3S_2$	13·0	12·8
(8) 2-m-*Nitrophenyl*-1-*phenyl-*	*m*-C_6H_4·NO_2	H	Ph	B	210—211	$C_{15}H_{12}O_2N_4S_2$	16·2	16·3
(9) 2-p-*Acetamidophenyl*-1-*phenyl-*	*p*-C_6H_4·NHAc	H	Ph	B	219—220	$C_{17}H_{16}ON_4S_2$	15·9	15·7
(10) 2-p-*Aminophenyl*-1-*phenyl-*[e]	*p*-C_6H_4·NH_2	H	Ph	B	203—204	$C_{15}H_{14}N_4S_2$	17·5	17·8
(11) 2-*Methyl*-1 : 2-*diphenyl-*	Ph	Me	Ph	B	198—198·5	$C_{16}H_{15}N_3S_2$	13·2	13·4
(12) 1-*Phenyl*-2-*styryl-*	Ph·CH:CH	H	Ph	B	201—202	$C_{17}H_{15}N_3S_2$	12·9	12·9
(13) 1-p-*Carboxyphenyl*-2-*phenyl-* ...	Ph	H	*p*-C_6H_4·CO_2H	A	231—232	$C_{16}H_{13}O_2N_3S_2$	12·4	12·2
(14) 2-Carboxymethyl-2-methyl-[f]	·CH_2·CO_2H	Me	Ph	B	208	$C_{12}H_{13}O_2N_3S_2$	14·3	14·2

[a] A = EtOH; B = BuOH; C = pyridine–ether; D = chlorobenzene. [b] Brodski (*loc. cit.*) records m. p. 237°. Foye and Hefferren (*loc. cit.*) record m. p. 236—238°. Both products were undepressed in m. p. by our product. [c] *Idem, ibid.*, record m. p. 239—240°. [d] *Idem, ibid.*, record m. p. 249—250°. [e] Prepared by alkaline hydrolysis of the foregoing compound. [f] Fromm and Philippe (*loc. cit.*) record m. p. 214—216°.

complete. Dilution with water gave an oil which soon crystallised (2·27 g.; m. p. 151—152°). Recrystallisation from light petroleum or methanol afforded pure 4-*phenyliminotetrahydro*-2 : 2 : 3-*trimethyl*-6-*methylthio*-1-*phenyl*-1 : 3 : 5-*triazine* (XIX; R = Ph), m. p. 153—154° (Found : N, 16·5. $C_{19}H_{22}N_4S$ requires N, 16·6%).

(e) *With sodium hydroxide.* N-Sodium hydroxide (102 c.c.; 1 equiv.) was added to a solution of the methiodide (42·6 g.) in methanol (70 c.c.), thiol being immediately liberated. After 2½ hr. the methanol was evaporated under reduced pressure to crystallisation point. A first crop (23·5 g.; m. p. 145—147°) was thus obtained and a second crop (0·48 g.; m. p. 142°) by further concentration. Recrystallisation from acetone afforded *tetrahydro*-2 : 2 : 3-*trimethyl*-6-*methylthio*-4-*oxo*-1-*phenyl*-1 : 3 : 5-*triazine* (XII) (15·3 g.), m. p. 156—157° (Found : C, 59·3; H, 6·5; N, 15·9. $C_{13}H_{17}ON_3S$ requires C, 59·3; H, 6·5; N, 16·0%). The *picrate* separated from ethanol in prisms, m. p. 161—161·5° (Found : C, 46·75; H, 4·0; N, 17·3. $C_{19}H_{20}O_8N_6S$ requires C, 46·35; H, 4·05; N, 17·1%).

Hydrolysis of Tetrahydro-2 : 2 : 3-*trimethyl*-4-*oxo*-1-*phenyl*-6-*methylthio*-1 : 3 : 5-*triazine* (XII). —This compound (1·0 g.) was heated on the steam-bath with 5N-hydrochloric acid (5 c.c.) for 3 hr., methanethiol being evolved. On cooling, a solid crystallised in plates. After filtration the mother-liquor was diluted with water, and sodium bromide (4 g.) was added and then aqueous sodium bromate until free bromine was detectable. The precipitated 2 : 4 : 6-tribromoaniline (1·17 g., 93·5%) had m. p. and mixed m. p. 116—117°.

Recrystallisation of the crystalline hydrolysis product (0·28 g.) from light petroleum and from ethyl acetate afforded N-*methyl*-N′-*methylthiocarbonylurea* (XV) as plates, m. p. 146—147°

(Found: C, 32·7; H, 5·9; N, 19·1. $C_4H_8O_2N_2S$ requires C, 32·4; H, 5·4; N, 18·9%). It was soluble in dilute aqueous sodium hydroxide but not in sodium carbonate, and its sulphur was not present as thiono-sulphur (negative sodium plumbite test). When warmed for a few minutes with an excess of aniline just below its b. p., it afforded 1 : 5-diphenylbiuret, which after repeated crystallisation from ethanol had m. p. 209—210° undepressed by authentic material prepared from phenylurea and phenyl *iso*cyanate (Kuhn and Hentschel, *Ber.*, 1888, **21**, 504).

Tetrahydro-2 : 2 : 3-trimethyl-6-methylthio-4-oxo-1-phenyl-1 : 3 : 5-triazine 5-Methiodide.—The foregoing material (2·08 g.) was heated with methyl iodide (20 c.c.) in a sealed tube at 70° for 96 hr. A small amount of needles (0·08 g.; m. p. >250°) was filtered off and identified as dimethylammonium iodide by conversion into the picrate, m. p. and mixed m. p. 158—160°. The mother-liquor was evaporated *in vacuo* and the residue was extracted with hot benzene (15 c.c.). Crystallisation of the benzene-insoluble fraction afforded the *5-methiodide* as plates, m. p. 127—128° (Found: C, 41·3; H, 5·0. $C_{14}H_{20}ON_3IS$ requires C, 41·5; H, 4·95%).

The methiodide (0·22 g.) was heated overnight under reflux with concentrated hydrochloric acid (5 c.c.). The solution was evaporated to dryness *in vacuo*, and the residue basified with 5N-sodium hydroxide and extracted with ether. The dried extract was evaporated after the addition of acetic anhydride (0·2 c.c.). Water (0·2 c.c.) was added to the residue whereupon acetanilide (0·016 g.) crystallised, having m. p. and mixed m. p. 112—113°. Evaporation of the mother-liquor furnished, after crystallisation from light petroleum, a further 0·012 g., making a total of 0·028 g. (35%).

Hexahydro-2 : 2 : 3-trimethyl-4 : 6-dioxo-1-phenyl-1 : 3 : 5-triazine (XVI; R = H).—Tetrahydro-2 : 2 : 3-trimethyl-6-methylthio-4-oxo-1-phenyl-1 : 3 : 5-triazine (3·40 g.) was dissolved in glacial acetic acid (13·5 c.c.) and hydrogen peroxide (3·4 c.c of 100-vol.) was added with water-cooling. After 12 hr. the solution was diluted with water and made alkaline with sodium carbonate. The crystalline precipitate was collected and recrystallised from ethanol, affording *hexahydro-2 : 2 : 3-trimethyl-4 : 6-dioxo-1-phenyl-1 : 3 : 5-triazine* as needles, m. p. 248—249° raised to 251—252° by further recrystallisation (Found: C, 61·8; H, 6·5; N, 18·1. $C_{12}H_{15}O_2N_3$ requires C, 61·8; H, 6·4; N, 18·0%). The compound was soluble in dilute aqueous sodium hydroxide but not in sodium carbonate.

Hexahydro-2 : 2 : 3 : 5-tetramethyl-4 : 6-dioxo-1-phenyl-1 : 3 : 5-triazine (XVI; R = Me).—(*a*) N-Sodium hydroxide (10 c.c., 2 equivs.) was added to a suspension of the foregoing compound (1·13 g.) in methanol (17·5 c.c.), a clear solution resulting. Excess of methyl iodide (1·0 c.c.) was added and the mixture kept 12 hr. after which it was neutral. The methanol was removed in a current of air, the product (0·98 g.) crystallising in plates, m. p. 138—140°. Repeated recrystallisation from light petroleum (b. p. 100—120°) afforded *hexahydro-2 : 2 : 3 : 5-tetramethyl-4 : 6-dioxo-1-phenyl-1 : 3 : 5-triazine* as needles, m. p. 146—147° with sintering at 141° [Found: C, 63·4; H, 7·1; OMe, 0·30, 0·25. $C_{13}H_{17}O_2N_3$ requires C, 63·1; H, 6·9; OMe, 0% (6·0% for 1OMe)]. It was feebly basic, insoluble in N- but soluble in 5N-hydrochloric acid from which it could be recovered unchanged after 12 hr.

(*b*) The foregoing 5-methiodide (0·15 g.) was dissolved in warm water (3 c.c.), the odour of methanethiol becoming immediately apparent. N-Sodium hydroxide (0·37 c.c., 1 equiv.) was then added. The solution was cooled and the crystalline product (0·06 g.) filtered off. Recrystallisation from light petroleum afforded the above compound (XVI; R = Me) as needles, m. p. and mixed m. p. 146—147° (Found: C, 62·8, 63·2; H, 6·7, 6·9%).

The compound (0·4 g.) was heated under reflux with 48% hydrobromic acid (5 c.c.), and the solution evaporated to dryness. The crystalline residue was basified with sodium hydroxide and steam-distilled and the steam-distillate extracted with ether. The extract was dried and treated for 1 hr. with pyridine (0·19 g.) and benzoyl chloride (0·25 g.). The solution was evaporated *in vacuo* and the residue triturated with water, affording benzanilide (0·24 g., 75%), m. p. and mixed m. p. 160—161°.

Tetrahydro-2-phenyl-4 : 6-dithiono-1 : 3 : 5-triazine (XX; X = S).—(*a*) 2 : 4-Dihydroxy-6-phenyl-1 : 3 : 5-triazine (Adams *et al.*, *loc. cit.*) (120 g.) was heated under reflux with phosphorus oxychloride (60 c.c.) for 1½ hr. The clear solution was poured on ice, and the 2 : 4-dichloro-6-phenyl-1 : 3 : 5-triazine (XXI; R = Cl) was isolated and crystallised from ethanol (8·4 g.; m. p. 119—120°) (Ostrogovich, *loc. cit.*, records m. p. 119—120°). A suspension of this compound (6·78 g.) in a solution of potassium hydrogen sulphide, prepared by saturating a solution of potassium hydroxide (7·9 g.) in water (10 c.c.) with hydrogen sulphide, was heated on the steam-bath for 10 min., the character of the solid undergoing considerable change. Addition of water (200 c.c.) gave a clear solution and acidification with acetic acid afforded *tetrahydro-2-phenyl-4 : 6-dithiono-1 : 3 : 5-triazine* as a yellow solid (5·3 g.), m. p. 246—248°. It crystallised from

ethanol in yellow needles, m. p. 248—249° (Found: C, 49·3; H, 3·5; N, 18·9. $C_9H_7N_3S_2$ requires C, 48·9; H, 3·2; N, 19·0%). Methylation in the usual manner gave 2 : ***4-dimethylthio-6-phenyl-1 : 3 : 5-triazine*** as colourless needles (from ethanol), m. p. 94—95° (Found: N, 16·9. $C_{11}H_{11}N_3S_2$ requires N, 16·9%).

(*b*) A solution of dithiobiuret (2·7 g.) in ethyl acetate (100 c.c.) was heated under reflux for 2 hr. with benzoyl chloride (2·4 c.c.). Ethyl acetate was then removed *in vacuo*, pyridine (5 c.c.) was added, and heating was continued for 2 hr. on the steam-bath. Addition of aqueous acetic acid gave a brown solid which was purified by solution in aqueous sodium hydroxide, filtration, and reprecipitation with acetic acid. Crystallisation from ethanol afforded yellow needles (1·2 g.), m. p. 245—247° undepressed by the previously described compound.

(*c*) The following methods were unsuccessful: (i) Fusion of benzamidine with perthiocyanic acid at 100° gave an almost quantitative yield of ***benzamidinium thiocyanate***, crystallising from *iso*propanol–ether in needles, m. p. 105—106° (Found: N, 23·2. $C_8H_9N_3S$ requires N, 23·5%), identical with the product obtained by evaporating a methanolic solution of benzamidine and ammonium thiocyanate. (ii) Equimolecular proportions of dithiobiuret and trimethyl orthobenzoate, suspended in ethanol and saturated with dry hydrogen chloride, afforded a solid hydrochloride. Liberation of the base and crystallisation from ethanol gave 2-*methyl*-2-iso***dithiobiuret***, m. p. 134—135° (Found: N, 28·0. $C_3H_7N_3S_2$ requires N, 28·2%). This was identical with the compound obtained by condensation of equimolecular quantities of dithiobiuret and methyl sulphate at 100°, basification of the product, and crystallisation of the free base. In the same way dithiobiuret and ethyl orthoformate yielded 2-*ethyl*-2-iso***dithiobiuret***, m. p. 94—96° (Found: C, 29·4; H, 5·6; N, 25·7. $C_4H_9N_3S_2$ requires C, 29·4; H, 5·5; N, 25·8%), as did dithiobiuret and diethyl sulphate at 100°.

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