The Action of Ammonia on 4-Alkylidene-2-thiothiazolid-5-ones.

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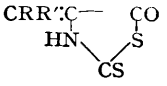
In addition to the previously reported 5-substituted 2-thiothiazolidine-4-carboxyamides the action of ammonia on 4-alkylidene-2-thiothiazolid-5-ones gives acidic substances, sometimes as the major products, which on the basis of chemical and physical properties are formulated as 5-substituted tetrahydro-2-thioglyoxaline-4-thiocarboxylic acids.

The action of aqueous ammonia on 4-substituted-methylene-2-thiothiazolid-5-ones (I) in which one of the groups R and R′ is aromatic (either benzenoid or heterocyclic) is known to lead to 5-substituted 2-thiothiazolidine-4-carboxyamides (II) or to 5-arylidene-2-thiohydantoins (III) or a mixture of both (Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337; Cook, Hunter, and Pollock, *J.*, 1950, 1892; Holland and Nayler, *J.*, 1953, 285). The corresponding reaction with 4-alkylidene-2-thiothiazolid-5-ones (I; R = alkyl, R′ = H or alkyl) has been less thoroughly studied but Cook, Hunter, and Pollock (*loc. cit.*) reported that the 4-*iso*propylidene and 4-*iso*butylidene compounds gave the amides (II; R = R′ = Me, and R = Pr^i, R′ = H, respectively) whereas 4-*cyclo*pentylidene-2-thiothiazolid-5-one (I; R + R′ = $[CH_2]_4$) afforded 5-*cyclo*pentylidene-2-thiohydantoin (III; R + R′ = $[CH_2]_4$).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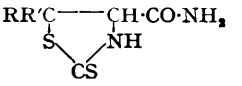
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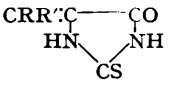
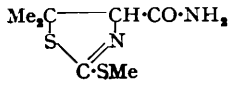

(III)

During attempts to synthesise *iso*leucine *via* derivatives of α-amino-β-mercapto-β-methylvaleric acid (cf. Doyle, Holland, Marflitt, Nayler, and O'Connor, *J.*, 1955, 1719), the action of ammonia on 4-*sec.*-butylidene-2-thiothiazolid-5-one (I; R = Me, R′ = Et) was found to give very little of the desired 5-ethyl-5-methyl-2-thiothiazolidine-4-carboxyamide (II; R = Me, R′ = Et) but yielded mainly an isomeric acidic product which appeared to be a mixture of two forms (see p. 2267). When the reaction was applied to 4-*iso*propylidene-2-thiothiazolid-5-one (I; R = R′ = Me), thus avoiding *cis-trans*-isomerism, only about 1% of 5 : 5-dimethyl-2-thiothiazolidine-4-carboxyamide (II; R = R′ = Me), m. p. 178—179°, identical with a specimen prepared from the corresponding methyl ester and ammonia, was obtained. The major product, m. p. 151° (decomp.), was isomeric with the amide (II; R = R′ = Me), and similar in general properties to the acidic product from the *sec.*-butylidene derivative. Similar results were obtained whether hot aqueous or cold alcoholic ammonia was used. Cook, Hunter, and Pollock (*loc. cit.*) reported only one product, m. p. 145°, from the reaction of 4-*iso*propylidene-2-thiothiazolid-5-one with ammonia, which they considered to be the amide (II; R = R′ = Me). This with methyl sulphate and potassium hydroxide gave a compound, m. p. 206°, which was assumed by these workers to be the *S*-methyl derivative (IV) although it did not give 5 : 5-dimethylthiazolidine-4-carboxyamide on reaction with aluminium amalgam. Cook *et al.* (*loc. cit.*) considered the latter reagent had caused isomerisation although the m. p. of the product (200°) was not depressed by admixture with the starting material. It appears likely, however, that the compound, m. p. 145°, was identical with our acid, m. p. 151° (decomp.), since the latter with methyl sulphate and alkali gave a methyl ester, m. p. 206°, which was unchanged by prolonged heating with aluminium amalgam.

The compound, m. p. 151° (decomp.), when heated with aqueous mineral acid yielded an acid, $C_6H_{10}O_2N_2S$, in which a thiol group had been replaced by hydroxyl. Cold methanolic or ethanolic hydrogen chloride effected a similar replacement to give a methyl and an ethyl ester, respectively. Both the latter ester and the methyl ester (m. p. 206°) on mild alkaline hydrolysis also gave the same acid $C_6H_{10}O_2N_2S$. These reactions indicated the presence of a thiocarboxyl group in the acid, m. p. 151° (decomp.). Of the possible structures (VI, VII, and VIII; R = R′ = Me) containing such a grouping (VI) appeared

to be unlikely since it would have been expected to cyclise either to the thiazolidone (I; R = R′ = Me) or, more probably, to the thiohydantoin (III; R = R′ = Me) on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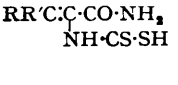
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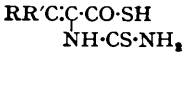
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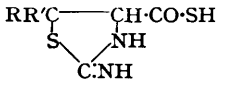
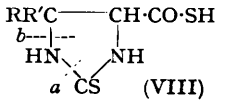

(VII)

treatment with mineral acid. The structure (V) would likewise have been expected to revert to the thiazolidone.

Of the remaining structures (VII and VIII; R = R′ = Me) evidence against the former was obtained by the action of Raney nickel on the derived acid, $C_6H_{10}O_2N_2S$. Behringer and Zillikens (*Annalen*, 1951, **574**, 140) found that 2-aminothiazoline-4-carboxylic acid, which is unaffected by mineral acid, yielded alanine when reduced by Raney nickel. The acid, $C_6H_{10}O_2N_2S$, under these conditions, however, lost only a sulphur atom to give a product, $C_6H_{10}O_2N_2$, which was tentatively formulated as the dihydroglyoxaline (IX or X; R = H): the acid $C_6H_{10}O_2N_2S$ would thus have the structure (XI; R = R′ = Me, R″ = H) and the original compound the structure (VIII; R = R′ = Me). The ester (XI; R = R′ = Me, R″ = Et) was also desulphurised with Raney nickel to give (IX or X; R = Et), isolated as a picrate.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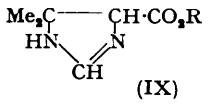
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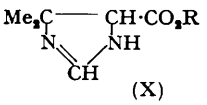
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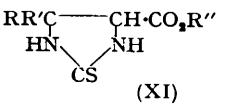
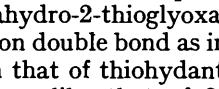

(XI)

Further support for structures (VIII—XI) was obtained by the action on the ester (XI; R = R′ = Me, R″ = Et) of (i) chloroacetic acid which gave a small quantity of a compound, $C_8H_{14}O_3N_2$, considered to be (XII), (ii) acetic anhydride which yielded a mixture of mono- and di-acetyl derivatives, and (iii) methyl iodide in dry acetone in the presence of potassium carbonate which yielded a basic methyl derivative, considered to be (XIII) or (XIV).

It appears from Baer and Lockwood's work (*J. Amer. Chem. Soc.*, 1954, **76**, 1162) that 2-alkylthiodihydroglyoxalines are more stable towards alkali than are acyclic *S*-alkyl*iso*-thioureas, and it was indeed found that brief heating of the substance (XIII or XIV) with aqueous sodium hydroxide gave no methanethiol and more prolonged treatment in the cold caused hydrolysis of the ester group only.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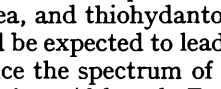
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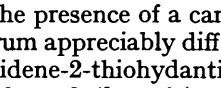
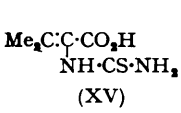

(XIV)

Further evidence in favour of structure (VIII; R = R′ = Me) was obtained from a comparison of ultraviolet spectra. This acid, the derived acid $C_6H_{10}O_2N_2S$, and the esters of both compounds all have an absorption maximum at 241—244 mμ, as have tetrahydro-2-thioglyoxaline, thiourea, and thiohydantoic acid. The presence of a carbon–carbon double bond as in (VI) would be expected to lead to a spectrum appreciably different from that of thiohydantoic acid since the spectrum of 5-*iso*propylidene-2-thiohydantion is quite unlike that of 2-thiohydantoin. Although Baer and Lockwood (*loc. cit.*) report $\lambda_{max.}$ 222 mμ (ε 10,500) for 2-*n*-butylthio-Δ^1-dihydroglyoxaline hydrochloride, neither dihydro-5 : 5-dimethyl-2-methylthioglyoxaline-4-carboxylic acid hydrochloride nor dihydro-2-methylthio-Δ^1-glyoxaline hydriodide showed ultraviolet absorption maxima at wavelengths greater than 210 mμ. Chemical evidence against an unsaturated acyclic structure was provided by the recovery of the acid (XI; R = R′ = Me, R″ = H) after attempted reduction with zinc and boiling acetic acid for 1 hr. or red phosphorus, iodine, and boiling moist acetic acid for 7 hours (cf. Miescher and Billeter, *Helv. Chim. Acta*, 1939, **22**, 601); treatment with sodium in liquid ammonia yielded no tractable product.

An alternative synthesis of the acid (XI; R = R′ = Me, R″ = H) *via* αβ-diamino-*iso*valeric acid failed when treatment of αβ-dibromo*iso*valeric acid with ammonia or potassium phthalimide yielded only 1-bromo*iso*butene (cf. Massot, *Ber.*, 1894, **27**, 1226; Farrell

and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 1281). When ethyl αβ-dibromo*iso*valerate was heated with ethanolic ammonia under pressure no definite organic product could be isolated.

Attempts to prepare ββ-dimethyl-α-thioureidoacrylic acid (XV) for comparison with the acid, $C_6H_{10}O_2N_2S$, were also unsuccessful. When 5-*iso*propylidene-2-thiohydantoin (III; R = R′ = Me), which was readily prepared from acetone and 2-thiohydantoin, was heated with dilute alkali the *iso*propylidene group was cleaved, to yield thiohydantoic acid. The structure of 5-*iso*propylidene-2-thiohydantoin was confirmed by heating it with aqueous chloroacetic acid to give 5-*iso*propylidenehydantoin which in turn was catalytically hydrogenated to 5-*iso*propylhydantoin. Another attempt was made to prepare the unsaturated acid (XV) by a method similar to that used for α-acetamido-ββ-dimethylacrylic acid ("The Chemistry of Penicillin," Oxford Univ. Press, 1949, p. 465). A mixture of dimethylpyruvic acid and thiourea was heated under reduced pressure, but no ββ-dimethyl-α-thioureidoacrylic acid was obtained. Instead, 5-*iso*propylidenehydantoin was isolated, together with two unidentified compounds.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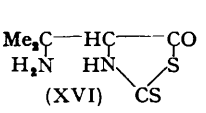
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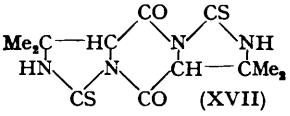
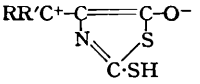
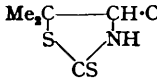

(XVII)

When tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-thiocarboxylic acid (VIII; R = R′ = Me) was heated for a short time in acetic acid, it gave 4-*iso*propylidene-2-thio-5-thiazolidone (I; R = R′ = Me) in 33% yield. Neither its methyl ester nor the derived carboxylic acid (XI; R = R′ = Me, R″ = H) underwent a comparable rearrangement. The thiazolidone could have arisen from (VIII; R = R′ = Me) either by ring opening at (*a*) and loss of ammonia from the amine (XVI) or *via* the acid (VI; R = R′ = Me) after cleavage at (*b*), although in the latter case the thiohydantoin (III; R = R′ = Me) would have been a probable product. Evidence for the former possibility was sought by including acetic anhydride in the reaction in the hope of isolating the acetyl derivative of the hypothetical intermediate (XVI), but neither it nor the thiazolidone (I; R = R′ = Me) was obtained. Instead, an acetyl derivative of the original acid was formed together with a neutral compound of empirical formula $C_6H_8ON_2S$. Both compounds apparently retained the tetrahydro-2-thioglyoxaline nucleus since each gave tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-carboxylic acid on hydrolysis. The acidic acetyl derivative also yielded the ethyl ester (XI; R = R′ = Me, R″ = Et) when treated with cold ethanolic hydrogen chloride. The neutral product, which was also obtained in small yield when the thio-acid was heated with acetic anhydride alone, is tentatively formulated as the diketopiperazine (XVII).

(XVIII)




(XIX)

The action of ammonia on 4-*sec.*-butylidene-2-thio-5-thiazolidone (I; R = Me, R′ = Et) gave a very small yield of 5-ethyl-5-methyl-2-thiothiazolidine-4-carboxyamide (II; R = Me, R′ = Et), which on hydrolysis afforded the corresponding acid (which is known), but the main product appeared to be a mixture of the geometrical isomers of 5-ethyltetrahydro-5-methyl-2-thioglyoxaline-4-thiocarboxylic acid (VIII; R = Me, R′ = Et). Crystallisation of the acidic mixture gave only a small quantity of one isomer (arbitrarily designated the β-form); attempted separation of the phenethylamine salts was not successful. However, when the mixed acids were kept for 24 hours in aqueous sodium hydroxide and then acidified, the α-form resulted, and subsequent reactions were carried out either on this form or on the mixed isomers. Results paralleled those in the dimethyl series and the α-isomers of methyl 5-ethyltetrahydro-5-methyl-2-thioglyoxaline-4-thiol-carboxylate and of the esters (XI; R = Me, R′ = Et, R″ = Me and Et) were obtained without difficulty. Treatment of the mixed isomers of the thio-acid with ethanolic hydrogen chloride afforded chiefly the β-form of ethyl 5-ethyltetrahydro-5-methyl-2-thioglyoxaline-4-carboxylate. The two isomers of the ester (XI; R = Me, R′ = R″ = Et)

yielded the two isomeric acids when hydrolysed with sodium hydroxide in the cold, which contrasts with the apparent inversion of the β-form of the thio-acid under similar conditions.

The ratio of neutral to acidic products obtained by the action of ammonia on 4-alkylidene-2-thiothiazolid-5-ones (I) in which one of the groups R and R′ was hydrogen differed markedly from that when both groups were alkyl. Thus we confirm Cook, Hunter, and Pollock's observation (*loc. cit.*) that the main product from 4-*iso*butylidene-2-thiothiazolid-5-one (I; R = Pr^i, R′ = H) is 5-*iso*propyl-2-thiothiazolidine-4-carboxyamide (II; R = Pr^i, R′ = H), but a very small quantity of tetrahydro-5-*iso*propyl-2-thioglyoxaline-4-thiocarboxylic acid (VIII; R = Pr^i, R′ = H) was also isolated. Ammonia and 4-ethylidene-2-thiothiazolid-5-one (I; R = Me, R′ = H) gave 5-methyl-2-thiothiazolidine-4-carboxyamide (II; R = Me, R′ = H) together with a little acidic gum which was considered to contain the thio-acid (VIII; R = Me, R′ = H) since in hot acetic acid it reverted to 4-ethylidene-2-thiothiazolid-5-one.

The behaviour of 4-*cyclo*pentylidene- and 4-*cyclo*hexylidene-2-thio-5-thiazolidones towards ammonia was intermediate between that of the mono- and di-alkyl types, each giving substantial quantities of both the amide (II) and the thio-acid (VIII). The structures of the former were confirmed by hydrolysis to the corresponding acids, and those of the latter by reconversion into the thiazolidones (I) in hot acetic acid. The case of 4-*cyclo*pentylidene-2-thio-5-thiazolidone was of particular interest since we obtained none of the compound, m. p. 252° (decomp.), which Cook, Hunter, and Pollock (*loc. cit.*) reported as their sole product and considered to be 5-*cyclo*pentylidene-2-thiohydantoin (III; R + R′ = $[CH_2]_4$). A specimen of the latter which we prepared from 2-thiohydantoin and *cyclo*pentanone had m. p. 319° (decomp.).

It appears from the above results that the formation of 5-substituted tetrahydro-2-thioglyoxaline-4-thiocarboxylic acids (VIII) as well as the previously reported 5-substituted 2-thiothiazolidine-4-carboxyamides (II) by the action of ammonia on 4-alkylidene-2-thiothiazolid-5-ones of type (I) is quite general, but there remains no evidence of the formation of 5-alkylidene-2-thiohydantoins (III) in this way. It is not clear whether the tetrahydroglyoxalines are formed by way of the hypothetical unsaturated thio-acids (VI) or by an initial nucleophilic attack by the ammonia on the alkylidene group of the thiazolidone (I), possibly reacting in the form (XVIII).

The reaction of 4-*iso*propylidene-2-thiothiazolid-5-one with ammonia to give chiefly tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-thiocarboxylic acid is in marked contrast to its behaviour with the sodium salts of glycine or alanine, where the products are the peptide precursors (XIX; R = H or Me) (Cook and Pollock, *J.*, 1950, 1898; unpublished work from these laboratories). It was hoped that the inclusion of a strong base in the ammonia reaction would increase the yield of 5 : 5-dimethyl-2-thiothiazolidine-4-carboxyamide (II; R = R′ = Me), but in fact in the presence of 1 equiv. of sodium hydroxide or 3 equivs. of triethylamine the main product was still the thio-acid (VIII; R = R′ = Me).

Experimental

Preparation of 4-Alkylidene-2-thio-5-thiazolidones.—4-*iso*Propylidene-, 4-ethylidene-, and 4-*iso*butylidene-2-thio-5-thiazolidones were prepared as described by Billimoria and Cook (*J.*, 1949, 2323), and Doyle, Holland, Marflitt, Nayler, and O'Connor's method (*loc. cit.*) was used for 4-*sec.*-butylidene-2-thiothiazolid-5-one. 4-*cyclo*Pentylidene- and 4-*cyclo*hexylidene-2-thio-5-thiazolidones were prepared from 2-thio-5-thiazolidone and the appropriate ketones in the presence of zinc chloride (cf. Cook and Pollock, *J.*, 1949, 3007).

Reaction of 4-Alkylidene-2-thiothiazolid-5-ones with Ammonia.—(*a*) A mixture of the thiazolidone (I) (20 g.) and aqueous ammonia (*d* 0·88; 130 ml.) was heated on the steam-bath for 30—60 min. and the clear solution was cooled and strongly acidified with hydrochloric acid to precipitate a pale solid or gum. (In the case of 4-*cyclo*pentylidene-2-thio-5-thiazolidone part of the neutral product separated from the hot solution before acidification, whilst the products from 4-ethylidene-2-thio-5-thiazolidone were water-soluble and were extracted from the acidified solution with ethyl acetate.) The solid or gum was suspended in water and treated with sodium hydrogen carbonate until effervescence ceased. The crude 5-substituted 2-thiothiazolidine-4-carboxyamide (II) was collected and washed with water: details of the purification of individual compounds are given in Table 1. Acidification of the filtrate precipitated the crude

5-substituted tetrahydro-2-thioglyoxaline-4-thiocarboxylic acid (VIII), which frequently separated as a gum in the first instance : the individual acids are recorded in Table 2.

TABLE 1. *5-Substituted 2-thiothiazolidine-4-carboyxamides* (II).

Starting material (I)	Yield (%)	Cryst. form and solvent	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
R = R′ = Me	{1 1 •	Needles, H_2O	178—179°	$C_6H_{10}ON_2S_2$	38·1	5·2	—	37·9	5·3	—
R = Me, R′ = Et	{1 3 •	Plates, H_2O	195—196	$C_7H_{12}ON_2S_2$	41·4	5·8	13·2	41·2	5·9	13·7
R = Me, R′ = H	17	Microcrystals, aq. EtOH	179—181	$C_5H_8ON_2S_2$	34·0	4·5	15·8	34·1	4·6	15·9
R = Pr^i, R′ = H	55	Needles, H_2O	156—157 †	$C_7H_{12}ON_2S_2$	41·5	5·8	13·9	41·2	5·9	13·7
R + R′ = $[CH_2]_4$	70	Prisms, EtOAc	168—169	$C_8H_{12}ON_2S_2$	45·2	6·0	13·2	44·4	5·6	12·9
R + R′ = $[CH_2]_5$	28	Needles, EtOH	211—212	$C_9H_{14}ON_2S_2$	47·4	6·2	11·8	46·9	6·1	12·2

• Method (*b*) used for preparation; in all other cases method (*a*) was used. † Cook, Hunter, and Pollock (*loc. cit.*) give m. p. 131°.

TABLE 2. *5-Substituted tetrahydro-2-thioglyoxaline-4-thiocarboxylic acids* (VIII).

Starting material (I)	Yield (%)	Cryst. form (from EtOH)	M. p. (decomp.)	Formula	Found (%) C	H	N	Required (%) C	H	N
R = R′ = Me	56	Prisms	151°	$C_6H_{10}ON_2S_2$	38·3	5·4	14·9	37·9	5·3	14·7
	69 •	—	—	—	—	—	—	—	—	—
R = Me, R′ = Et	56 †	—	—	—	—	—	—	—	—	—
	38 †	—	—	—	—	—	—	—	—	—
R = Me, R′ = H	Small ‡	—	—	—	—	—	—	—	—	—
R = Pr^i, R′ = H	1	Powder	176—177	$C_7H_{12}ON_2S_2$	41·2	6·0	13·8	41·2	5·9	13·7
R + R′ = $[CH_2]_4$	13	Needles	Indef. >180°	$C_8H_{12}ON_2S_2$	44·7	5·7	12·5	44·4	5·6	12·9
R + R′ = $[CH_2]_5$	67	Needles	Indef. >210°	$C_9H_{14}ON_2S_2$	47·3	6·0	11·9	46·9	6·1	12·2

• See footnote * to Table 1. † Mixture of isomers : isolation of the pure components is described later. ‡ Obtained only as a crude gum which, when heated in acetic acid, gave 4-ethylidene-2-thio-5-thiazolidone, m. p. and mixed m. p. 196° (decomp.).

(*b*) A suspension of the thiazolidone (I) (20 g.) in methanol (200 ml.) was saturated with ammonia and the resulting solution was kept at room temperature for 48 hr., then evaporated *in vacuo*. The residue was treated with dilute hydrochloric acid and worked up as in (*a*).

The four pure thio-acids listed in Table 2 all had an absorption maximum at 244 mμ (ε 17,350) in EtOH (cf. thiourea, $\lambda_{max.}$ 242 mμ, ε 12,780, tetrahydro-2-thioglyoxaline, $\lambda_{max.}$ 241 mμ, ε 16,500, and thiohydantoic acid, $\lambda_{max.}$ 242 mμ, ε 13,710).

Methyl Tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-thiolcarboxylate.—A solution of tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-thiocarboxylic acid (4 g.) in N-potassium hydroxide (30 ml.) was shaken with methyl sulphate (2·5 ml.) and after 90 min. the *methyl ester* (3·04 g., 71%) was collected and crystallised from water or aqueous alcohol as colourless needles, m. p. 206° (Found : C, 41·6; H, 5·8; N, 13·4. $C_7H_{12}ON_2S_2$ requires C, 41·2; H, 5·9; N, 13·7%). Absorption : $\lambda_{max.}$ 244 mμ, ε 18,000 in EtOH.

Methyl Tetrahydro-5 : 5-pentamethylene-2-thioglyoxaline-4-thiolcarboxylate.—The thio-acid (VIII; R + R′ = $[CH_2]_4$) was methylated with methyl sulphate and alkali as above; the *ester* (66%), crystallised from ethanol, had m. p. 217° (decomp.) (Found : C, 49·1; H, 6·6; N, 11·4. $C_{10}H_{16}ON_2S_2$ requires C, 49·1; H, 6·6; N, 11·5%).

Tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-carboxylic Acid.—(*a*) The thio-acid (VIII; R = R′ = Me) (2 g.) in 5N-hydrochloric acid (20 ml.) was refluxed for 90 min., then cooled to 0°. The hydrated *acid* (XI; R = R′ = Me, R″ = H) (1·38 g., 68%) was collected and crystallised from water in colourless prisms, m. p. 185—186° (Found : C, 37·4; H, 6·4; N, 15·1; S, 16·4. $C_6H_{10}O_2N_2S,H_2O$ requires C, 37·5; H, 6·3; N, 14·6; S, 16·7%). Absorption : $\lambda_{max.}$ 242·5 mμ, ε 16,600 in EtOH.

(*b*) The thio-acid (13 g.), suspended in dry ethanol (130 ml.), was saturated with hydrogen chloride at 0°, and the resulting solution was kept at room temperature for 24 hr. The solution was evaporated *in vacuo* and the residue was triturated with sodium hydrogen carbonate solution to yield *ethyl tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-carboxylate* (11·37 g., 82%) which, crystallised from benzene, had m. p. 102—104° (Found : C, 47·3; H. 7·1; N, 14·3; S, 15·9. $C_8H_{14}O_2N_2S$ requires C, 47·5; H, 7·0; N, 13·9; S, 15·9%). Absorption : $\lambda_{max.}$

242·5 mμ, ε 18,450 in EtOH. The *methyl ester*, similarly prepared in 71% yield and crystallised from ethyl acetate, had m. p. 173—174° (Found: C, 44·5; H, 6·3; N, 15·0. $C_7H_{12}O_3N_2S$ requires C, 44·7; H, 6·4; N, 14·9%).

The ethyl ester (7 g.) in alcohol (35 ml.) was treated with 5N-aqueous sodium hydroxide (35 ml.) and set aside for 48 hr. Removal of the alcohol *in vacuo* and acidification of the residue gave the hydrated acid (5·83 g., 88%), identical with the product from (*a*). Hydrolysis of methyl tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-thiolcarboxylate in a similar manner gave the same acid (80%).

Dihydro-5 : 5-dimethylglyoxaline-4-carboxylic Acid.—A solution of tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-carboxylic acid monohydrate (2 g.) in hot water (50 ml.) was refluxed for 4 hr. with Raney nickel, added in two portions. After removal of the nickel, the filtrate was evaporated *in vacuo*, and the residual gum was taken up in alcohol, and the evaporation repeated. The sticky greenish-blue residue was washed with alcohol–ether, and then with alcohol alone, to leave *dihydro-5 : 5-dimethylglyoxaline-4-carboxylic acid* as a white powder (0·81 g.) which crystallised from water–alcohol as needles of the monohydrate, m. p. 191—192° (decomp.) (Found: C, 45·0; H, 7·5; N, 17·3. $C_6H_{10}O_2N_2,H_2O$ requires C, 45·0; H, 7·6; N, 17·5%). The compound gave no colour with ninhydrin.

Reactions of Ethyl Tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-carboxylate.—(a) *With Raney nickel.* The ester (3 g.) in ethanol (30 ml.) was refluxed for 4 hr. with Raney nickel, added in two portions. After removal of the nickel, the filtrate was evaporated *in vacuo* to a green water-soluble gum which did not crystallise. A solution of the gum in warm ethanol was treated with picric acid (7 g.) in the same solvent and the yellow crystals which separated on cooling were collected (3·02 g.). *4-Ethoxycarbonyldihydro-5 : 5-dimethylglyoxaline picrate* crystallised from alcohol in yellow plates, m. p. 207° (Found: C, 42·2; H, 4·2; N, 17·8. $C_{14}H_{17}O_9N_5$ requires C, 42·1; N, 17·5%).

(b) *With chloroacetic acid.* A mixture of the ester (2 g.), chloroacetic acid (3 g.), and water (15 ml.) was refluxed for 2 hr., cooled, and neutralised with sodium hydrogen carbonate. The solution was evaporated *in vacuo*, and the residue extracted with hot ethyl acetate. Evaporation of the extracts gave a gum which afforded a white powder (0·19 g.) when rubbed with ether. *Ethyl tetrahydro-5 : 5-dimethyl-2-oxoglyoxaline-4-carboxylate* (XII) crystallised from ethyl acetate in needles, m. p. 157—158° (Found: C, 51·2; H, 7·7; N, 14·4. $C_8H_{14}O_3N_2$ requires C, 51·6; H, 7·6; N, 15·0%).

(c) *With acetic anhydride.* The ester (3 g.) in acetic anhydride (20 ml.) was refluxed for 16 hr., and the solution evaporated *in vacuo*. The residual solid was washed with water, dried, and boiled with light petroleum (50 ml., b. p. 60—80°). The insoluble residue (0·69 g.) was collected and crystallised from alcohol to give colourless needles of the *monoacetyl derivative*, m. p. 213—214° (Found: C, 49·5; H, 6·7; N, 11·1; S, 12·3. $C_{10}H_{16}O_3N_2S$ requires C, 49·2; H, 6·6; N, 11·5; S, 13·1%). Concentration of the petroleum extracts afforded the *diacetyl derivative* (2·58 g.), which crystallised from the same solvent in colourless prisms, m. p. 62—63° (Found: C, 50·6; H, 6·2; N, 9·6; S, 11·1. $C_{12}H_{18}O_4N_2S$ requires C, 50·3; H, 6·3; N, 9·8; S, 11·2%).

(d) *Methylation.* A mixture of the ester (30·3 g.), dry acetone (150 ml.), potassium carbonate (20·7 g.), and methyl iodide (10·5 ml.) was refluxed with stirring for 4 hr., cooled, and filtered. The solvent was removed *in vacuo* and the residual oil was triturated with light petroleum to give a white solid (29·3 g., 90%). *Ethyl dihydro-5 : 5-dimethyl-2-methylthioglyoxaline-4-carboxylate* crystallised from light petroleum in sheaves of rhombic plates, m. p. 75—77° (Found: C, 50·0; H, 7·3; N, 12·7. $C_9H_{16}O_2N_2S$ requires C, 50·0; H, 7·5; N, 13·0%). The base was stable to distillation (b. p. 91°/0·2 mm.).

Dihydro-5 : 5-dimethyl-2-methylthioglyoxaline-4-carboxylic Acid Hydrochloride.—A solution of the foregoing ester (3·7 g.) in alcohol (18 ml.) was treated with aqueous 5N-sodium hydroxide (18 ml.), set aside at room temperature for 24 hr., acidified with hydrochloric acid, and evaporated *in vacuo*. The residue was dried in a vacuum-desiccator (KOH) and extracted with several portions of hot ethanol. Evaporation of the extracts left a gum which crystallised when rubbed with ethyl acetate–methanol (5 : 1). The *hydrochloride* (2·71 g.) crystallised from ethanol–ethyl acetate in colourless rosettes, m. p. 183—185° (decomp.) (Found: C, 37·3; H, 5·8; N, 12·7. $C_7H_{13}O_2N_2SCl$ requires C, 37·4; H, 5·8; N, 12·5%).

5-iso*Propylidene-2-thiohydantoin.*—A mixture of 2-thiohydantoin (15 g.), acetone (40 ml.), and piperidine (40 ml.) was refluxed for 1 hr., poured into water (700 ml.), and acidified. *5-iso*-Propylidene-2-thiohydantoin (17·9 g.) was collected and crystallised from alcohol (charcoal) in colourless needles, m. p. 261° (decomp.) (Found: C, 45·9; H, 4·9; N, 18·0. Calc. for $C_6H_8ON_2S$:

C, 46·1; H, 5·2; N, 17·9%). Dupré, Hems, and Robinson (Committee for Penicillin Synthesis Report No. 38) give m. p. 258°. Absorption : $\lambda_{max.}$ 238, 269·5, 327 mμ, ε 5320, 6530, 28,300 in EtOH (cf. 2-thiohydantoin : $\lambda_{max.}$ 220, 264 mμ, ε 10,000, 18,050).

Hydrolysis of 5-iso*Propylidene-2-thiohydantoin.*—The thiohydantoin (4 g.) in 10% sodium hydroxide solution (40 ml.) was refluxed for 30 min., cooled, and acidified. After 2 hr. at 0° the colourless crystals were collected, and concentration of the mother-liquor afforded a further crop of thiohydantoic acid (2 g. in all). It formed prismatic needles (from water), m. p. 172—173° (decomp.) [lit., m. p. 170—171° (decomp.)] (Found : C, 27·3; H, 4·7. Calc. for $C_3H_6O_2N_2S$: C, 26·9; H, 4·5%). With boiling 2N-hydrochloric acid the acid afforded 2-thiohydantoin (82%), m. p. and mixed m. p. 230—231° (decomp.). When 5-*iso*propylidene-2-thiohydantoin (1 g.) was boiled with barium hydroxide octahydrate (3 g.) in water (50 ml.) for 15 min., cooled and acidified, 0·15 g. was recovered unchanged together with 0·26 g. of thiohydantoic acid.

5-iso*Propylidenehydantoin.*—A suspension of 5-*iso*propylidene-2-thiohydantoin (3 g.) in 20% aqueous chloroacetic acid (20 ml.) was refluxed for 45 min., during which the thiohydantoin gave place to longer crystals of the hydantoin. The mixture was cooled and 5-*iso*propylidenehydantoin (2·36 g.) was collected. It formed fine colourless needles (from alcohol), m. p. 274° (decomp.) not depressed by admixture with a specimen prepared from acetone and hydantoin in piperidine at 130° (Boon, Carrington, and Jones, Committee for Penicillin Synthesis Report No. 20). We thus confirm the m. p. given by Boon *et al.* and by Tatsuoka and Miyamoto (*J. Pharm. Soc. Japan*, 1949, **69**, 294), whereas the values of 240° (decomp.) and 245° (decomp.) are quoted in Committee for Penicillin Synthesis Report No. 237 and by Cook, Heilbron, and Hunter (*J.*, 1949, 1443).

5-iso*Propylhydantoin.*—A solution of 5-*iso*propylidenehydantoin (2·1 g.) in dilute sodium hydroxide (pH 10) was hydrogenated over Raney nickel at room temperature and pressure : 1 mol. of hydrogen was taken up in about 40 hr. The catalyst was removed and the filtrate was acidified and concentrated *in vacuo* to give colourless plates of 5-*iso*propylhydantoin (1·35 g.), m. p. 145—146° alone or mixed with an authentic specimen (Gaudry, *Canad. J. Res.*, 1946, **24**, *B*, 301).

Reaction of Dimethylpyruvic Acid and Thiourea.—A mixture of dimethylpyruvic acid (Ramage and Simonsen, *J.*, 1935, 532) (3·25 g.) and thiourea (2·13 g.) was heated under reduced pressure (*ca.* 60 mm.) in an oil-bath at 120° for 3 hr. and then at 140° for 2 hr. The gummy mixture was warmed with acetone (30 ml.), and the insoluble white powder (0·62 g.) was collected and crystallised from alcohol to give needles of 5-*iso*propylidenehydantoin, m. p. and mixed m. p. 274° (decomp.) (Found : C, 51·5; H, 5·5; N, 19·8. Calc. for $C_6H_8O_2N_2$: C, 51·4; H, 5·7; N, 20·0%). The acetone solution was evaporated to a gum which on trituration with chloroform deposited 0·75 g. of unchanged thiourea. The chloroform solution was evaporated and the residual oil was triturated with sodium hydrogen carbonate solution, whereupon it crystallised. The neutral *product* (0·60 g.) separated from benzene as a white powder, m. p. 128—130° (Found : C, 52·0; H, 6·2; N, 15·3; S, 17·1. $C_8H_{12}ON_2S$ requires C, 52·2; H, 6·5; N, 15·2; S, 17·4%). The aqueous solution was acidified, whereupon a fawn solid (0·38 g.) slowly separated. This *acid*, which contained no sulphur, crystallised from alcohol in colourless rectangular prisms, m. p. 158—160° (slight decomp.) (Found: C, 52·1; H, 6·5; N, 11·0. $C_{11}H_{16}O_5N_2$ requires C, 51·6; H, 6·3; N, 10·9%).

Reactions of 5-Substituted Tetrahydro-2-thioglyoxaline-4-thiocarboxylic Acids with Acetic Acid.—A solution of tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-thiocarboxylic acid (1 g.) in acetic acid (10 ml.) was refluxed for 30 min. The yellow solution gave a crystalline product when cooled and a further crop was obtained by addition of water. The combined solids (0·30 g., 33%) crystallised from alcohol as rectangular lemon platelets of 4-*iso*propylidene-2-thio-5-thiazolidone, m. p. and mixed m. p. 213—214° (Found : N, 8·0; S, 36·8. Calc. for $C_6H_7ONS_2$: N, 8·1; S, 37·0%). In a similar manner tetrahydro-5 :5-pentamethylene-2-thioglyoxaline-4-thiocarboxylic acid afforded 4-*cyclo*hexylidene-2-thio-5-thiazolidone (28%), which separated from 2-ethoxyethanol in brilliant yellow rhombic plates, m. p. and mixed m. p. 229° (decomp.) (Found : N, 6·6. Calc. for $C_9H_{11}ONS_2$: N, 6·6%). 5-Ethyltetrahydro-5-methyl- and tetrahydro-5 : 5-tetramethylene-2-thioglyoxaline-4-thiocarboxylic acids likewise gave 4-*sec.*-butylidene- and 4-*cyclo*pentylidene-2-thio-5-thiazolidones respectively, identified by mixed m. p.

Reaction of Tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-thiocarboxylic Acid with Acetic Acid and Acetic Anhydride.—A solution of the thio-acid (12 g.) in acetic acid (80 ml.) and acetic anhydride (40 ml.) was refluxed for 30 min., during which a white solid separated. After cooling, the solid (1·97 g.) was collected. This *compound* (possibly XVII) was insoluble in most solvents, but dissolved in boiling dimethylformamide, from which it separated after addition

of alcohol as a powder, m. p. 340° (decomp.) (Found: C, 46·6; H, 5·6; N, 18·1; S, 20·5. $C_{12}H_{16}O_2N_4S_2$ requires C, 46·1; H, 5·2; N, 17·9; S, 20·5%). (When this substance was boiled with 48% hydrobromic acid for 2 hr. it gave tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-carboxylic acid in 55% yield.)

The original filtrate was diluted with an equal volume of water and after 3 days the cream-coloured solid was collected (1·58 g.) and crystallised from ethyl acetate as colourless crystals of an *acetyl derivative*, m. p. 183°, of the thio-acid (Found: C, 41·7; H, 5·1; N, 11·5; S, 27·2. $C_8H_{12}O_2N_2S_2$ requires C, 41·4; H, 5·2; N, 12·1; S, 27·6%). The compound dissolved in sodium hydrogen carbonate solution with effervescence. With 5N-hydrochloric acid (90 min.; reflux) it gave tetrahydro-5 : 5-dimethyl-2-thioglyoxaline-4-carboxylic acid (53%), whereas with saturated ethanolic hydrogen chloride (19 hr.; cold) the corresponding ester was obtained in 46% yield.

Hydrolysis of 5-Substituted 2-Thiothiazolidine-4-carboxyamides.—5-Ethyl-5-methyl-2-thiothiazolidine-4-carboxyamide (0·4 g.) was refluxed in 5N-hydrochloric acid (20 ml.) for 7 hr. The cooled solution was extracted with ether and the extracts, after being washed, were themselves extracted with sodium hydrogen carbonate solution. Acidification of the aqueous phase and extraction with ether afforded 5-ethyl-5-methyl-2-thiothiazolidine-4-carboxylic acid as a gum, which was characterised as the phenethylamine salt (0·37 g.), m. p. 182—183° (decomp.) alone or mixed with an authentic specimen (Doyle, Holland, Marflitt, Nayler, and O'Connor, *loc. cit.*). Hydrolysis of 5 : 5-tetramethylene-2-thiothiazolidine-4-carboxyamide (1 g.) with boiling 5N-hydrochloric acid (25 ml.) gave the carboxylic acid (0·58 g.), which crystallised from water in colourless plates, m. p. 167—168° alone or mixed with an authentic specimen (Cook and Pollock, *J.*, 1949, 3007) (Found: C, 44·3; H, 5·2; N, 6·4. Calc. for $C_8H_{11}O_2NS_2$: C, 44·2; H, 5·1; N, 6·5%). The 5 : 5-pentamethylene analogue similarly afforded 5 : 5-pentamethylene-2-thiothiazolidine-4-carboxylic acid (92%), colourless needles (from water), m. p. 202—204° alone or mixed with an authentic specimen (Billimoria, Cook, and Heilbron, *J.*, 1949, 1437) (Found: C, 46·3; H, 5·6; N, 6·5. Calc. for $C_9H_{13}O_2NS_2$: C, 46·7; H, 5·7; N, 6·1%).

Experiments with 5-Ethyltetrahydro-5-methyl-2-thioglyoxaline-4-thiocarboxylic Acid.—Repeated crystallisation of the low-melting mixture of isomers of the thio-acid (VIII; R = Me, R′ = Et) (Table 2) from methylene dichloride gave a very small recovery of the pure β-*isomer*, m. p. 155—156° (decomp.) (Found: C, 40·8; H, 6·0; N, 13·6; S, 30·9. $C_7H_{12}ON_2S_2$ requires C, 41·2; H, 5·9; N, 13·7; S, 31·4%). Absorption: $\lambda_{max.}$ 244 mμ, ε 17,350 in EtOH.

A solution of the mixed isomers (from 6 g. of 4-*sec.*-butylidene-2-thio-5-thiazolidone) in alcohol (15 ml.) was treated with 10% aqueous sodium hydroxide (30 ml.), set aside for 24 hr., and acidified with concentrated hydrochloric acid to precipitate the crude α-isomer of the acid (4·58 g.), m. p. 117—123° (decomp.). Crystallisation from ethanol gave white clumps of the pure α-*isomer*, m. p. 138° (decomp.) (Found: C, 41·3; H, 5·6; N, 13·8; S, 31·3%). Absorption: $\lambda_{max.}$ 244 mμ, ε 17,350 in EtOH. The m. p.s of the α- and the β-acid were depressed on admixture. The final purification of the α-acid could be accomplished with smaller loss by treating a solution of the material, m. p. 117—123° (decomp.), in a little chloroform with phenethylamine, whereupon the almost pure α-*isomer* of *phenethylamine 5-ethyltetrahydro-5-methyl-2-thioglyoxaline-4-thiolcarboxylate* separated in high yield, m. p. 163—164° (decomp)., unchanged on crystallisation from water (needles) (Found: C, 55·5; H, 7·0; N, 13·1; S, 20·0. $C_{15}H_{23}ON_3S_2$ requires C, 55·4; H, 7·1; N, 12·9; S, 19·7%). Treatment of the salt with dilute hydrochloric acid gave the pure α-acid, m. p. 138° (decomp.).

The thio-acid (α-isomer, 2 g.) and potassium hydroxide (0·7 g.) in water (20 ml.) were shaken with methyl sulphate (1·2 ml.). After 30 min., *methyl 5-ethyltetrahydro-5-methyl-2-thioglyoxaline-4-thiolcarboxylate* (1·15 g.) was collected and crystallised from ethyl acetate in colourless prisms, m. p. 145—147° (Found: C, 43·7; H, 6·7; S, 29·2. $C_8H_{14}ON_2S_2$ requires C, 44·0; H, 6·5; S, 29·4%).

The thio-acid (α-isomer; 1 g.) in methanol (25 ml.) was saturated with dry hydrogen chloride at 0°, and set aside for 24 hr. After removal of solvent *in vacuo*, the oily residue was washed with sodium hydrogen carbonate solution, dried, and rubbed with ether to induce crystallisation. The α-*isomer* of *methyl 5-ethyltetrahydro-5-methyl-2-thioglyoxaline-4-carboxylate* (0·5 g.) crystallised from water in colourless needles, m. p. 146—148° (Found: C, 47·7; H, 7·8; N, 14·2; S, 16·4. $C_8H_{14}O_2N_2S$ requires C, 47·5; H, 7·0; N, 13·9; S, 15·9%). The α-*isomer* of the corresponding ethyl ester, similarly prepared in 81% yield and crystallised from ethyl acetate, had m. p. 111—112° (Found: C, 50·2; H, 7·9; N, 13·4; S, 15·4. $C_9H_{16}O_2N_2S$ requires C, 50·0; H, 7·5; N, 13·0; S, 14·8%).

The thio-acid (mixed isomers; 10·45 g.) was treated with ethanolic hydrogen chloride as

above to give a crude product (7·23 g.), m. p. 104—105°, mixed m. p. with the α-ester 95—96°. Crystallisation from ethyl acetate gave the β-*isomer* of the ethyl ester (4·61 g.), m. p. 111—112°, mixed m. p. with the α-isomer 97—99° (Found : C, 50·1; H, 7·8; N, 13·3; S, 15·2%).

The above ethyl ester (α-isomer; 1·45 g.) in alcohol (7 ml.) was set aside with aqueous 5N-sodium hydroxide (7 ml.) for 48 hr. Alcohol was removed *in vacuo*, and the residue acidified with hydrochloric acid. On storage at 0° the α-*isomer* of 5-ethyltetrahydro-5-methyl-2-thioglyoxaline-4-carboxylic acid (0·67 g.) separated; it crystallised from water in colourless prisms, m. p. 197—198° (Found : C, 44·7; H, 6·2; N, 15·2. $C_7H_{12}O_2N_2S$ requires C, 44·7; H, 6·4; N, 14·9%). The β-*isomer* of the acid, similarly prepared from the β-ester, crystallised from water as the hemihydrate, m. p. 193—195° (Found : C, 42·4; H, 6·6; N, 14·0; S, 15·8. $C_7H_{12}O_2N_2S,0·5H_2O$ requires C, 42·6; H, 6·6; N, 14·2; S, 16·3%). A mixture of the isomeric acids had m. p. 173—177°.

5-cyclo*Pentylidene-2-thiohydantoin*.—A mixture of 2-thiohydantoin (2 g.), *cyclo*pentanone (8 ml.), and piperidine (8 ml.) was refluxed for 90 min., cooled, and poured into an excess of dilute hydrochloric acid. The crude 5-cyclo*pentylidene-2-thiohydantoin* (2·3 g.) was collected and crystallised from 2-methoxyethanol (charcoal) in small yellow crystals, m. p. 319° (decomp.) (Found : C, 52·9; H, 5·5; N, 15·8. $C_8H_{10}ON_2S$ requires C, 52·7; H, 5·5; N, 15·4%).

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