Reactions of α-Thioacylamino-acids. Their Conversion into Thiazolones and Derivatives Thereof.

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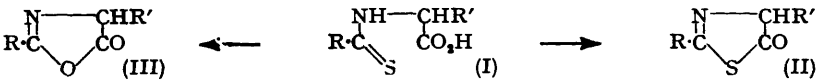
[Reprint Order No. 6126.]

A number of α-amino-acids have been thioacylated by various agents, including thion-esters, then cyclised to thiazolones (II) and under certain conditions acyloxythiazoles (VIII). The thiazolone ring opened readily with amines to give thioacylamino-amides, and condensation with acetone and aromatic aldehydes gave the corresponding alkylidene derivatives. The " orthoformate " synthesis applied to thiohippuric acid gave the oxonols (IX), the heteroalkylidenethiazolones being obtained from sodium thiohippurate and acid anhydrides.

Dehydration of α-acylamino-acids to oxazol-5-ones is a general reaction, the products being useful intermediates in the synthesis of amino-acids and amino-ketones (Carter, " Organic Reactions," Vol. III, p. 198). It seemed of interest to investigate the ring closure of α-thioacylamino-acids (I) which could give thiazol-5-ones (II) by loss of water, or oxazol-5-ones (III) by loss of hydrogen sulphide. A preliminary account of certain aspects of this work was given by McOmie (*Ann. Reports*, 1948, **45**, 207, 209).



The first α-thioacylamino-acid, thiohippuric acid (Gatewood and Johnson, *J. Amer. Chem. Soc.*, 1928, **50**, 2904), was obtained by the action of phosphorus pentasulphide on ethyl hippurate followed by hydrolysis, but in poor yield owing partly to the further formation of alkoxythiazoles (Tarbell, Hirschler, and Carlin, *J. Amer. Chem. Soc.*, 1950, **72**, 3138), and the method sometimes fails (Todd, Bergel, and Karimullah, *J.*, 1936, 1557).

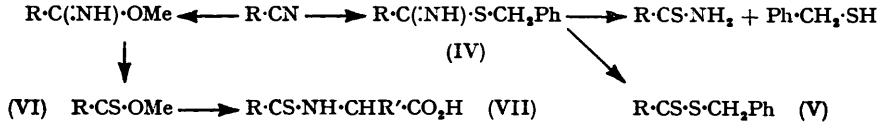
Thioacylation of amines by dithio-acids, developed first by Todd *et al.* (*loc. cit.*) and used by Wuytes and Vaerenburgh (*Bull. Soc. chim. belges*, 1939, **48**, 329), was applied to a number of amino-acids with the use of dithiophenylacetic acid by several groups of workers in the penicillin field (" Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 778). To avoid the earlier difficulties Todd and Topham (Manchester Group, Committee of Penicillin Synthesis, Report No. 93, 1944) and other workers used methyl dithiophenylacetate, purified by distillation, but the supply of such esters was governed by the availability of the acids.

(Thiobenzoylthio)acetic acid (Ph·CS·S·CH_2·CO_2H), which can be purified by crystallisation, was used by Holmberg (Svedberg Memorial Volume, Uppsala, 1944, p. 299) to thiobenzoylate a number of amino-acids, and later by Kjaer (*Acta Chem. Scand.*, 1950, **4**, 1347; 1952, **6**, 1374) who also used (phenylthioacetylthio)acetic acid (*ibid.*, 1952, **6**, 327). We have found this method satisfactory for the thioacylation of all the amino-acids tried except α-amino*iso*butyric acid for which no method was successful.

Houben and Zivadinovich (*Ber.*, 1936, **59**, 2352) obtained benzyl dithioformate (V; R = H) by the action of hydrogen sulphide on benzyl thioformimidate (IV; R = H). We prepared other benzyl thioimidates (IV; R = Me or CH_2Ph) but no evidence of the formation of the dithioesters (V) was obtained on treatment with hydrogen sulphide; decomposition into the thiol and the thioamide resulted. This parallels the hydrolysis of imidates in that formimidates and aromatic imidates give the corresponding esters whereas aliphatic imidates give the amides (cf. Hartigan and Cloke, *J. Amer. Chem. Soc.*, 1945, **67**, 709; McElvain and Fajardo-Pinzon, *ibid.*, p. 690).

As monothiol esters are powerful acylating agents (Schwyzer, *Helv. Chim. Acta*, 1953, **36**, 414), we considered monothion-esters would be useful thioacylating agents. Methyl thionbenzoate (VI; R = Ph), prepared from methyl benzimidate and hydrogen sulphide

(Sakurada, *Mem. Coll. Sci. Eng. Kyoto*, 1926, **10**, 67), proved very suitable for the thiobenzoylation of amino-acids. Good yields were obtained with glycine, alanine, phenylalanine, aspartic acid, and glutamic acid, the products being identical with those prepared by the Holmberg method (*loc. cit.*). Although the yields were not so high as in the latter case,



the method is of wider scope and can be applied with aliphatic thion-esters. For example (as reported by Jepson and McOmie, Theses, Oxford, 1946), thiohexanoylglycine (VII; R = C_5H_{11}, R′ = H) can be prepared in much higher yield by using methyl thionhexanoate from methyl hexanimidate than by using dithiohexanoic acid (*op. cit.*, p. 710).

Reaction at room temperature of the thioacylamino-acids (VII) with ethanolic silver nitrate gave the oxygen analogues, together with silver sulphide. This constitutes a convenient method for the identification of the thion group (Karjala and McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 2966).

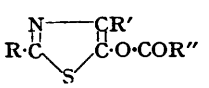
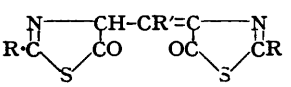
Simultaneous desulphurisation and ring closure of thiohippuric acid (VII; R = Ph, R′ = H) by reaction with fresh silver oxide gave 2-phenyloxazol-5-one (III; R = Ph, R′ = H) smoothly in 61% yield. Other sulphur-removing agents were less successful. The reaction supports the probability of oxazolone intermediates in the reactions of phenylthioacetamido-acids (*op. cit.*, p. 730) but it was the only oxazolone actually isolated from this type of reaction.

Those reagents used for the preparation of oxazolones from acylamino-acids gave the corresponding dehydrative ring closure with thioacylamino-acids, yielding the thiazol-5-ones (II). For example, acetic anhydride (in the absence of a basic catalyst) gave the free thiazolones, whereas phosphorus tribromide yielded the corresponding hydrobromides from which the free bases could be liberated. Thiobenzoyl-aspartic and -glutamic acid formed thiazolones, in contrast to the oxygen analogues which give anhydrides (Swan, *Nature*, 1952, **169**, 826; Lawson, *J.*, 1953, 1046). Such structures were assigned on the basis of their acid reaction, failure to react rapidly with ethanolic silver nitrate, and the similarity of their ultraviolet absorption spectra to that of other thiazolones (see Table 2) and in contrast to that of benzoylaspartic anhydride ($\lambda_{max.}$ 2300 and 3030 Å; ε 10,230 and 316 in EtOH).

In the presence of traces of pyridine, thioacyl-glycine and -alanine with acyl anhydrides gave acyl derivatives (VIII) of the enolised thiazolones, which were also obtained as their hydrochlorides when the free thiazolones were warmed with acyl chlorides in benzene. Chemical evidence for the structure assigned to these substances was their basicity, their hydrolysis to the original thioacylamino-acids, their failure to react with amines or aldehydes, and the preparation of analogous compounds from glycine and alanine derivatives. The formation of such acyl derivatives under these conditions is in contrast to the behaviour of oxazolones.

The ring-opening reactions of thiazolones were analogous to those of the oxazolones. By reaction with ammonia, amines, and phenylhydrazine the expected derivatives were readily obtained. Thiohydantoins, however, were not formed with ammonium thiocyanate.

2-Phenylthiazol-5-one (II; R = Ph, R′ = H) with acetone and aromatic aldehydes, in the absence of an acid anhydride, gave the 4-alkylidene derivatives, also obtained directly

(VIII)   (IX)

from thiohippuric acid under azlactonising conditions and identical with the products obtained by treating the corresponding oxazolones with thioacids or hydrogen sulphide (*op. cit.*, p. 791; Lurye and Gatsenko, *J. Gen. Chem., U.S.S.R.*, 1952, **22**, 256; Behringer and Jepson, *Chem. Ber.*, 1952, **85**, 138).

The " orthoformate " synthesis used by several groups of workers to prepare 4-heteromethylene-5-oxazolones (*op. cit.*, p. 743) was applied to thioacylamino-acids by Abraham, Baker, Chain, and Robinson (*op. cit.*, p. 847), who from phenylthioacetylglycine and ethyl orthoformate obtained a product to which they assigned the methinoxonol structure (IX; R = CH_2Ph, R' = H). The same product was later obtained by du Vigneaud (Cornell Group, Committee of Penicillin Synthesis, Report No. 470, 1945) who formulated it as the double anhydride of phenylthioacetylglycine. A homologue of this substance has been prepared by using ethyl orthoacetate, and both thiohippuric acid and 2-phenylthiazol-5-one have been employed to obtain the analogous derivatives (IX; R = Ph) from ethyl orthoformate and other orthoesters. Direct chemical evidence in favour of the methinoxonol structure was provided by the reaction between 4-ethoxyethylidene-2-phenylthiazol-5-one, obtained from thiohippuric acid under modified conditions, and 2-phenylthiazol-5-one which gave the product (IX; R = Ph, R' = Me) obtainable directly from thiohippuric acid and ethyl orthoacetate. The ready formation of these oxonols, in particular, methinoxonols, shows a further difference in the reactivity of the hydrogen atoms in the 4-position of thiazolones and of oxazolones. The oxonols having a phenyl substituent on the thiazole ring gave intensely blue or red solutions, but the colours were not light-fast enough to make the substances useful as photographic sensitisers.

4-Ethoxyethylidene-2-phenylthiazolone behaved rather differently from the corresponding oxazolone. It reacted as expected with aniline to give the 4-anilinoethylidene-2-phenylthiazolone, but in boiling water the thiazole ring remained intact and the 4-hydroxyethylidene-2-phenylthiazolone, unaffected by boiling 5N-hydrochloric acid, was obtained. This substance and the corresponding analogues were prepared from sodium thiohippurate with acetic, propionic, and phthalic anhydride respectively, by the method used in the oxazolone series (Bullerwell and Lawson, *J.*, 1952, 1350).

Experimental

Benzyl Phenylthioacetimidate.—Dry hydrogen chloride was passed through a solution of equimolar quantities of benzyl cyanide and toluene-ω-thiol in ether at 0°. The *hydrochloride* which crystallised overnight had m. p. 138—142° (decomp.) (from acetone–chloroform) (Found: C, 64·3; H, 5·9; Cl, 13·4. $C_{15}H_{16}NClS$ requires C, 65·0; H, 5·8; Cl, 12·8%). The hydrochloride (5·7 g.) was added slowly to cold aqueous potassium carbonate [3·5 g. (3 equiv.) in 20 ml.], covered with ether, and shaken till dissolved. Removal of the ether gave *benzyl phenylthioacetimidate* (4·4 g., 89%), m. p. 47—48° (decomp.), colourless plates from ethanol (Found: C, 74·5; H, 6·3. $C_{15}H_{15}NS$ requires C, 74·7; H, 6·2%). Decomposition into benzyl cyanide and toluene-ω-thiol took place slowly on storage and very rapidly with alkali. Passing hydrogen sulphide into an ethereal solution of the phenylthioacetimidate gave toluene-ω-thiol (80%) and phenylthioacetamide (64%). Similarly benzyl thioacetimidate (m. p. of hydrochloride was 156°; Houben *et al.*, *loc. cit.*, gave 153°) by reaction with hydrogen sulphide gave toluene-ω-thiol (91%) and thioacetamide (81%).

Methyl Hexanimidate Hydrochloride.—*n*-Hexanonitrile and methanol similarly gave this *hydrochloride* (90%), m. p. 91° (plates from dioxan–ether) (Found: N, 8·3; Cl, 22·1. $C_{17}H_{16}ONCl$ requires N, 8·4; Cl, 21·5%). The free *imidate*, a colourless oil with a characteristic odour, b. p. 60—62°/18 mm., was liberated from the hydrochloride by 5N-sodium hydroxide and extracted with ether (80%) (Found: C, 65·4; H, 11·7; N, 10·7. $C_7H_{15}ON$ requires C, 65·2; H, 11·6; N, 10·8%).

Thiohexanoylglycine.—Dry hydrogen sulphide was passed through a cooled dry ethereal solution of the imidate until precipitation of the ammonium sulphide was complete. After removal of the precipitate by treatment with water, the yellow ether solution containing the thionester was shaken with a solution of glycine in 3N-sodium hydroxide for 18 hr. Acidification of the aqueous layer with concentrated hydrochloric acid at 0°, followed by ether-extraction, gave thiohexanoylglycine, m. p. 108° (white plates from water), in 40% overall yield from the nitrile. Identical material was obtained by using dithiohexanoic acid but the maximum yield was only 3·5% from pentyl bromide.

Methyl Thionbenzoate.—Dry hydrogen sulphide was passed through a solution of methyl benzimidate, b. p. 106°/24 mm. (25 g.), in ether (25 ml.) at 0°. After 1 hr. the yellow solution was shaken with water to remove ammonium sulphide, and the ether layer was dried ($MgSO_4$)

and again treated with hydrogen sulphide for a further 2 hr. After being shaken with water the ether layer was quickly separated, then dried, and the ether removed. The yellow methyl thionbenzoate (81%) distilled at 112—116°/21 mm., leaving a residue of thiobenzamide.

Thiobenzoylation of Amino-acids.—Methyl thionbenzoate (8·2 g., 0·05 mol.) in ether (25 ml.) was vigorously shaken for 18 hr. with a solution of the amino-acid (0·055 mol.) in 3N-sodium hydroxide (30 ml.). The yellow aqueous layer was separated and acidified with concentrated hydrochloric acid at 0°. By this method (A) the yield of thiohippuric acid was 73%, against 37% by Gatewood and Johnson's method (*loc. cit.*) (B) and 78% by Holmberg's method (*loc. cit.*) (C). The new thiobenzamido-acids prepared are shown in Table 1.

TABLE 1. *Thiobenzamido-acids*, Ph·CS·NH·CHR'·CO_2H.

Amino-acid	R'	Method	Yield (%)	M. p.[a]	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
DL-Aspartic acid ...	$CH_2·CO_2H$	A	52	162°	$C_{11}H_{11}O_4NS$	52·1	4·5	52·2	4·3
,, ...	,,	C	79	,,	,,	—	—	—	—
DL-Glutamic acid ...	$[CH_2]_2·CO_2H$	A	47	159	$C_{12}H_{13}O_4NS$	54·1	5·0	53·9	4·9
		C	76	,,	,,	—	—	—	—
DL-Valine	Pr^i	C	73	90	$C_{12}H_{15}O_2NS$	60·9	6·1	60·8	6·3
DL-Norleucine	Bu^n	C	72	142	$C_{13}H_{17}O_2NS$	61·9	6·6	62·2	6·8
DL-Phenylacetic acid	Ph	C	80	145	$C_{15}H_{13}O_2NS$	66·2	4·7	66·4	4·8
DL-Phenylalanine ...	CH_2Ph	A	70	115	$C_{16}H_{15}O_2NS$	67·0	5·1	67·4	5·3
,, ...	,,	C	78	,,	,,	—	—	—	—
DL-Tyrosine	$CH_2·C_6H_4·OH$	C	40	108[b]	$C_{16}H_{15}O_3NS$	63·4	4·8	63·8	5·0
DL-Serine	$CH_2·OH$	C	83	139[c]	$C_{10}H_{11}O_3NS$	53·6	4·9	53·3	4·9
DL-Methionine	$CH_2·CH_2·SMe$	C	75	95[c]	$C_{12}H_{15}O_2NS_2$	53·5	5·6	53·5	5·6

[a] Solvent: ethyl acetate, except as stated. [b] From water. [c] From benzene.

2-Phenyloxazol-5-one.—Thiohippuric acid (2·0 g.) and fresh silver oxide (7·8 g.) were shaken together in dry ether (70 ml.) for 40 hr. The red ethereal solution was centrifuged and evaporated to give the oxazolone, m. p. 86° (1 g., 61%), as pink prisms from ethanol. The use of silver benzenesulphonate in chloroform solution at 0° instead of silver oxide in this reaction gave an inferior yield.

2-Phenylthiazol-5-one.—A solution of thiohippuric acid (2 g.) in acetic anhydride (25 ml.) was heated on the steam-bath for 1 hr. and evaporated under reduced pressure. The residue was extracted with boiling light petroleum (b. p. 40—60°) from which the *thiazolone* crystallised on cooling. Repeated crystallisation from light petroleum gave colourless plates, m. p. 84° (Found: C, 61·3; H, 4·0; N, 7·7; S, 18·0. C_9H_7ONS requires C, 61·1; H, 4·0; N, 7·9; S, 18·1%). *2-Phenylthiazol-5-one hydrochloride*, obtained by passing anhydrous hydrogen chloride into an ether solution of the base, had m. p. 149° (needles from ethyl acetate) (Found: C, 50·7; H, 3·4. C_9H_8ONSCl requires C, 50·6; H, 3·3%); light absorption: $\lambda_{max.}$ 2950 Å, ε 10,470 in EtOH. The *picrate* (needles from ethyl acetate) had m. p. 122° (Found: C, 45·0; H, 2·6. $C_{15}H_{10}O_8N_4S$ requires C, 44·3; H, 2·5%). 2-Phenylthiazol-5-one was also obtained by treating thiohippuric acid with phosphorus trichloride or tribromide in dry dioxan or ether and shaking a suspension of the precipitated salt in ether with sodium acetate. The other thiazolones shown in Table 2, except for the aspartic and glutamic acid derivatives, were prepared from the corresponding thioacylamino-acids by using acetic anhydride as for 2-phenylthiazolone above. Their picrates are described in Table 3. Thiobenzoylaspartic and glutamic acid were converted into

TABLE 2. *Thiazol-5-ones* (II).

Parent amino-acid	R	R'	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H	Light absorption in EtOH $\lambda_{max.}$ (Å)	ε
Alanine	Ph	Me	96[a,d]	$C_{10}H_9ONS$	62·5	4·7	62·8	4·7	3050	9120
Valine	Ph	Pr^i	69[b,e]	$C_{12}H_{12}ONS$	65·1	5·8	65·8	5·9	—	—
Leucine	Ph	Bu^i	41[c,e]	$C_{13}H_{15}ONS$	66·3	6·3	66·9	6·4	—	—
Phenylalanine	Ph	CH_2Ph	72—73[a,e]	$C_{16}H_{15}ONS$*	71·5	4·7	71·9	4·9	3050	14,450
Aspartic acid	Ph	$CH_2·CO_2H$	154[c,f]	$C_{11}H_9O_3NS$	55·9	3·9	56·2	3·8	3050	12,300
Glutamic acid	Ph	$[CH_2]_2·CO_2H$	152[c,f]	$C_{12}H_{11}O_3NS$	58·1	4·7	57·8	4·4	3050	12,880
Glycine	Ph·CH_2	H	45[b,e]	$C_{10}H_9ONS$	62·1	5·0	62·8	4·7	—	—
Alanine	Ph·CH_2	Me	87[a,e]	$C_{11}H_{11}ONS$	64·0	5·2	64·4	5·4	—	—

[a] Needles. [b] Plates. [c] Prisms. [d] From ethyl acetate. [e] From light petroleum. [f] From benzene. * Lurye and Gatsenko (*loc. cit.*) give m. p. 112° for a compound claimed to have this structure.

the thiazolones by dissolving them in warm acetic anhydride, adding benzene, and cooling. They did not form picrates. Other thiazolones were not purified (see footnote, Table 4).

TABLE 3. *Picrates of thiazolones* (II).

R	R	Form, solvent	M. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Ph	Me	Needles, EtOAc	154°	$C_{16}H_{12}O_8N_4S$	45·2	3·0	45·4	2·9
Ph	Pr^i	Prisms, EtOH	117	$C_{18}H_{16}O_8N_4S$	48·6	3·8	48·2	3·6
Ph	Bu^t	Needles, EtOH	98	$C_{19}H_{18}O_8N_4S$	50·0	4·25	49·35	3·9
Ph	Ph·CH$_2$	Needles, EtOH	123	$C_{22}H_{16}O_8N_4S$	53·2	3·4	53·2	3·2
Ph·CH$_2$	H	Needles, EtOH	106	$C_{16}H_{12}O_8N_4S$	45·9	2·8	45·4	2·9
Ph·CH$_2$	Me	Needles, EtOH	144	$C_{17}H_{14}O_8N_4S$	47·5	3·4	47·0	3·2

2-Phenyl-4 : 5-benzo-1 : 3-thiazin-6-one.—(Thiobenzoyl)anthranilic acid (2 g.) was dissolved in warm acetic anhydride (10 ml.). On cooling, the *thiazinone* crystallised. It had m. p. 113° (felted needles from light petroleum) (Found: C, 71·0; H, 3·7. $C_{14}H_9ONS$ requires C, 70·3; H, 3·8%). Light absorption: $\lambda_{max.}$ 2500, 2950, and 3450 Å, ε 30,200, 11,200, and 9120 in EtOH.

Thioacylaminoamides (*Table* 4).—These were prepared by boiling the thiazolones in toluene with the appropriate amine for a few minutes and cooling. The thiazolones and ammonia in boiling dioxan gave the thioacylamino-acid amides identical with those prepared by Kjaer (*loc. cit.*).

TABLE 4. *Thioacylamino-acid derivatives.*

	M. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Thiobenzoylglycine anilide	152° [a]	$C_{15}H_{14}ON_2S$	66·5	5·4	66·7	5·2
Thiobenzoylglycine morpholide	158 [b]	$C_{13}H_{16}O_2N_2S$	58·9	6·3	59·1	6·1
Thiobenzoylglycine phenylhydrazide ...	190 [b]	$C_{15}H_{15}ON_3S$	63·4	5·3	63·2	5·3
Phenyl(thioacetyl)glycine anilide	165 [a]	$C_{16}H_{16}ON_2S$	67·7	5·7	67·6	5·6
Phenyl(thioacetyl)glycine benzylamide	130 [a]	$C_{17}H_{18}ON_2S$	68·3	6·1	68·5	6·1
Thiobenzoyl-DL-alanine anilide	155 [a]	$C_{16}H_{16}ON_2S$	67·2	5·8	67·6	5·6
Phenyl(thioacetyl)-DL-alanine anilide...	159 [a]	$C_{17}H_{18}ON_2S$	68·7	5·9	68·5	6·1
Thiobenzoyl-DL-valine anilide	215 [a]	$C_{18}H_{20}ON_2S$	69·15	6·4	69·2	6·4
Thiobenzoyl-DL-leucine anilide	164 [a]	$C_{19}H_{22}ON_2S$	69·5	6·6	70·0	6·75
Thiobenzoyl-DL-norleucine anilide * ...	165 [b]	$C_{19}H_{22}ON_2S$	69·7	6·7	70·0	6·75
Phenyl(thioacetyl)-DL-leucine anilide *	170 [b]	$C_{20}H_{24}ON_2S$	70·0	7·4	70·6	7·6
Thiobenzoyl-DL-phenylalanine anilide	176—177 [a]	$C_{22}H_{20}ON_2S$	73·0	5·7	73·3	5·6
Thiohexanoylglycine anilide *.....	113 [a]	$C_{14}H_{20}ON_2S$	63·4	7·4	63·6	7·6

[a] From aqueous ethanol. [b] From ethanol. * The crude thiazolones were made to react directly with aniline.

4-Benzylidene-2-phenylthiazol-5-one.—2-Phenylthiazolone (1·7 g.) was dissolved in ethanol (5 ml.), and benzaldehyde (1 ml.) and pyridine (1 drop) were added. After 30 min. on the steam-bath the thiazolone was collected and crystallised from ethanol (yield 1·8 g.); it had m. p. 130° and $\lambda_{max.}$ 3800 and 2900 Å, ε 22,400 and 15,850 in EtOH. The thiazolone heated for 3 hr. in benzene with aniline and a crystal of aniline hydrochloride gave an 89% yield of *thiobenzamidocinnamic anilide*, m. p. 149° (needles from ethanol) (Found: C, 73·2; H, 5·0. $C_{22}H_{18}ON_2S$ requires C, 73·7; H, 5·0%).

4-4′-Methylbenzylidene-2-phenylthiazol-5-one.—This *compound*, prepared as above from 2-phenylthiazolone and *p*-tolualdehyde, crystallised from ethanol in red silky needles, m. p. 121° (yield 68%) (Found: C, 72·7; H, 4·7. $C_{19}H_{13}ONS$ requires C, 73·0; H, 4·7%).

4-(2 : 3-Dimethoxybenzylidene)-2-phenylthiazol-5-one.—This *compound*, prepared as above, crystallised from ethanol in yellow needles, m. p. 127° (70%) (Found: C, 66·4; H, 4·7. $C_{18}H_{15}O_3NS$ requires C, 66·0; H, 4·7%).

2-Phenyl-4-isopropylidenethiazol-5-one.—2-Phenylthiazolone (1·5 g.), anhydrous sodium acetate (0·75 g.), and dry acetone (25 ml.) were heated under reflux with a few drops of pyridine for 15 hr. The solution was then poured on crushed ice, and the bulky precipitate crystallised from ethanol. It had m. p. 99° (yield 54%) and was identical with the substance prepared from phenyl*iso*propylideneoxazolone (*op. cit.*, p. 791).

5-Acetoxy-2-phenylthiazole.—Method A. Thiohippuric acid (4 g.) was heated in acetic anhydride (20 ml.) containing pyridine (5 drops) on the steam-bath for 1 hr. The red oil remaining after removal of the excess of acetic anhydride *in vacuo* crystallised from ethanol to give the *thiazole*, colourless needles, m. p. 59° (88%) (Found: C, 60·5; H, 4·4; N, 6·2; S, 14·6. $C_{11}H_9O_2NS$ requires C, 60·3; H, 4·1; N, 6·4; S, 14·6%).

Method B. 2-Phenylthiazolone was warmed with excess of acetyl chloride in benzene. The

precipitated thiazole hydrochloride was collected and triturated with 3N-sodium hydroxide under ether. The dried ether layer on evaporation gave the thiazole. The *picrate* crystallised from ethanol in needles, m. p. 125° (Found : C, 45·8; H, 2·8. $C_{17}H_{12}O_9N_4S$ requires C, 45·5; H, 2·7%).

5-Acetoxy-2-benzylthiazole.—The thiazole was prepared from 2-benzylthiazolone as above. It did not crystallise but gave a *picrate*, needles (from ethanol), m. p. 147° (Found : C, 47·4; H, 2·9. $C_{13}H_{14}O_9N_4S$ requires C, 47·8; H, 3·0%).

5-Acetoxy-4-methyl-2-phenylthiazole.—The *thiazole*, prepared from 4-methyl-2-phenylthiazolone as above, crystallised from ethanol in colourless needles, m. p. 110° (Found : C, 61·6; H, 4·7. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·7%). The *picrate*, needles from ethanol, had m. p. 155° (Found : C, 47·5; H, 2·7. $C_{18}H_{14}O_9N_4S$ requires C, 47·8; H, 3·0%).

5-Acetoxy-2-benzyl-4-methylthiazole.—The *thiazole*, prepared by the above method, b. p. 140°/0·1 mm., solidified to colourless plates, m. p. 33° (Found : C, 63·1; H, 5·4. $C_{13}H_{13}O_2NS$ requires C, 63·2; H, 5·3%). It gave a labile *monohydrate*, m. p. 46° (Found : C, 59·3; H, 5·7. $C_{13}H_{13}O_2NS,H_2O$ requires C, 59·0; H, 5·7%), and a *picrate*, rhombs (from ethanol), m. p. 108° (Found : C, 47·8; H, 3·0. $C_{19}H_{16}O_9N_4S$ requires C, 48·0; H, 3·4%).

5-Benzoyloxy-2-phenylthiazole.—The *thiazole*, prepared by method *B* (above), using benzoyl chloride, crystallised from ethanol in pale brown needles, m. p. 129° (Found : C, 68·2; H, 3·8. $C_{16}H_{11}O_2NS$ requires C, 68·4; H, 3·9%). The *picrate*, plates from ethanol, had m. p. 162—163° (Found : C, 52·2; H, 2·6. $C_{22}H_{14}O_9N_4S$ requires C, 51·8; H, 2·8%).

4-Ethoxyethylidene-2-phenylthiazol-5-one.—Thiohippuric acid (3·2 g.) was heated with ethyl orthoacetate (3 ml.) and acetic anhydride (3 ml.) in xylene (150 ml.) on the steam-bath for 1 hr. Removal of the solvents *in vacuo* left a red oil which was repeatedly extracted with hot light petroleum from which (after decolorisation with charcoal) the *thiazolone* (1 g.) crystallised in colourless needles, m. p. 96° (Found : C, 62·5; H, 5·5; N, 5·4. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; N, 5·7%).

4-Hydroxyethylidene-2-phenylthiazol-5-one.—Method A. The 4-ethoxy-derivative (above) (1 g.) was boiled with water (10 ml.) for 15 min. The oily *thiazolone* which crystallised on cooling crystallised from water as yellow needles (0·5 g.), m. p. 129° (Found : C, 60·6; H, 4·2. $C_{11}H_9O_2NS$ requires C, 60·3; H, 4·1%). Light absorption : $\lambda_{max.}$ 3400 and 2600 Å, ε 28,200 and 19,950 in EtOH.

Method B. Sodium thiohippurate (4·3 g.), 2-picoline (6 ml.), and acetic anhydride (6 ml.) were heated on the steam-bath for 30 min. Ethanol (4 ml.) was added to remove acetic anhydride, and the solution was poured into water (30 ml.) which was then acidified with 5N-hydrochloric acid (20 ml.). The brown precipitate of the thiazolone was crystallised as above (yield 3 g.). *4-Anilinoethylidene-2-phenylthiazol-5-one* was prepared by treating the ethoxyethylidenethiazolone with aniline at room temperature and crystallising the product from ethanol from which it was obtained as yellow needles, m. p. 138° (Found : C, 69·1; H, 4·9. $C_{17}H_{14}ON_2S$ requires C, 69·4; H, 4·8%).

4-Hydroxypropylidene-2-phenylthiazol-5-one.—This *compound*, obtained as above (method B) by using propionic anhydride, formed yellow needles, m. p. 84° (Found : C, 61·7; H, 4·4. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·7%).

2-Phenyl-4-phthalidylidenethiazol-5-one.—Sodium thiohippurate (2 g.), acetic anhydride (4 ml.), and phthalic anhydride were heated on the steam-bath for 1·5 hr. The solid *product* was washed with ethanol and recrystallised from toluene as orange prisms, m. p. 274° (Found : C, 66·5; H, 2·9; N, 4·3. $C_{17}H_9O_3NS$ requires C, 66·6; H, 2·9; N, 4·6%).

Reaction between Thioacylamino-acids and Orthoesters.—Thiohippuric acid (3·2 g.), ethyl orthoformate (2·8 ml.), and acetic anhydride (3 ml.) were heated under reflux on an oil-bath. After 10 min. the solid mass was washed with ethanol and recrystallised from toluene–ethyl acetate, to give *di-(2-phenyl-4-thiazol-5-one)methinoxonol* (IX; R = Ph, R′ = H) (2·5 g.), dark brown needles, m. p. 245° (decomp.) (Found : C, 61·9; H, 3·7. $C_{19}H_{12}O_2N_2S_2$ requires C, 62·6; H, 3·3%). Light absorption $\lambda_{max.}$ 5350 and 2900 Å, ε 28,200 and 22,400 in $CHCl_3$.

Di-(2-p-nitrophenyl-4-thiazol-5-one)methinoxonol, black needles, m. p. 286° (decomp.), was obtained by the same method from *N*-4-nitrobenzoylglycine (Found : C, 50·3; H, 2·5. $C_{19}H_{10}O_6N_4S_2$ requires C, 50·2; H, 2·2%). Light absorption : $\lambda_{max.}$ 5800 and 3000 Å, ε 35,500 and 19,900 in $CHCl_3$.

Methyldi-(2-phenyl-4-thiazol-5-one)methinoxonol (IX; R = Ph, R′ = Me) was obtained as above by using ethyl orthoacetate, as brown needles (from toluene), m. p. 284° (decomp.) (Found : C, 62·7; H, 4·0%; *M*, 393. $C_{20}H_{14}O_2N_2S_2$ requires C, 63·4; H, 3·7%; *M*, 378). Light absorption : $\lambda_{max.}$ 5300 and 2860 Å, ε 25,100 and 22,900 in $CHCl_3$. The same substance was

obtained by refluxing a solution in toluene of equimolecular amounts of 2-phenylthiazol-5-one and 4-ethoxyethylidene-2-phenylthiazol-5-one with a few drops of acetic anhydride or triethylamine.

Methyldi-(2-benzyl-4-thiazol-5-one)methinoxonol (IX; R = CH_2Ph, R′ = Me) was obtained from phenylthioacetylglycine (2·1 g.) and ethyl orthoacetate (1·8 ml.) at the b. p. with acetic anhydride (1·9 ml.) for 2 hr. The product (1·0 g.) crystallised from ethyl acetate in red rhombs, m. p. 170° (decomp.) (Found: C, 64·7; H, 4·2%; *M*, 420. $C_{22}H_{18}O_2N_2S_2$ requires C, 65·0; H, 4·4%; *M*, 406). Light absorption: $\lambda_{max.}$ 4550 and 3800 Å, ε 26,300 and 5010 in EtOH.

Ethyldi-(2-phenyl-4-thiazol-5-one)methinoxonol (IX; R = Ph, R′ = Et) was obtained as above by using ethyl orthopropionate, as red lustrous needles (from toluene), m. p. 246° (decomp.) (50%) (Found: C, 64·1; H, 4·2%; *M*, 400. $C_{21}H_{16}O_2N_2S_2$ requires C, 64·3; H, 4·1%; *M*, 392). Light absorption: $\lambda_{max.}$ 5200 and 2800 Å, ε 17,780 and 13,180 in EtOH.

We thank Mr. J. O. Stevens for technical assistance. One of us (V. D. L.) thanks the Reid Trustees for a post-graduate research grant. Part of the work by J. B. J. was carried out at the Dyson Perrins Laboratory, Oxford, under the M.R.C. Penicillin Project.

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