152. α-*Tetronic Acids and the* 3,6-*Dihydro*-2H-1,3-*thiazine Ring.*[1]

By D. M. Green, A. G. Long, P. J. May, and A. F. Turner.

Cephalosporin C and its derivatives (I) contain the hitherto unknown 3,6-dihydro-2*H*-1,3-thiazine ring. Attempts are described at making such systems from α-tetronic acids with β-ethoxycarbonyl (*i.e.*, α-oxoparaconic esters), β-mercaptomethyl, β-dimethylaminomethyl, and β-piperidinomethyl substituents. Fusion of some of these enols with ammonium acetate gave the corresponding enamines, but the lactones were not of use for syntheses of dihydrothiazines.

Addition of thioacetamide to ethyl 3-methyl-2-oxobut-3-enoate (XIV) gave, as a result of nucleophilic attack by the sulphur atom and subsequent cyclization, the hydroxy-dihydrothiazine (XVIII; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = CO_2Et$). Reduction, elimination of the hydroxy-group, and shift of the resulting double bond yielded the dihydrothiazine (III; $R^1 = R^3 = Me$, $R^2 = Et$).

The ultraviolet absorption spectra of the derivatives of α-tetronic acid and of the dihydro-1,3-thiazines are discussed; the evidence suggests that the maxima in the spectra of the cephalosporins (I) and the lactones (II) are due to *d*-orbital resonance in the excited state, so that the sulphur and the ring-nitrogen atom and the double bond, but not the 4-substituent, are essential for the absorption.

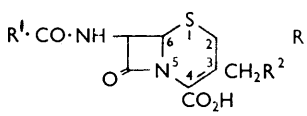
Abraham and Newton [2] isolated the antibiotic cephalosporin C (I; $R^2 = OAc$) and established its structure. Treatment with acid gave a lactone (II). These compounds and congeners with the dihydrothiazine chromophore afford aqueous or ethanolic solutions with $\lambda_{max.}$ 255—265 mμ (ε 7000—10,000), a property not expected in molecules of this type since simple substituted acrylic acids and butenolides have maxima at <230 mμ.

We describe here attempts at making dihydrothiazines that might be adapted to syntheses of cephalosporin C and its lactone. Some of the attempts exploited α-oxoparaconic esters and α-tetronic acids; these exist, when possible, in the enolic form, in which the lone pair or negative charge on the exocyclic oxygen atom helps to stabilize the cyclic system.[3-6] Acid-catalysed decarboxylation of the β-alkyl-α-oxoparaconates (*e.g.*, V; $R^1 = CO_2Et$, $R^2 = Me$) yields the corresponding α-tetronic acids, because it entails conversion of β-keto-acids into stable enolic compounds; decarboxylation of ethyl α-oxoparaconate, which is already enolic, is more difficult. The stability of the ring of the required type does not prevent use of these lactones in the syntheses.[7]

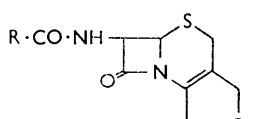
Fusion of β-ethoxycarbonyl-α-tetronic acid (IV; $R^1 = CO_2Et$, $R^2 = OH$, $R^3 = H$) with ammonium acetate gave the lactam (VI; $R^1 = CO_2Et$, $R^2 = NH_2$, X = NH), and fusion with a mixture of ammonium acetate and thioacetamide afforded, in low yield, the amino-thiolactone (VI; $R^1 = CO_2Et$, $R^2 = NH_2$, X = S).[8] With a view to introducing at the β-position of the acid a group useful in the synthesis of the lactone (II), we tried Mannich reactions, but these yielded only the hydroxymethyl compound (V; $R^1 = CO_2Et$, $R^2 = CH_2{\cdot}OH$).[9] The action of acetyl chloride and pyridine on this compound produced the acetate (V; $R^1 = CO_2Et$, $R^2 = CH_2{\cdot}OAc$), but other attempts at substitution

[1] Part of this work has been published in summary (Long and Turner, *Tetrahedron Letters*, 1963, 421).
[2] Abraham and Newton, *Biochem. J.*, 1961, **79**, 377.
[3] Olsen and Havre, *Acta Chem. Scand.*, 1954, **8**, 47.
[4] Wermuth *et al.*, *Compt. rend.*, 1960, **250**, 1668, 2587; **251**, 391.
[5] Schinz and Hinder, *Helv. Chim. Acta*, 1947, **30**, 1349.
[6] Gordon, Onno, and Gault, *Compt. rend.*, 1959, **249**, 2332.
[7] Suquet, *Ann. Chim.* (*France*), 1953, **8**, 545.
[8] Parker, in "Organic Sulfur Compounds," ed. Kharasch, Pergamon Press, Oxford, 1961, Vol. 1, p. 108; Kresze, Schramm, and Cleve, *Chem. Ber.*, 1961, **94**, 2060; Vaughan and Baumann, *J. Org. Chem.*, 1962, **27**, 739.
[9] Fischhof, *Ann. Chim.* (*France*), 1951, **6**, 227.

failed, probably owing to the neopentyl nature of the alcohol. Reaction with piperidine in non-polar solvents cleaved the ring of the hydroxymethyl compound, affording piperidine hydrogen oxalate, whereas the ester (IV; $R^1 = CO_2Et$, $R^2 = OH$, $R^3 = H$) gave the piperidine salt of its enol.[7] Our attempts failed to alkylate salts of β-ethoxycarbonyl-α-tetronic acid at the β-position (for instance, with acetylthiomethyl chloride, $AcS{\cdot}CH_2Cl$).[10,11]



(I)



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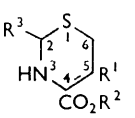
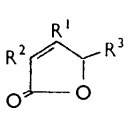
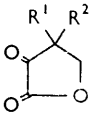


(III)

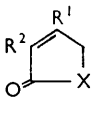


(IV)

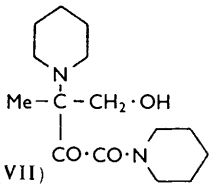


(V)

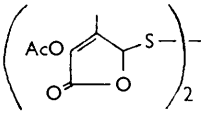
$R^1 = [CH_2]_3{\cdot}CH(NH_2){\cdot}CO_2H$ $R = [CH_2]_3{\cdot}CH(NH_2){\cdot}CO_2H$



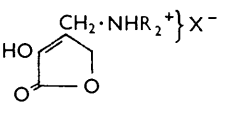
(VI)



(VII)

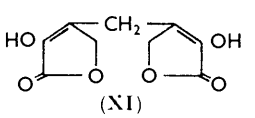


(VIII)

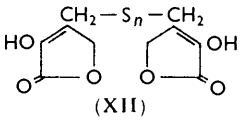


(IX) a: R = Me

b: $NHR_2 = HN<[CH_2]_5$



(XI)



(XII)

Acylation of β-methyl-α-tetronic acid[5,12] yielded the enol acetate (IV; $R^1 = Me$, $R^2 = OAc$, $R^3 = H$), hydrolysis of which with hydrochloric acid at 100° gave back the tetronic acid (IV; $R^1 = Me$, $R^2 = OH$, $R^3 = H$). Methylation with methyl iodide and potassium t-butoxide produced the ether (IV; $R^1 = Me$, $R^2 = OMe$, $R^3 = H$), and fusion of β-methyl-α-tetronic acid or its acetate (IV; $R^1 = Me$, $R^2 = OH$ or OAc, $R^3 = H$) with ammonium acetate gave the enamine (IV; $R^1 = Me$, $R^2 = NH_2$, $R^3 = H$), which had been detected in the degradation products[2] from cephalosporin C. Acid converted the enamine into the α-tetronic acid (IV; $R^1 = Me$, $R^2 = OH$, $R^3 = H$), the lactone ring of which we failed to open with thioacetamide or dithiocarbamic acid, in various conditions. With a platinum catalyst in ethanol, hydrogenation of the amine (IV; $R^1 = Me$, $R^2 = NH_2$, $R^3 = H$) gave DL-valine.

With aqueous bromine or with *N*-bromosuccinimide in carbon tetrachloride β-methyl-α-tetronic acid afforded β-bromo-β-methyl-α-oxobutyrolactone (V; $R^1 = Br$, $R^2 = Me$),[5] which with piperidine in benzene gave piperidinium bromide and β-hydroxymethyl-α-oxo-β-piperidinobutyroyl piperidide (VII). The structure of this amide was confirmed by measurements of nuclear magnetic resonance.

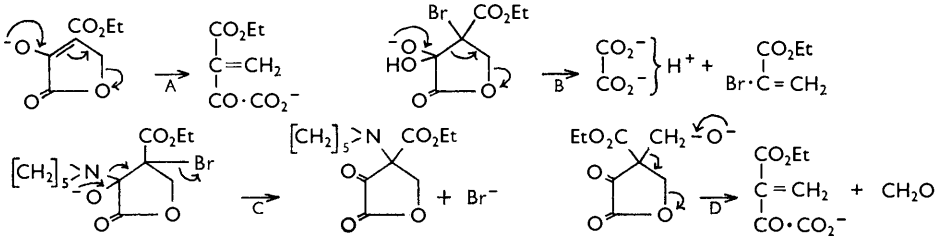
Cleavage and fragmentation of the α-tetronic acid ring take place according to the enolic or ketonic state of the compound. Ammonia and thioacetamide can attack β-ethoxycarbonyl-α-tetronic acid (IV; $R^1 = CO_2Et$, $R^2 = OH$, $R^3 = H$) as shown in (A); addition and cyclization complete the observed reactions, which are sluggish. Nucleophiles act on the keto-forms more rapidly and with different results. Aqueous sodium hydrogen carbonate converts ethyl β-bromo-α-oxoparaconate (V; $R^1 = Br$,

[10] Cf. Böhme *et al.*, *Chem. Ber.*, 1953, **86**, 1414; *Arch. Pharm.*, 1958, **291**, 566; 1959, **292**, 164, 456; *Annalen*, 1959, **623**, 92.

[11] Cf. Brandström, *Arkiv Kemi*, 1953, **6**, 155; Parker, *Quart. Rev.*, 1962, **16**, 163.

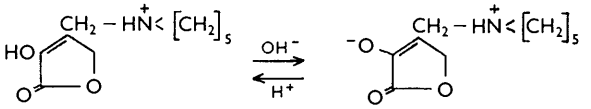
[12] Fleck, Rossi, Hinder, and Schinz, *Helv. Chim. Acta*, 1950, **33**, 130.

$R^2 = CO_2Et$) into ethyl β-bromoacrylate,[13] in a change (B). With piperidine in non-aqueous solvents cleavage of the ring, but not fragmentation, occurs; this denotes simple acyl–oxygen fission, with replacement of the halogen atom directly or as shown in (C). Piperidine degrades the hydroxymethyl-lactone (V; $R^1 = CH_2{\cdot}OH$, $R^2 = CO_2Et$) into



the oxalate ion; diagram (B) depicts a change that might be responsible for this conversion. In this instance a further possibility exists,[14,15] in which the change involves process (D).

N-Bromosuccinimide in carbon tetrachloride converted the enol ester (IV; $R^1 = Me$, $R^2 = OAc$, $R^3 = H$) into the γ-bromo-compound (IV; $R^1 = Me$, $R^2 = OAc$, $R^3 = Br$), which contrasts with the halogenation of the enol at the β-position. Cognate differences between the esters and enols extend to the ultraviolet spectra (which are discussed below) and analogies exist in the behaviour of the corresponding α-keto-lactams.[16] The nuclear magnetic resonance supported the structure of the γ-bromo-β-methylbutenolide (IV; $R^1 = Me$, $R^2 = OAc$, $R^3 = Br$). The halogen atom was readily displaced: reduction with chromous chloride gave the lactone (IV; $R^1 = Me$, $R^2 = OAc$, $R^3 = H$), and potassium acetate in acetone and thioacetamide in acetic acid gave, respectively, the diacetate (IV; $R^1 = Me$, $R^2 = R^3 = OAc$) and the *S*-substituted thioisoamide (IV;



(IV; $R^1 = CH_2{\cdot}\overset{+}{N}H{<}[CH_2]_5$, $R^2 = OH$, $R^3 = H$) (X)

$R^1 = Me$, $R^2 = OAc$, $R^3 = S{\cdot}CMe{:}NH_2{}^+Br$); oxidation with dichromate solution or with hydrogen peroxide converted the thioamide into the disulphide (VIII), $\lambda_{max.}$ 241—242 and 289—291 mμ [electronic effects in the rings of this molecule (see below) influence the disulphide chromophore, which normally has a weak maximum [17] at ~250 mμ].

Mannich and Bauroth,[18] treating pyruvic acid with dimethylamine hydrochloride and formaldehyde, obtained β-dimethylaminomethyl-α-tetronic acid as its hydrochloride (IXa; X = Cl); they obtained likewise the hydrochloride of the piperidino-compound (IXb; X = Cl), and we have made the sulphate (IXb; $X = \frac{1}{2}SO_4$) of this base. We prepared the free bases by using anion-exchange resins on the hydrochlorides or by the action of barium hydroxide on the sulphate. The products yielded picrates, the ultraviolet absorption of which could be used in ascertaining the molecular weights of the

[13] Niell, *J. Amer. Chem. Soc.*, 1945, **67**, 1145.
[14] Cf. Tchoubar, *Bull. Soc. chim., France*, 1955, 1363; Searles, Nickerson, and Witsiepe, *J. Org. Chem.*, 1959, **24**, 1839.
[15] Cf. Cromwell and Hess, *J. Amer. Chem. Soc.*, 1961, **83**, 1237.
[16] Southwick *et al.*, *J. Org. Chem.*, 1963, **28**, 1332, and earlier papers.
[17] Passerini, in "Organic Sulfur Compounds," ed. Kharasch, Pergamon Press, Oxford, 1961, Vol. 1, pp. 57 *et seq.*
[18] Mannich and Bauroth, *Ber.*, 1924, **57**, 1108.

bases.[19] Our efforts failed to produce β-methylene-α-oxobutyrolactone by pyrolysis of the bases, presumably because such a compound arises as a methide that polymerizes readily.[20]

Salts of the Mannich bases had $\lambda_{max.}$ 234 and 267 mμ (in water). Alkaline solutions of the bases and salts had a single $\lambda_{max.}$ ~267 mμ, and acid solutions a maximum at ~233 mμ. We attribute the lower maximum to the enol form (see the annexed diagrams) and the higher to the betaine (X) which, as a potential ylide, is able to exist in other canonical forms. Their absorption indicates that aqueous solutions of the salts contain the two species, the betaine form predominating.

Mannich and Bauroth[18] obtained from their reactions a by-product, m. p. 225°, described as an acid, $C_{15}H_{14}O_{10}$. We obtained a compound with similar properties, except that its analysis indicated formula $C_9H_8O_6$; this result and the compound's other properties fit structure (XI). Fried and his co-workers[21] also obtained this by-product and it has been recognized as one of the products of reaction of formaldehyde with pyruvic acid.[3,22]

Reactions of the type $R{\cdot}CH_2{\cdot}NHMe_2^+ + Y^- \longrightarrow R{\cdot}CH_2{\cdot}Y + Me_2NH$ between Mannich bases and nucleophiles[23] gave the lead to our next experiments. Two factors were favourable: sulphur nucleophiles are highly suitable for substitutions of this type, and the Mannich bases we intended to use probably exist in the zwitterionic state (X), even in slightly acid solution (see above).

In methanolic sodium methoxide the hydrochloride (IXa; X = Cl) reacted with toluene-ω-thiol, giving β-benzylthiomethyl-α-tetronic acid (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2Ph$, $R^2 = OH$, $R^3 = H$). Diazomethane converted this product into an enol ether (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2Ph$, $R^2 = OMe$, $R^3 = H$), and acetic anhydride and pyridine afforded the enol acetate (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2Ph$, $R^2 = OAc$, $R^3 = H$). Fusion of the enol (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2{\cdot}Ph$, $R^2 = OH$, $R^3 = H$) with ammonium acetate gave a weakly basic enamine (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2{\cdot}Ph$, $R^2 = NH_2$, $R^3 = H$): it was not protonated in M-formic acid, the solvent we used for electrophoresis of such bases, and ultraviolet absorption spectroscopy indicated changes due to protonation only when the solution was <0·5N in mineral acid. Prolonged treatment with acid regenerated the enol. Raney nickel in benzene converted the enamine into the α-amino-β-methylbutenolide (IV; $R^1 = Me$, $R^2 = NH_2$, $R^3 = H$), which behaved as a weak base (pK ~ 2). Measurements of nuclear magnetic resonance showed that only the two hydrogen atoms of the NH_2 group were replaced by deuterium when a solution of the enamine in deuteriochloroform was shaken with deuterium oxide.

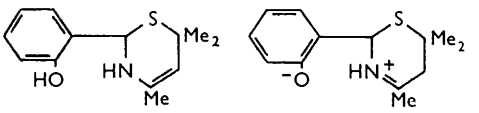
Reaction of the base hydrochloride (IXa; X = Cl) with methanolic sodium hydrogen sulphide yielded an insoluble product, identified as a sulphide (XII; $n = 1$) obtained by degradation[2] of cephalosporin C. Fried's group[21] isolated the same compound from experiments similar to ours. The mother-liquors contained a thiol (IV; $R^1 = CH_2{\cdot}SH$, $R^2 = OH$, $R^3 = H$). However, this method of making it was inefficient and capricious. The action of sodium disulphide in alcoholic solvents was also unreliable; in one experiment we isolated a crude disulphide (XII; $n = 2$), reduction of which with zinc and acetic acid gave, in very low yield, the lead salt of the thiol. In the reactions described above the sulphide (XII; $n = 1$) may have arisen by attack on $R{\cdot}NHMe_2^+$ of RS^- or [24] of S^{2-}.

Asinger, Thiel, and their co-workers[25] have made dihydro-1,3-thiazines from β-mercapto-ketones (or the corresponding αβ-unsaturated ketones and hydrogen sulphide),

[19] Cunningham, Dawson, and Spring, *J.*, 1951, 2305.
[20] Mann and Stewart, *J.*, 1954, 2826, 4127; Gardner, Rafsanji, and Rand, *J. Amer. Chem. Soc.*, 1959, **81**, 3364.
[21] Galantay, Szabo, and Fried, *Tetrahedron Letters*, 1963, 415.
[22] Feofilaktow, *Ber.*, 1926, **59**, 2765; *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 1145; Olsen, Hendriksen, and Bauer, *Annalen*, 1959, **628**, 1.
[23] Hellmann and Opitz, "α-Aminoalkylierung," Verlag Chemie, Weinheim, 1960, pp. 223 *et seq.*
[24] Cf. Ellis and Reid, *J. Amer. Chem. Soc.*, 1932, **54**, 1674; Schöberl and Wagner, in "Methoden der Organischen Chemie," ed. Müller, Georg Thieme Verlag, Stuttgart, 1955, Vol. IX, p. 7.
[25] Asinger, Thiel, *et al.*, *Annalen*, 1957, **602**, 37; **610**, 1; 1958, **619**, 137; 1959, **622**, 107.

aldehydes or ketones, and ammonia. They describe their products as 5,6-dihydro-2*H*-1,3-thiazines, but without spectroscopic evidence for preferring this structure over the 3,6-dihydro-forms (III) (and even the 3,4-dihydro-isomers cannot be excluded). Unfortunately we could not accomplish similar reactions with the thiol (IV; $R^1 = CH_2{\cdot}SH$, $R^2 = OH$, $R^3 = H$) and we could not debenzylate the sulphides (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2Ph$, $R^2 = OH$, $R^3 = H$); therefore we resorted to means of making 1,3-thiazines, which might be selectively reduced to the required dihydrothiazines.

Jansen and Mathes [26] have described reactions between αβ-unsaturated ketones and dithiocarbamic acid that yield 2-mercapto-1,3-thiazines (possibly in the thione form), but they did not try simple thioamides in such conditions. We have studied reactions of the βγ-unsaturated α-oxo-ester (XIV) with thioacetamide and dithiocarbamic acid. Dihydro-1,3-thiazines were eventually obtained, but not thiazines.

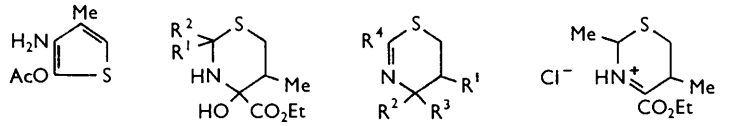


(a) (XIII) (b)

$CH_2{:}CMe{\cdot}CO{\cdot}CO_2Et$ (XIV) $CH_2{:}CMe{\cdot}CH(OH){\cdot}CO_2Et$ (XV)

$AcS{\cdot}CH_2{\cdot}CMe{:}C(OR){\cdot}CO_2Et$ (XIX)

$RS{\cdot}CH_2{\cdot}CHMe{\cdot}CH(OR){\cdot}CO_2Et$ (XX)



(XVI) (XVII) (XVIII) (XXI)

Oxidation of the hydroxy-ester [27] (XV) with potassium dichromate or, better, with manganese dioxide in chloroform (the course of reaction being followed by infrared spectroscopy) yielded ethyl 3-methyl-2-oxobut-3-enoate (XIV) which, with hydrogen sulphide and triethylamine, furnished the thiolactone (VI; $R^1 = Me$, $R^2 = OH$, X = S). Fusion of the thiolactone with ammonium acetate gave the enamine (VI; $R^1 = Me$, $R^2 = NH_2$, X = S). These compounds are similar in chemical properties to the corresponding α-tetronic acids; in both series the enols consume only one equivalent of alkali (in the presence of which the thiolactones give no colour with sodium nitroprusside), because the rings are stable. Acetic anhydride transformed the enamine (VI; $R^1 = Me$, $R^2 = NH_2$, X = S) into the amide (VI; $R^1 = Me$, $R^2 = NHAc$, X = S) in a reaction that might have involved an " enol acetate " (XVI).[28] The infrared spectra of these thio-α-tetronic acids are unusual in having carbonyl absorption at ~1665 cm.$^{-1}$ and a band at ~1710 cm.$^{-1}$ due to the double bond, the first at a surprisingly low and the latter at a high frequency.[29]

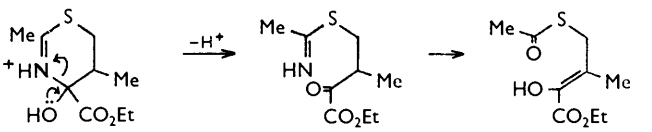
Dithiocarbamic acid in the presence of aqueous hydrochloric acid converted the keto-ester (XIV) into a cyclic ester, $\lambda_{max.}$ 240 and 290 mμ; these maxima and infrared absorption at 3370 (NH) and 1490 cm.$^{-1}$ (N·C:S) and nuclear magnetic resonance at 0·9 τ (NH) indicated the thione (XVII; $R^1R^2 = S$) rather than the thiol structure (XVIII; $R^1 = Me$, $R^2 = OH$, $R^3 = CO_2Et$, $R^4 = SH$).[26,30]

Acidic or basic conditions may be used for such cyclizations. For reactions with thioacetamide we used triethylamine; progress of the cyclization could be watched by the disappearance of the ultraviolet absorption of thioacetamide, $\lambda_{max.}$ 266 mμ. Infrared-absorption spectroscopy confirmed the presence in the product of hydroxyl and ethoxycarbonyl groups, and the absence of >NH; nuclear magnetic resonance diagrams also

[26] Jansen and Mathes, *J. Amer. Chem. Soc.*, 1955, **77**, 2866.
[27] Vogel and Schinz, *Helv. Chim. Acta*, 1950, **33**, 116.
[28] Hornfeldt and Gronowitz, *Acta Chem. Scand.*, 1962, **16**, 529.
[29] (*a*) Hurd and Kreuz, *J. Amer. Chem. Soc.*, 1950, **72**, 5543; Gronowitz and Hoffmann, *Arkiv Kemi*, 1960, **15**, 498; (*b*) Pryor, " Mechanisms of Sulfur Reactions," McGraw-Hill, New York, **1962**, p. 31.
[30] Koch, *J.*, 1949, 401; cf. Jansen, *Rec. Trav. chim.*, 1960, **79**, 454, 464, 1068.

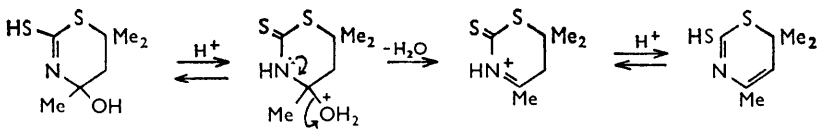
supported structure (XVIII; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = CO_2Et$). Protonation of this base, $\lambda_{max.}$ 237 mμ, resulted in an ion, $\lambda_{max.}$ 250 mμ, that gave no colour with ferric chloride and therefore was not enolic and probably was still cyclic. This behaviour corresponds to that of 2-methyl-5,6-dihydro-4*H*-1,3-thiazine (XVIII; $R^1 = R^2 = R^3 = H$, $R^4 = Me$), $\lambda_{max.}$ 234 mμ, which gives the conjugate acid,[31] $\lambda_{max.}$ 247 mμ. Electrophoresis of our base (XVIII; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = CO_2Et$) in M-formic acid revealed a chemical change: in such conditions the ring opened to give the *S*-acetate (XIX; R = H), $\lambda_{max.}$ 232 mμ ($\lambda_{max.}$ 247 mμ in alkali), which gave a violet ferric chloride colour and yielded a yellow 2,4-dinitrophenylhydrazone, $\lambda_{max.}$ 227 and 355 mμ. Acetylation produced the diacetate (XIX; R = Ac), $\lambda_{max.}$ 226 mμ; transacylation from sulphur to oxygen in the monoacetate was not detected.[32] The ultraviolet absorption of these compounds includes contributions from the chromophores in a substituted acrylic ester ($\lambda_{max.}$ ~225 mμ) and in a thiol ester ($\lambda_{max.}$ ~230 mμ).[17]

In this ease of cleavage, the hydroxy-ester (XVIII; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = CO_2Et$) differs from the simple 5,6-dihydro-4*H*-1,3-thiazine (XVIII; $R^1 = R^2 = R^3 = H$, $R^4 = Me$); nonetheless, the product of the change confirmed the view that the sulphur rather than the nitrogen atom of the thioamide had made the nucleophilic attack on ethyl 3-methyl-2-oxobut-3-enoate (XIV). We attribute the facility of cleavage to participation by the hydroxy-group, as shown in the annexed diagrams.



(XVIII; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = CO_2Et$) (XIX; R = H)

In pure formic acid this change was much slower; many attempts failed to achieve acid-catalysed conversion of the 4-hydroxydihydrothiazine (XVIII; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = CO_2Et$) into a 1,3-thiazine, as did efforts at converting the hydroxy-group into an ester, with a view to its subsequent elimination. In strongly acid conditions protonation of the hydroxyl group would prevent the ring opening depicted above. Failure of the elimination can be attributed to unfavourable stereochemistry of the α-hydroxy-ester part or to the fact that the double bond in the ester (XVIII; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = CO_2Et$) does not move to the exocyclic position, so that elimination may ensue in a carbinolamine system; in earlier examples[26] this condition would have been attained by tautomerization of a thionamide system, as shown:



Our reactions gave few signs of the production in diastereoisomeric forms of 5,6-dihydro-4*H*- or -2*H*-1,3-thiazines or 1,3-thiazans.

The hydroxy-group could, however, be removed when the dihydrothiazine (XVIII; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = CO_2Et$) was reduced to the thiazan (XVII; $R^1 = H$, $R^2 = Me$). Sodium borohydride yielded products that gave a violet colour with sodium nitroprusside, which suggested that thiols had been formed by cleavage of the ring, but the required reduction was achieved with aluminium amalgam in moist ether.[33] The

[31] Martin and Parcel, *J. Amer. Chem. Soc.*, 1961, **83**, 4830.
[32] Cf. Martin and Hedrick, *J. Amer. Chem. Soc.*, 1962, **84**, 106.
[33] Cf. Cook, Hunter, and Pollock, *J.*, 1950, 1892.

product had no absorption maximum between 220 and 300 mμ, its infrared absorption spectra contained bands attributable to >NH, hydroxy-, and saturated ethoxycarbonyl groups, and the nuclear magnetic resonance of the compound corresponded to the suggested structure. The base yielded a crystalline oxalate. Treatment of the thiazan with ethanol yielded the thiolactone (VI; R^1 = Me, R^2 = OH, X = S); even in basic conditions, this product arises in the cyclic, enolized form.[34]

A by-product of the reduction just described was also a product of reactions with zinc and acetic acid. It lacked ketonic properties and failed to change the colour of solutions of ferric chloride. However, it behaved as a thiol in giving a violet solution with sodium nitroprusside, and this and spectroscopic evidence indicated that it was ethyl α-hydroxy-γ-mercaptoisovalerate (XX; R = H); it was converted by acetic anhydride in pyridine into a diacetate (XX; R = Ac), $\lambda_{max.}$ 230—231 mμ.

Hydrogen chloride in ether converted the hydroxythiazan (XVII; R^1 = H, R^2 = Me) into a salt (XXI), $\nu_{max.}$ 1660 and 1706 cm.$^{-1}$ (αβ-unsaturated ester system), that lacked infrared absorption due to hydroxyl groups. Treatment of this hydrochloride with alkali yielded a base, with infrared bands due to >NH and at 1730 and 1705 cm.$^{-1}$ (αβ-unsaturated ester group); the band due to the double bond shifted as a result of this conversion from 1660 to 1635 cm.$^{-1}$, which is in keeping with a move from the 3,4-position in the salt (XXI) to the 4,5-position in the vinylamine (III; R^1 = R^3 = Me, R^2 = Et).[35] The nuclear magnetic resonance supported these views. Treatment of the base with hydrogen chloride in ether yielded, with shift of the double bond, the dihydrothiazinium salt (XXI).

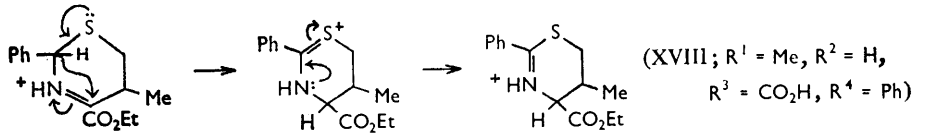
The base (III; R^1 = R^3 = Me, R^2 = Et) was the first synthetic example of an authenticated 2,3-dihydro-6*H*-1,3-thiazine, and we shall consider below the relevance of its ultraviolet absorption, $\lambda_{max.}$ 285 mμ (ε 3100), to that of cephalosporin C and its congeners. Other likely examples of this system have been mentioned above. We repeated the conversion of 2-mercapto-2-methylpentan-4-one, salicylaldehyde, and ammonia into a pale yellow compound already described (in its Δ^3-form) as the salicyl derivative (XIIIa).[25] Paper electrophoresis demonstrated its purity. The nuclear magnetic resonance of this compound indicated the presence of one CH_2 group and of one proton replaceable by deuterium (from deuterium oxide), facts that suit the betaine structure (XIIIb) in which the position of the double bond accords with the precedents cited in the foregoing account; the ultraviolet absorption of this compound, $\lambda_{max.}$ 278 and 302 mμ, can be included in this interpretation.[36]

By heating their dihydrothiazines with an acid catalyst and a carbonyl compound, Asinger, Thiel, and Höringklee[25] exchanged substituents at the 2-position. They attributed the transformation to opening of the ring, exchange of the carbonyl component, and recyclization. We showed that the thiazan (XVII; R^1 = H, R^2 = Me) and the dihydrothiazine (III; R^1 = R^3 = Me, R^2 = Et) and its salt (XXI) yielded acetaldehyde (isolated as its dimedone complex or 2,4-dinitrophenylhydrazone) in mildly acid conditions. The exchange method seemed to offer means of making, from a dihydrothiazine or 4-hydroxythiazan and appropriate aldehydes or ketones, 3,6-dihydro-2*H*-1,3-thiazines variously substituted at the 2-position. However, a different rearrangement occurred. Treatment of ethyl 2,5-dimethyl-2,3-dihydro-6*H*-1,3-thiazine-4-carboxylate, as its hydrochloride (XXI) or oxalate, with benzaldehyde at 70—80° gave acetaldehyde, the hydroxythiazan (XVII; R = H, R^1 = Me), and two new dihydrothiazines (XVIII; R^1 = Me, R^2 = H, R^3 = CO_2Et, R^4 = Me and Ph): the first, $\lambda_{max.}$ 235—237 mμ, was protonated to its conjugate acid, $\lambda_{max.}$ 250 mμ, and its infrared spectrum (which confirmed the absence of >NH and hydroxyl groups) contained absorption due to a saturated ester as well as

[34] Stewart and Woolley, *J. Amer. Chem. Soc.*, 1959, **81**, 4951.
[35] Cf. Leonard and Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781; Schöpf and Müller, *Annalen*, 1960, **633**, 127.
[36] See Murray, *Ind. Eng. Chem., Analyt. Edit.*, 1949, **21**, 941; Burawoy and Chamberlain, *J.*, 1952, 2310.

a band at 1640 cm.$^{-1}$ due to a double bond; the second, $\lambda_{max.}$ 239 mμ, gave a conjugate acid, $\lambda_{max.}$ 263—265 mμ, and was similar in infrared absorption to the other, except for bands at 1605 (double bond) and 762 and 690 cm.$^{-1}$ (Ph). The S·CR:N chromophores lead to bands, due to the double bond, at ~1610 (R = Me) and ~1640 cm.$^{-1}$ (R = Ph), so the infrared spectra of these 5,6-dihydro-4*H*-1,3-thiazines resemble those of comparable compounds described here and elsewhere.[37]

We see now that acid rearranges Δ^4-dihydrothiazines to Δ^3- and then to Δ^2-compounds. The first step is a simple isomerization; the second is an internal redox reaction that we explain by the 1,3-hydride shift illustrated in the accompanying diagrams. This sequence,



(XVIII; R^1 = Me, R^2 = H, R^3 = CO_2H, R^4 = Ph)

or another involving an intermediate of the ethyleneimine type, has precedent in the isomerization of the oxazolidine ring in diterpenoid alkaloids (for instance, in the conversion of veatchine into garryine).[38]

We can now consider the ultraviolet absorption of some of the compounds described in this paper.[2]

β-Alkylbutenolactones of type (IV; R^1 = Alkyl, R^2 = R^3 = H) absorb strongly[39] at 217 mμ. Absorption in the lactones bearing α-substituents is related to the electron-donating power of the group R^2 and to the capacity of the group R^1 and the γ-carbon atom to accommodate a negative charge; therefore, the effects of R^1 and R^2 are concerted. For instance, when R^1 = Me, or CH_2·S·CH_2Ph in structure (IV), the bathochromic effect of the group R^2 increases in the order shown from left to right in Table 1.

TABLE 1.

Effects of substituents on the ultraviolet absorption of some butenolides (IV; R^2 = H).*

R^1	R^2	NH_2^+	OAc	OMe	OH	NH_2	O^-
Me	$\lambda_{max.}$ (mμ)	<220	<220	223	232	255	267
	$10^{-3}\varepsilon$			8·95	10·8	7·55	8·0
CH_2·S·CH_2Ph	$\lambda_{max.}$ (mμ)	—	<220	<220	232	266	276
	$10^{-3}\varepsilon$				19·8	10·8	10·5

* Ascorbic acid [IV; R^1 = R^2 = OH, R^3 = CH(OH)·CH_2·OH], $\lambda_{max.}$ 265 mμ (ε ~10,000) (in H_2O), 245 mμ (ε 7900) (in EtOH), is a special case; addition of acid suppresses ionization and shifts the peak to shorter wavelengths.[40] The large effect of solvent is in keeping with a highly polar excited state.

When R^2 = OH or O^- the effects of R^1 on the absorption appear from Table 2.

The diagrams (XXII) depict some of the forms responsible for absorption by the enolates.

Facts that bear out these opinions are the isomerization of α- and β-angelicalactone and of the corresponding thiolactones,[41] and the formation by such compounds of benzylidene derivatives and esters of the " enolic " forms (cf. XVI). Generation of the chromophores in structures such as (XXII) would be favoured by the development of a negative charge at the γ-position or on the exocyclic carbon atom. In the Mannich bases (IV;

[37] Meyers, *J. Org. Chem.*, 1960, **25**, 1147; 1961, **26**, 218.

[38] Wiesner and Valenta, in " Fortschritte der Chemie der Organischer Naturstoffe," Springer-Verlag, Vienna, 1958, p. 26; Leonard, Conrow, and Sauers, *J. Amer. Chem. Soc.*, 1958, **80**, 5185; Pelletier, *Tetrahedron*, 1961, **14**, 76.

[39] Dorfman, *Chem. Rev.*, 1953, **53**, 90.

[40] Mohler and Lohr, *Helv. Chim. Acta*, 1938, **21**, 485; Kumler and Sah, *J. Amer. Pharm. Assoc., Sci. Edn.*, 1952, **41**, 445.

[41] Dalgleish, Johnson, and Haynes, in " Chemistry of the Carbon Compounds," Elsevier, Amsterdam, 1952, Vol. 1B, p. 844; Zimmer, Gracian, and Rothe, *J. Org. Chem.*, 1960, **25**, 838; Olsen and Russwurm, *Annalen*, 1961, **639**, 1; refs. 28 and 29.

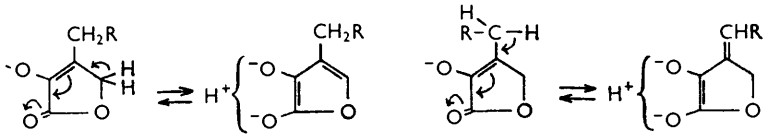
TABLE 2.

Effects of substituents on the ultraviolet absorption of some α-tetronic acids (IV; R^2 = OH and O^-, R^3 = H).

	R^1 =	H	$CH_2{\cdot}BH^+$ *	Me	$Ph{\cdot}CH_2{\cdot}S{\cdot}CH_2$	$CH_2{\cdot}S{\cdot}$ †	$CH_2{\cdot}$ ‡	SH^-	CO_2Et
R^2 = OH	$\lambda_{max.}$ (mμ)	227	232	232	232	235	236	241	255
	$10^{-3}\varepsilon$	7·2	13·4	10·8	19·8	14·8	17·5	6·5	11·8
R^2 = O^-	$\lambda_{max.}$ (mμ)	260	267	267	276	279	277	278	303
	$10^{-3}\varepsilon$	2·5	9·4	8·0	10·5	20·3	18·1	3·5	15·6

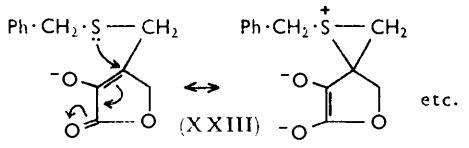
* $CH_2{\cdot}BH^+$ = $CH_2{\cdot}NHMe_2^+$ and $CH_2{\cdot}^+HN{<}[CH_2]_5$. † Values for the sulphide (XII; n = 1) (two lactone systems per mol.). ‡ Values for the methylene compound (XI) (two lactone systems per mol.).

R^1 = $CH_2{\cdot}NHMe_2^+$ and $CH_2{\cdot}^+HN{<}[CH_2]_5$, R^2 = O^-, R^3 = H) an ylide form fulfils this function; in the sulphides, *e.g.*, (IV; R^1 = $CH_2{\cdot}S{\cdot}CH_2{\cdot}Ph$, R^2 = O^-, R^3 = H) the sulphur atom may expand its outer shell to a dectet [42] and so stabilize an anion in the



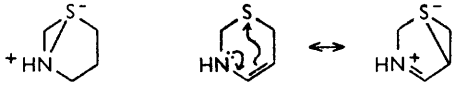
(XXII)

system $Ph{\cdot}CH_2{\cdot}S{\cdot}CH^{-}{\cdot}$ ⟷ $Ph{\cdot}CH_2{\cdot}S^{-}{:}CH{\cdot}$ ⟷ $Ph{\cdot}CH{:}S^{-}{\cdot}CH_2{\cdot}$ ⟷ $Ph{\cdot}CH^{-}{\cdot}S{\cdot}CH_2{\cdot}$. Sulphur-containing substituents offer the further possibility of contributions from forms such as (XXIII), for which some precedent exists.[43]



(XXIII) etc.

The amino-groups are so feebly basic in the enamines (IV; R^1 = Me, and $CH_2{\cdot}S{\cdot}CH_2{\cdot}Ph$, R^2 = NH_2, R^3 = H) as to curtail some of the possibilities suggested by formula (XXII). This restriction is reflected in the figures given in Table 1, which also shows that the bathochromic effect of the amino-group is greater in the sulphide than in the methyl compound although the latter has the more strongly basic amino-group. Further clues to the absorption due to the system S·C·C:C·N can be drawn from the spectra of the cephalosporin derivatives (I) and (II), $\lambda_{max.}$ ~260 mμ, and from the newly synthesized 3,6-dihydro-2*H*-1,3-thiazines, *e.g.*, (III; R^1 = R^3 = Me, R^2 = Et), $\lambda_{max.}$ 285 mμ. In these thiazines and in the acids (I), structures such as (XXII) are improbable, and conjugation of the type shown in (XXIII) ignores the concerted effects of the sulphur and nitrogen atoms; therefore we suggest that the ultraviolet absorption of the 3,6-dihydro-2*H*-1,3-thiazine system can be traced to *d*-orbital resonance, in which species such as (XXIV) and (XXV) participate.



(XXIV) (XXV)

[42] Cilento, *Chem. Rev.*, 1960, **60**, 147; Baliah and Uma, *Tetrahedron*, 1963, **19**, 455; ref. 29*b*.
[43] Cf. Fehnel and Carmack, *J. Amer. Chem. Soc.*, 1949, **71**, 84; Baddeley, *J.*, 1950, 663; Galantay, Szabo, and Fried, *J. Org. Chem.*, 1963, **28**, 98.

This interpretation is supported by the absorption of the thiazolines:[44] for 2- and 3-thiazolines, $\lambda_{max.}$ ~230 mμ, the absorption is similar to that of the 4,5-dihydro-3*H*-1,3-thiazines, whereas 4-thiazoline, $\lambda_{max.}$ 251 mμ, shows a bathochromic effect like that discussed for the 3,6-dihydro-2*H*-1,3-thiazines. (Spectra of 2-thiazolines include another peak at ~248 mμ, probably due to the chromophore[45] ·S̈·C:N· ⟷ ⁺·S:C·N⁻.) The evidence confirms the bathochromic effect in systems in which the nitrogen atom is weakly basic, and probably accounts for most of the absorption of molecules such as (I), in which this atom is implicated in a β-lactam system.

Experimental

M. p.s were determined on a Kofler hot-stage microscope. Magnesium or sodium sulphate was used for drying organic solvents. Refractive indices were recorded in daylight. Ultraviolet spectra were obtained for solutions in ethanol; $\lambda_{max.}$ (HCl) and $\lambda_{max.}$ (NaOH) signify maxima for ethanolic solutions containing a drop of 2N-hydrochloric acid or 2N-sodium hydroxide, respectively. Infrared spectra were determined for carbon disulphide solutions, unless otherwise stated. Nuclear magnetic resonance spectra were obtained with tetramethylsilane as an internal standard, and τ values refer to the centre of singlets, doublets (d), triplets (t), and quadruplets (q).

3-Hydroxy-4-methylfuran-2(5H)-one[12] (IV; R^1 = Me, R^2 = OH, R^3 = H).—Prepared by the method of Fleck *et al.*, this lactone had m. p. 90—92° (lit.,[12] 90—92°), $\lambda_{max.}$ 232 mμ (ε 11,900), $\lambda_{max.}$ (NaOH) 267—268 mμ (ε 8000), $\nu_{max.}$ 1768 and 1750 cm.$^{-1}$ (γ-lactone).

The 3-acetate had b. p. 106°/0·2 mm. (lit.,[12] m. p. 32—33°, b. p. 145—150°/11 mm.), n_D^{25} 1·4689, $\nu_{max.}$ 1785 (γ-lactone), 1750, and 1194 (enol OAc), and 1700 cm.$^{-1}$ (C=C) (Found: C, 53·7; H, 5·15. Calc. for $C_7H_8O_4$: C, 53·85; H, 5·15%), and on treatment with dilute hydrochloric acid at 100° for 30 min. regenerated the enol in 90% yield.

Ethyl 2,5-Dihydro-4-hydroxy-5-oxofuran-3-carboxylate (IV; R^1 = CO_2Et, R^2 = OH, R^3 = H).—Prepared by Fischhof's method,[9] this ester had m. p. 104—108° (lit., 108°), $\lambda_{max.}$ 255 and 302 mμ (ε 11,800 and 1530, respectively), $\lambda_{max.}$ (NaOH) 303 mμ (ε 15,600), $\nu_{max.}$ 1796 (γ-lactone), 1696 and 1238 cm.$^{-1}$ (C=C·CO_2R).

Piperidine (1·47 ml.) was added dropwise to an ice-cooled solution of the ester (2 g.) in ether, and the solution was kept at room temperature overnight, then evaporated without heating so that crystals (2·77 g.), m. p. 121°, separated. Recrystallization from ether afforded the *piperidine salt* (2·18 g.) of the enol, m. p. 119°, $\lambda_{max.}$ 302 mμ (ε 14,900), $\lambda_{max.}$ (NaOH) 303 mμ (ε 16,000), $\nu_{max.}$ (in Nujol) 1748 (cyclopentenone), 1696 and 1200 cm.$^{-1}$ (C=C·CO_2R) (Found: C, 56·15; H, 7·55; N, 5·1; OEt, 17·8. $C_{12}H_{19}NO_5$ requires C, 56·0; H, 7·45; N, 5·45; OEt, 17·6%).

Ethyl 4-Amino-5-oxo-3-pyrroline-3-carboxylate (VI; R^1 = CO_2Et, R^2 = NH_2, X = NH).—The lactone (IV; R^1 = CO_2Et, R^2 = OH, R^3 = H) (10 g.) and ammonium acetate (10 g.) were heated under nitrogen at 120—130° for 3 hr. Sublimation of the product gave a yellow solid (800 mg.), crystallization of which once from ethanol and twice from acetone afforded the *pyrroline ester*, m. p. 214—215° (lit.,[7] 212—214°), $\lambda_{max.}$ 232—233 and 292 mμ (ε 4050 and 14,600, respectively), $\lambda_{max.}$ (NaOH) 291—292 mμ (ε 14,200), $\nu_{max.}$ (in Nujol) 3415, 3310, and 3200 (NH_2 and NH), 1720 and 1275 (CO_2R), and 1688 cm.$^{-1}$ (CO·C=C), τ (in pyridine), 5·70q and 8·80t (CH_3·CH_2O) and 5·87 (CH_2) (Found: C, 49·4; H, 6·1; N, 16·5. Calc. for $C_7H_{10}N_2O_3$: C, 49·4; H, 5·9; N, 16·45%).

Ethyl 4-Amino-2,5-dihydro-5-oxothiophen-3-carboxylate (VI; R^1 = CO_2Et R^2 = NH_2, X = S).—The lactone (VI; R^1 = CO_2Et, R^2 = OH, R^3 = H) (5·16 g.), thioacetamide (4·5 g.), and ammonium acetate (500 mg.) were fused and stirred at 125° for 4 hr. After cooling, the cherry-red mixture was partitioned between benzene and water. Evaporation of the washed organic layer afforded a brown solid which was recrystallized from benzene (charcoal) and then several times from methanol to provide the *thiophen ester*, m. p. 102—103°, $\lambda_{max.}$ 271 and 320 mμ (ε 4800 and 8600, respectively), $\nu_{max.}$ 3480 and 3350 (NH_2), 1695 and 1680 (thiolactone and

[44] Asinger and Gluch, *Annalen*, 1961, **649**, 103.
[45] Cf. Jones and Katritzky, *J.*, 1958, 3610; refs. 30 and 37.

αβ-unsaturated ester), and 1640 cm.$^{-1}$, τ (in $CDCl_3$) 8·65t and 5·78q (CH_3·CH_2·O), 6·08 (CH_3), 4·25 (broad; NH_2) (Found: C, 45·1; H, 5·1; N, 7·7; S, 16·95; OEt, 24·45%; *M*, 182. $C_7H_9NO_3S$ requires C, 44·9; H, 4·9; N, 7·5; S, 17·2; OEt, 24·0%; *M*, 187).

The compound gave no colour with alkaline sodium nitroprusside or with alcoholic ferric chloride.

Treatment of Ethyl β-Hydroxymethyl-α-oxoparaconate (V; $R^1 = CO_2Et$, $R^2 = CH_2$·OH) *with Piperidine.*—Piperidine (1 ml.) was added to a stirred suspension of ethyl β-hydroxymethyl-α-oxoparaconate [9] (2·02 g.) in benzene (10 ml.) at 0°. After 3 days at 0° the deposited crystals (1·19 g.) were removed and recrystallized from methanol–ether at room temperature, to provide *piperidine oxalate* (443 mg.), m. p. 148—153° (capillary), undepressed on admixture with authentic material (prepared by neutralization of oxalic acid with 1 equiv. of piperidine), $\nu_{max.}$ (in Nujol) 1620 cm.$^{-1}$ (CO_2^-) [Found: C, 48·1; H, 7·4; N, 8·4%; Equiv., 179 (by titration). $C_7H_{13}NO_4$ requires C, 48·0; H, 7·5; N, 8·0%; Equiv., 175].

3-*Methoxy*-4-*methylfuran*-2(5H)-*one* [5] (IV; R^1 = Me, R^2 = OMe, R^3 = H).—Prepared by methylation of the enol (IV; R^1 = Me, R^2 = OH, R^3 = H) (3·63 g.) in t-butyl alcohol (70 ml.) containing potassium (1·18 g.) with methyl iodide (19 ml.) at room temperature for three days, this ether had m. p. 42—46° (capillary) (from n-hexane) (lit.,[5] 42—43°), b. p. 74°/0·5 mm., $\lambda_{max.}$ 223—234 mμ (ε 8900), $\nu_{max.}$ 1790—1765 (γ-lactone) and 1696 cm.$^{-1}$ (C=C) (Found: C, 56·0; H, 6·15. Calc. for $C_6H_8O_3$: C, 56·25; H, 6·3%).

3-*Amino*-4-*methylfuran*-2(5H)-*one* (IV; R^1 = Me, R^2 = NH_2, R^3 = H).—A mixture of the enol (IV; R^1 = Me, R^2 = OH, R^3 = H) (10 g.) and ammonium acetate (12·5 g.) was heated at 100—110° for 5 hr. whilst a slow stream of nitrogen was bubbled through the mixture. Acetic acid was removed *in vacuo* and the cooled residue extracted three times with small portions of methanol. The residual solid was sublimed at 100—120°/0·1 mm., to give 3-*amino*-4-*methylfuran*-2(5H)-*one* (7·9 g.), m. p. 144—145°. The analytical sample (from methanol) had m. p. 145°, $\lambda_{max.}$ 255 mμ (ε 7600), $\lambda_{max.}$ (0·1N-HCl) 208 and 246—249 mμ (ε 10,400 and 1400, respectively), $\nu_{max.}$ (in $CHBr_3$) 3480, 3380 (NH_2), 1760 (γ-lactone), and 1700 cm.$^{-1}$ (C=C), τ (in $CDCl_3$) 8·1 (CH_3), 6·5 (NH_2), and 5·4 (CH_2) (Found: C, 53·1; H, 6·3; N, 12·55. $C_5H_7NO_2$ requires C, 53·1; H, 6·25; N, 12·4%). Hydrolysis of the enamine with 1·7N-hydrochloric acid on the steam-bath for 2 hr. afforded the tetronic acid (IV; R^1 = Me, R^2 = OH, R^3 = H) in 90% yield; it was identified by m. p. and spectroscopic characteristics.

The enamine was prepared, in 36% yield, by fusion of the acetate (IV; R^1 = Me, R^2 = OAc, R^3 = H) (1·61 g.) and ammonium acetate (2·55 g.) under nitrogen for 4 hr. at 130°.

The enamine was also obtained by addition of Raney nickel W-7 catalyst [46] (previously washed with benzene) to a stirred solution of the benzyl sulphide (IV; $R^1 = CH_2$·S·CH_2·Ph, $R^2 = NH_2$, R^3 = H) (48 mg.) in benzene (20 ml.). After 2·5 hr. the mixture was filtered and evaporated, and the residue (20 mg.) crystallized from benzene–hexane. The crystals (5 mg.) were sublimed at 100°/0·2 mm., to give needles of 3-amino-4-methylfuran-2(5*H*)-one (IV; R^1 = Me, $R^2 = NH_2$, R^3 = H).

Hydrogenation of the enamine in ethanol with Adams catalyst gave DL-valine, m. p. 230—232°, identified spectroscopically and by paper chromatography with authentic material.

4-*Bromo*-4-*methyltetrahydrofuran*-2,3-*dione* [5] (V; R^1 = Me, R^2 = Br).—Prepared by the method of Schinz and Hinder,[5] this keto-lactone had m. p. 94° (from benzene–hexane) (lit.,[5] 95—97°), $\nu_{max.}$ 1810 and 1785 cm.$^{-1}$ (C:O in 5-membered ring) (Found: Br, 41·25. Calc. for $C_5H_5BrO_3$: Br, 41·4%).

The bromo-lactone was also prepared by treatment of the enol (IV; R^1 = Me, R^2 = OH, R^3 = H) (4·15 g.) with *N*-bromosuccinimide (6·5 g.) for 30 min. in refluxing carbon tetrachloride (80 ml.). The product (4·15 g.) had m. p. 72—82° and an infrared spectrum resembling that of material prepared by the preceding method.

1-(β-*Hydroxymethyl*-α-*oxo*-β-*piperidinobutyroyl*)*piperidine* (VII).—4-Bromo-4-methyltetrahydrofuran-2,3-dione (1·37 g.) in benzene (15 ml.) was treated with piperidine (2·1 ml.) at room temperature for 65 hr. Removal of the precipitated piperidine hydrobromide (995 mg.) and evaporation of the solvent at <45° afforded a partially crystalline residue, which was extracted with dry ether. Evaporation of the ether and recrystallization of the residue from methanol–water (without heating) provided 1-(β-*hydroxymethyl*-α-*oxo*-β-*piperidinobutyroyl*)*piperidine* (509 mg.), m. p. 93—97° (capillary), ultraviolet end absorption only, $\nu_{max.}$ 3520 (bonded OH),

[46] Adkins and Billica, *Org. Synth.*, 1949, **29**, 24.

1715 (C:O), and 1640 cm.$^{-1}$ (CO·N), τ (in $CDCl_3$) 8·63 (CH_3) and 7·82 (CH_2) (Found: C, 63·35; H, 9·35; N, 9·7. $C_{15}H_{26}N_2O_3$ requires C, 63·8; H, 9·3; N, 9·9%). The compound was insoluble in aqueous sodium hydrogen carbonate and sodium hydroxide, but soluble in dilute hydrochloric acid.

3-*Acetoxy*-5-*bromo*-4-*methylfuran*-2(5H)-*one* (IV; R^1 = Me, R^2 = OAc, R^3 = Br).—3-Acetoxy-4-methylfuran-2(5*H*)-one (11·9 g.) and *N*-bromosuccinimide (15 g.) in dry carbon tetrachloride (100 ml.) containing a little benzoyl peroxide were refluxed for 25 min. After cooling, the mixture was washed with water, and the aqueous washings were extracted with carbon tetrachloride. The combined organic fractions were dried and evaporated *in vacuo* to give a pale yellow oil. Distillation afforded 3-*acetoxy*-5-*bromo*-4-*methylfuran*-2(5H)-*one* (12·06 g.), b. p. 116°/0·5 mm., n_D^{22} 1·5120, $\nu_{max.}$ 1810 (γ-lactone), 1790, 1180 (enol OAc), and 1698 cm.$^{-1}$ (C=C), τ (in CCl_4) 7·97 (CH_3), 7·72 (Ac), and 3·20 (CH) (Found: C, 35·45; H, 3·1; Br, 34·6. $C_7H_7BrO_4$ requires C, 35·75; H, 3·0; Br, 34·0%).

A solution of the allylic bromide (5 g.) in acetone (50 ml.) containing a small lump of solid carbon dioxide at −40° was treated with a solution of electrolytic chromium (3·32 g.) in concentrated hydrochloric acid (16·5 ml.) containing water (16·5 ml.), and the mixture was kept at room temperature for 1 hr. Evaporation of the solvent *in vacuo* and extraction of the residue with ether afforded 3-acetoxy-4-methylfuran-2(5H)-one (2·57 g., 77·5%), identified by spectroscopy. Recrystallization from ether at −80° produced the pure enol acetate (IV; R^1 = Me, R^2 = OAc, R^3 = H) (2·18 g.).

3,5-*Diacetoxy*-4-*methylfuran*-2(5H)-*one* (IV; R^1 = Me, R^2 = R^3 = OAc).—Addition of dry potassium acetate (13·39 g.) to a clear colourless solution of the bromo-lactone (IV; R^1 = Me, R^2 = OAc, R^3 = Br) (3·42 g.) in acetone (60 ml.) at room temperature rapidly caused the mixture to become chocolate-brown. After 21 hr. at room temperature, the mixture was refluxed for 3 hr., and then most of the solvent evaporated *in vacuo*. Extraction with ether, distillation, and crystallization produced 3,5-*diacetoxy*-4-*methylfuran*-2(5H)-*one* (890 mg.), m. p. 58—61° (from methanol), b. p. 126—127°/0·4 mm., ultraviolet end absorption only, $\nu_{max.}$ 1805 (γ-lactone), 1782 and 1180 (enol OAc), and 1710 cm.$^{-1}$ (C=C). Its nuclear magnetic resonance spectrum showed the appropriate signals for three methyl groups (two acetyl and one *C*-methyl) (Found: C, 50·4; H, 4·7. $C_9H_{10}O_6$ requires C, 50·5; H, 4·7%).

1-(4-*Acetoxy*-2,5-*dihydro*-3-*methyl*-5-*oxo*-2-*furylthio*)*ethaniminium Bromide* (IV; R^1 = Me, R^2 = OAc, R^3 = S·CMe:$NH_2^+Br^-$).—Freshly prepared bromo-lactone (IV; R^1 = Me, R^2 = OAc, R^3 = Br) (3·09 g.) and thioacetamide (985 mg.) in acetic acid (5 ml.) were kept at room temperature for 16 hr. Filtration gave the *iminium bromide* (1·46 g.), m. p. 150° (decomp.) (capillary) (from acetic acid), $\lambda_{max.}$ 243—247 mμ (on storage), $\nu_{max.}$ (in Nujol) 1795 (γ-lactone), 1780 and 1200 (enol OAc), and 1700 cm.$^{-1}$ (C=C) (Found: C, 34·45; H, 3·9; Br, 25·7; S, 10·4. $C_9H_{12}BrNO_4S$ requires C, 34·85; H, 3·9; Br, 25·7; S, 10·35%).

Di-(4-*acetoxy*-2,5-*dihydro*-3-*methyl*-5-*oxo*-2-*furyl*) *Disulphide* (VIII).—(1) The preceding bromide (1·1 g.) was treated with 0·33M-potassium dichromate in 4N-sulphuric acid (15 ml.) at room temperature. The mixture became warm and darkened. The cooled solution was extracted with ether and the extract washed with water until colourless. Evaporation of the solution *in vacuo* and recrystallization of the residue from methanol afforded the *disulphide* (VIII) (69 mg.), m. p. 149—152° (decomp.), $\nu_{max.}$ (in Nujol) 1790 (γ-lactone), 1770 and 1190 (enol OAc), and 1700 cm.$^{-1}$ (C=C), $\lambda_{max.}$ 241—242 and 289—291 mμ (ε 13,400 and 3200, respectively) (Found: C, 44·85; H, 4·0; N, 0; S, 16·95. $C_{14}H_{14}O_8S_2$ requires C, 44·9; H, 3·75; S, 17·15%).

(2) The bromide (424 mg.) was treated with hydrogen peroxide (6 ml.; 100-vol.) at room temperature. After about 1 min. the mixture was cooled and the supernatant liquid decanted from the precipitated oil. After being washed with water, the product was twice crystallized from methanol to afford the disulphide (VIII) (54 mg.) as plates, m. p. 150—153°, identical with the product described in the preceding paragraph.

1-(2,5-*Dihydro*-4-*hydroxy*-5-*oxo*-3-*furylmethyl*)*piperidine* (X).—99—100% Pyruvic acid (88 g.) was treated with a solution of sulphuric acid (56·8 ml.) in water (15 ml.) to which piperidine (105 ml.) had been added. Paraformaldehyde (44·8 g.) was added, and the mixture heated for 5 hr. under nitrogen on the steam-bath. The ingredients dissolved quickly. The cooled solution was treated with dry ethanol (500 ml.). Scratching initiated crystallization of the *piperidinium sulphate* (IXb; $X^- = \frac{1}{2}SO_4^{2-}$) (74 g., 29%), m. p. 125—128° (decomp.), $\lambda_{max.}$ (in H_2O) 233—234 and 259—267 mμ (ε 15,400 and 8650, respectively), $\nu_{max.}$ (in Nujol) 3620

(OH), 3100—2400 (bonded OH), 1765 (C:O in butenolide), and 1674 cm.$^{-1}$ (C=C), which occurred in at least two crystalline forms (as shown by the infrared spectra of mulls) (Found: N, 5·3; S, 6·7. $C_{10}H_{15}NO_3,\frac{1}{2}H_2SO_4$ requires N, 5·7; S, 6·5%). The nuclear resonance magnetic spectrum was the same as that of the free base (X).

A solution of the sulphate (IXb; $X^- = \frac{1}{2}SO_4^{2-}$) (15·0 g.) in water (250 ml.) was stirred and treated with 0·228N-barium hydroxide (262 ml.) until the solution was at pH 8·5 (this pH was not exceeded during the addition). The precipitate was centrifuged off and the solution evaporated at $<50°$ in a rotary evaporator until crystals separated. Two crops were obtained, and were washed with ethanol and ether to give the pure *piperidine* (X) (8·62 g., 72%), m. p. 128—131° (decomp.), $\lambda_{max.}$ (in H_2O) 235 and 267 mμ (ε 5400 and 5250, respectively), $\lambda_{max.}$ (NaOH) 267 mμ (ε 9350), $\lambda_{max.}$ (HCl) 232·5 mμ (ε 13,400), $\nu_{max.}$ (in Nujol) 3100—2400 (bonded OH), 1765 (C:O in butenolide) and 1684 cm.$^{-1}$ (C=C), τ (in D_2O) 5·00 (ring CH_2), 5·85 ($^+NH{\cdot}CH_2$), 6·25, 6·46, 6·70, 7·15 (CH_2 groups in α-position in piperidine ring) and 7·90—8·50 (β- and γ-methylene groups in piperidine ring) (Found: C, 60·7; H, 7·4; N, 6·9. $C_{10}H_{15}NO_3$ requires C, 60·9; H, 7·7; N, 7·1%). This base was also obtained by percolating the hydrochloride (IXb; X = Cl) through any one of the ion-exchange resins De-Acidite-FF or IRA-400 or -G (OH^-).

The derived *picrate* had $\lambda_{max.}$ (in 1 : 1 H_2O–EtOH) 242—245 and 375 mμ (ε 15,700 and 15,800, respectively) (Found: N, 13·2%; *M*, 431. $C_{16}H_{18}N_4O_{10}$ requires N, 13·1%; *M*, 426). Molecular weights of the picrates were determined spectroscopically.[19]

1-(2,5-*Dihydro*-4-*hydroxy*-5-*oxo*-2-*furylmethyl*)*dimethylammonium Chloride* (IXa; X = Cl).—Prepared by the method of Mannich and Bauroth [18] this salt had m. p. 157—166° (decomp.) (fine needles from 0·1N-hydrochloric acid), $\lambda_{max.}$ (in H_2O) 234 and 266 mμ (ε 6800 and 4200, respectively), $\lambda_{max.}$ (NaOH) 267 mμ (ε 9700), $\nu_{max.}$ (in Nujol) 1770 (γ-lactone) and 1690 cm.$^{-1}$ (C=C) (Found: C, 43·5; H, 6·3; Cl, 18·3; N, 6·9. Calc. for $C_7H_{12}ClNO_3$: C, 43·4; H, 6·3; Cl, 18·3; N, 7·2%). The derived *picrate* had $\lambda_{max.}$ (in 1 : 1 EtOH–H_2O) 231 and 355—360 (ε 16,000 and 15,300, respectively) (Found: N, 14·0%; *M*, 395. $C_{13}H_{14}N_4O_{10}$ requires N, 14·5%; *M*, 386).

4,4′-*Methylenedi*-(3-*hydroxyfuran*-2(5H)-*one*) (XI).—The *compound* obtained by the method that gave the "$C_{15}H_{15}O_{10}$-acid" of Mannich and Bauroth [18] had m. p. 240—241° (decomp., sublimation at $>230°$) (from water), $\lambda_{max.}$ (in H_2O) 238—239 mμ (ε 17,600), $\lambda_{max.}$ (HCl) 239—240 mμ (ε 19,900), $\lambda_{max.}$ (NaOH) 277—278 mμ (ε 18,100), $\nu_{max.}$ (in Nujol) 3350 (OH) and 1760 cm.$^{-1}$ (γ-lactone) (Found: C, 51·2; H, 3·75. Calc. for $C_9H_8O_6$: C, 50·9; H, 3·8%) [lit.,[21,22] m. p. 234°, 242°, $\lambda_{max.}$ 241 mμ (ε 20,400)].

4-*Benzylthiomethyl*-3-*hydroxyfuran*-2(5H)-*one* (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2Ph$, $R^2 = OH$, $R^3 = H$).—The hydrochloride (IXa; X = Cl) (41·6 g.) was added to methanolic sodium methoxide (24·8 g. in 2·4 l.) containing toluene-ω-thiol (156 ml.). The mixture was refluxed for 2 hr. in an atmosphere of nitrogen, cooled, and acidified with 2N-hydrochloric acid. The excess of thiol was removed by steam-distillation *in vacuo*; the residual mixture was then extracted with ether. Evaporation afforded an oil (55 g.) that was run in ether–ethyl acetate (9 : 1) on to a column of Florisil (180 g.); elution with this solvent (1 l.) and evaporation of the eluate left a solid that crystallized from hexane–carbon tetrachloride as white needles of 4-*benzylthiomethyl*-3-*hydroxyfuran*-2(5H)-*one* (20·7 g.), m. p. 79—82°. Crystallization from carbon tetrachloride furnished a specimen, m. p. 80—81°, $\lambda_{max.}$ 232 mμ (ε 19,800), $\lambda_{max.}$ (NaOH) 276—277 mμ (ε 10,500), $\nu_{max.}$ 3500 and 3300 (bonded OH), 1765 and 1745 (γ-lactone), 1700 (C=C), and 696 cm.$^{-1}$ (Ph) (Found: C, 60·2; H, 5·0; S, 13·7. $C_{12}H_{12}O_3S$ requires C, 61·0; H, 5·1; S, 13·6%). Diazomethane in ether gave the 3-*methyl ether*, b. p. (bath-temp.) 190—195°/0·05 mm., $\nu_{max.}$ 1764 (γ-lactone), 1678 (C=C), 1102 (C·O·C), and 698 cm.$^{-1}$ (Ph) (Found: C, 62·6; H, 5·8; S, 12·7. $C_{13}H_{14}O_3S$ requires C, 62·4; H, 5·6; S, 12·8%), which in solution had no absorption maximum between 220 and 300 mμ. Treatment of the enol (0·49 g.) with acetic anhydride (5 ml.) and pyridine (5 ml.) at 3° for 16 hr. and evaporation of the solution furnished a gum that was kept for 20 min. at 100°/10 mm. Addition of benzene, ether, and hexane yielded crystals (0·45 g.), m. p. 58—62°, that were recrystallized from ether as needles (0·37 g.) of the 3-*acetate*, m. p. 63—64°, $\nu_{max.}$ 1790 (γ-lactone), 1790 and 1190 (enol OAc), 1700 (C=C), and 700 cm.$^{-1}$ (Ph) (Found: C, 60·6; H, 5·0; S, 11·7. $C_{14}H_{14}O_4S$ requires C, 60·4; H, 5·1; S, 11·5%).

3-*Amino*-4-*benzylthiomethylfuran*-2(5H)-*one* (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2Ph$, $R^2 = NH_2$, $R^3 = H$).—A mixture of the sulphide (IV; $R^1 = CH_2{\cdot}S{\cdot}CH_2Ph$, $R^2 = OH$, $R^3 = H$) (10·0 g.) and ammonium acetate (6·4 g.) was heated at 120° for 2·5 hr. under nitrogen. The resulting gum

was leached with hot carbon tetrachloride, and the extracts were filtered and evaporated, leaving a gum that was dissolved in benzene–ether (9 : 1) and washed with water. Ethyl acetate (1% by volume) was added to the dried solution, which was then filtered through a short column of Florisil. Evaporation of the eluates left a residue that crystallized from carbon tetrachloride to furnish the *amine* (6·9 g.) as pale orange plates, m. p. 84°. A recrystallized specimen was pale yellow and had m. p. 84—86°, $\lambda_{max.}$ 266 mμ (ε 10,800) (unchanged in 0·04N-hydrochloric acid and 0·04N-sodium hydroxide), $\lambda_{max.}$ (in 0·5N-HCl) 267 mμ (ε 5350), $\nu_{max.}$ 3460 and 3360 (NH_2), 1770 (γ-lactone), 1692 (C=C), and 698 cm.$^{-1}$ (Ph), τ (in $CDCl_3$) 2·70 (Ph), 5·43 (ring CH_2), 6·29 (CH_2·S and NH_2), and 6·75 (S·CH_2) (addition of D_2O caused disappearance of the resonance due to the NH_2 protons) (Found: C, 61·1; H, 5·5; N, 5·6; S, 13·7. $C_{12}H_{13}NO_2S$ requires C, 61·2; H, 5·6; N, 5·9; S, 13·6%). In electrophoresis this compound did not behave as a base.

A solution of the amine (49 mg.) in ethanol (0·5 ml.) and 2N-hydrochloric acid (0·5 ml.) was refluxed for 1 hr. and then evaporated. A solution of the residue in chloroform was washed, dried, and evaporated, leaving an oil (31 mg.) that yielded needles (26 mg.), m. p. 77—79° (from hexane–carbon tetrachloride), of the enol (IV; R^1 = $CH_2S{\cdot}CH_2Ph$, R^2 = OH, R^3 = H).

Bis-(2,5-dihydro-4-hydroxy-5-oxo-3-furylmethyl) Sulphide (XII; n = 1).—A solution of the hydrochloride (IXa; X = Cl) (4·0 g.) in M-sodium hydrogen sulphide in methanol (104 ml.) was refluxed for 3 hr., nitrogen being bubbled through the mixture. The product was acidified with hydrochloric acid, the mixture evaporated, and a solid (1·14 g.), m. p. 128—131°, filtered off. Crystallization from methanol gave needles (0·68 g.), m. p. 128—131°; recrystallization and drying of the crystals at 70° *in vacuo* gave the *sulphide* (XII; n = 1) as its *hydrate*, m. p. 125—128° (solidifies and remelts at 147—148°) (Found: C, 43·4; H, 4·4; S, 11·8. $C_{10}H_{10}O_6S,H_2O$ requires C, 43·5; H, 4·4; S, 11·6%). Drying *in vacuo* at 110° gave the anhydrous form as needles, m. p. 127—128° and 147—148°, $\lambda_{max.}$ (in H_2O) 235—236 mμ (ε 14,800), $\lambda_{max.}$ (NaOH) 278—280 mμ (ε 20,300) (Found: C, 46·7; H, 4·0; S, 12·4. Calc. for $C_{10}H_{10}O_6S$: C, 46·5; H, 3·9; S, 12·4%) [lit.,[2,21] m. p. 147—148°, $\lambda_{max.}$ 236 mμ (ε 13,700), $\lambda_{max.}$ (NaOH) 281 mμ (ε 13,600)].

3-Hydroxy-4-mercaptomethylfuran-2(5H)-one (IV; R^1 = CH_2·SH, R^2 = OH, R^3 = H).—Hydrogen sulphide was bubbled for 24 hr. through a solution of the hydrochloride (IXa; X = Cl) (10 g.) in M-sodium hydrogen sulphide in methanol (300 ml.). The mixture was acidified with 2N-hydrochloric acid, the methanol distilled off, and the residue continuously extracted for 8 hr. with ether. The aqueous phase and insoluble material were discarded. The ethereal solution yielded, on evaporation, a solid (2·3 g.) that gave no colour with sodium nitroprusside and was discarded. The filtered ethereal solution was made up to 200 ml. with ether; part (80 ml.) of this solution was evaporated at >20° and the residue dissolved in methanol. Saturated methanolic lead acetate was added, and a precipitate collected and washed with methanol, 5% acetic acid in water, and water, and dried. The resulting brown powder (0·63 g.) was added to a mixture of ethanol (25 ml.) and ether (25 ml.) and shaken with hydrogen sulphide. Absorption of gas ceased after 30 min. A black precipitate (0·294 g.) was filtered off and the solvent evaporated to leave the *mercaptan*, $\lambda_{max.}$ 241—242 mμ (ε 6500), $\lambda_{max.}$ (NaOH) 276—279 and 328—332 mμ (ε 3500 and 1400, respectively), $\nu_{max.}$ (in $CHBr_3$) 3460 (OH), 1758 (γ-lactone), and 1656 cm.$^{-1}$ (C=C) (Found: C, 40·5; H, 4·1; S, 22·1. $C_5H_6O_3S$ requires C, 41·1; H, 4·1; S, 21·9%). The rest (120 ml.) of the ethereal solution was evaporated and the residue was dissolved in methanol (200 ml.); half of this solution was treated with methanolic lead acetate to yield the *lead salt* of the mercaptan as a yellow powder (0·15 g.) that darkened on drying (Found: C, 23·7; H, 2·0; S, 12·4. $C_{10}H_{10}O_6PbS_2$ requires C, 24·1; H, 2·0; S, 12·9%). Preparations of the mercaptan and its lead salt were unreliable. With diazomethane in ether the mercaptan gave the O-*methyl ether* (IV; R^1 = CH_2·SH, R^2 = OMe, R^3 = H), b. p. (bath-temp.) 190—210°/0·5 mm., $\lambda_{max.}$ 231 mμ (ε 6300), $\nu_{max.}$ (in $CHBr_3$) 1758 (γ-lactone), 1675 (C=C), and 1266 cm.$^{-1}$ (enol ether) (Found: S, 20·9. $C_6H_8O_3S$ requires S, 20·0%).

The piperidino-base (IV; R^1 = $CH_2{\cdot}NC_5H_{10}$, R^2 = OH, R^3 = H) (1·0 g.) in suspension in propan-2-ol (50 ml.) was shaken with sodium disulphide (0·66 g.) in water (2·3 ml.) under nitrogen for 21 hr. Dissolution occurred quickly, then a pale yellow precipitate (0·34 g.) separated that gave no colour with sodium nitroprusside, even in alkaline solution; it turned ferric chloride solution brownish-red. Treatment of some (0·168 g.) of the product with hydrochloric acid and isolation with ether gave the crude disulphide (XII; n = 2) as a pale

yellow solid (0·085 g.), m. p. 120—129° (lit.,[21] 131—132°), $\nu_{max.}$ (in Nujol) 3230 (bonded OH), 1740 (γ-lactone), and 1700 cm.$^{-1}$ (C=C) (Found: S, 22·6. Calc. for $C_{10}H_{10}O_6S_2$: S, 22·1%).

Reduction of the disulphide (0·20 g.) with acid-washed zinc dust (0·226 g., in three lots) in acetic acid (5 ml.) at 90° for 20 min., with subsequent extraction with 2N-hydrochloric acid and ether, gave an ether extract that deepened the colour of solutions of sodium nitroprusside. Evaporation left a residue that was treated with methanolic lead acetate to give the lead salt of the mercaptan (IV; $R^1 = CH_2{\cdot}SH$, $R^2 = OH$, $R^3 = H$).

Ethyl 3-*Methyl*-2-*oxobut*-3-*enoate* (XIV).—Ethyl 2-hydroxy-3-methylbut-3-enoate [27] (6 g.) in cyclohexane (600 ml.) was shaken with manganese dioxide (30 g.) prepared according to the directions of Attenburrow *et al.*[47] At intervals aliquot parts were removed and their optical densities measured at 225 mμ. A further portion of manganese dioxide (30 g.) was added after 2 hr., and after 6 hr. the mixture was centrifuged and distilled, to afford the *ester* (XIV), b. p. 71°/14 mm., n_D^{23} 1·4325, $\lambda_{max.}$ 223—224 mμ (ε 6700), $\nu_{max.}$ 1745 and 1240 (CO_2Et), 1690 (C:C·C:O), and 940 cm.$^{-1}$ ($C{=}CH_2$) (Found: C, 58·7; H, 7·3. $C_7H_{10}O_3$ requires C, 59·1; H, 7·1%) [2,4-*dinitrophenylhydrazone* (from chloroform–methanol), m. p. 115—117° (runs 155—160°) (capillary), $\lambda_{max.}$ 364—365 mμ (ε 28,600), infl. 244—254 mμ (ε 12,500), $\nu_{max.}$ (in Nujol), 3300 (NH),1720 and 1255 (CO_2Et), 1520 and 1350 (NO_2), and 918 cm.$^{-1}$ ($C{=}CH_2$) (Found: C, 47·8; H, 4·3; N, 16·5. $C_{13}H_{14}N_4O_6$ requires C, 48·4; H, 4·4; N, 17·4%).

The oxidation could also be performed satisfactorily in t-butyl alcohol, light petroleum–ether, hexane, anhydrous ether, or chloroform.

3-*Hydroxy*-4-*methylthiophen*-2(5H)-*one* (VI; $R^1 = Me$, $R^2 = OH$, X = S).—Ethyl 3-methyl-2-oxobut-3-enoate [from the 2-hydroxy-ester (10 g.) in cyclohexane (500 ml.)] was treated with triethylamine (0·5 ml.) and hydrogen sulphide for 20 hr. When kept at room temperature for a further 40 hr. the solution deposited 3-*hydroxy*-4-*methylthiophen*-2(5H)-*one* (2·78 g.) as stout prisms, m. p. 142° (sublimation >100°). The sample, obtained by sublimation, had m. p. 126—128°, $\lambda_{max.}$ 246 mμ (ε 9800), $\lambda_{max.}$ (NaOH) 245—246 and 304 mμ (ε 6300 and 6100, respectively), $\nu_{max.}$ 1710 (C=C) and 1665 cm.$^{-1}$ (thiolactone), τ (in $CHCl_3$) 7·93q (CH_3), 6·27t (CH_2), and 3·95 (OH) (Found: C, 46·5; H, 4·7; S, 24·3. $C_5H_6O_2S$ requires C, 46·1; H, 4·7; S, 24·6%). A second crop (289 mg.), m. p. 130—131°, was obtained by passing more hydrogen sulphide through the reaction mixture.

The thiolactone was also obtained by treatment of ethyl 3-methyl-2-oxobut-3-enoate with sodium hydrogen sulphide solution saturated with hydrogen sulphide at room temperature for 16 hr. It gave a deep colour with alcoholic ferric chloride, but did not appear to react with alkaline sodium nitroprusside solution or Brady's reagent. Only one equivalent of 0·1N-sodium hydroxide was consumed.

3-*Amino*-4-*methylthiophen*-2(5H)-*one* (VI; $R^1 = Me$, $R^2 = NH_2$, X = S).—The preceding compound (698 mg.) and ammonium acetate (1·0 g.) were ground together and heated at 100° under nitrogen. After 2 hr. the red liquid was cooled, triturated with warm water (3 ml.), and cooled in ice. The light brown crystalline product (517 mg.), m. p. 76—79°, recrystallized from ether to give 3-*amino*-4-*methylthiophen*-2(5H)-*one* (336 mg.), m. p. 64°, $\lambda_{max.}$ 249—250 and 288 mμ (ε 6100 and 3900, respectively), $\lambda_{max.}$ (HCl) 230 and 249—251 mμ (ε 5000 and 4600, respectively), infl. 269—289 mμ (ε 2600), $\nu_{max.}$ 3450 and 3360 (NH_2), 1692 (thiolactone), and 1668 cm.$^{-1}$ (C=C), τ 8·03t (CH_3), 6·27q (CH_2) and ~6·6 (NH_2) (Found: C, 46·5; H, 5·5; N, 11·1; S, 24·7. C_5H_7NOS requires C, 46·5; H, 5·5; N, 10·8; S, 24·8%). The N-*acetyl derivative* formed needles (from methanol), m. p. >340° when freshly prepared, but 18 months later m. p. 187—190°, $\lambda_{max.}$ 239—240 mμ (ε 7700) (unchanged in ethanolic HCl), $\nu_{max.}$ (in $CHBr_3$) 3400 (NH), 1688 (thiolactone), 1652 and 1500 cm.$^{-1}$ (CO·NH), τ (in pyridine) 7·87 (CH_3), 7·77 ($CH_3{\cdot}CO$), and 6·42 (CH_2) (Found: C, 49·3; H, 5·4; N, 7·9; S, 18·4. $C_7H_9NO_2S$ requires C, 49·1; H, 5·3; N, 8·2; S, 18·7%).

Ethyl 4-*Hydroxy*-5-*methyl*-2-*thiothiazan*-4-*carboxylate* (XVII; $R^1R^2 = S$).—Crude ethyl 3-methyl-2-oxobut-3-enoate (884 mg.) was added to a stirred slurry of dithiocarbamic acid [prepared from concentrated hydrochloric acid (0·52 ml.) and ammonium dithiocarbamate (667 mg.) in a little water] and washed in with t-butyl alcohol (1 ml.). The solid (1·12 g.) which separated afforded the *thiothiazan ester*, m. p. 104—108° (from ether), $\lambda_{max.}$ 240 and 290 mμ (ε 8400 and 14,500, respectively), $\nu_{max.}$ (in $CHBr_3$) 3550 (OH), 3370 (NH), 1740 (CO_2Et), and 1490 cm.$^{-1}$ (N·C:S), τ (in $CDCl_3$) 8·62t and 5·62q ($CH_3{\cdot}CH_2{\cdot}O$), 8·96d ($CH_3{\cdot}CH$), 7·9—6·4

[47] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

(S·CH_2·CH), 6·05 (OH), 5·90, 5·73, 5·55, and 5·37 (CH_2·CH_3), and 0·9 (broad; NH) (Found: C, 40·9; H, 5·8; N, 5·7; S, 26·7. $C_8H_{13}NO_3S_2$ requires C, 40·8; H, 5·6; N, 5·9; S, 27·3%).

Ethyl 5,6-*Dihydro*-4-*hydroxy*-2,5-*dimethyl*-4H-1,3-*thiazine*-4-*carboxylate* (XVIII; R^1 = R^4 = Me, R^2 = OH, R^3 = CO_2Et). Thioacetamide (1·35 g.) and triethylamine (0·35 ml.) were added to a solution of ethyl 3-methyl-2-oxobut-3-enoate (2·55 g.), in t-butyl alcohol (3 ml.), and the mixture was gently warmed until the thioacetamide had dissolved. The mixture was kept at room temperature for 96 hr., then evaporated *in vacuo* to an oil which was partitioned between ether and water. The ether layer afforded a semicrystalline mass which, on crystallization from ether, afforded the *thiazine ester*, m. p. 67—69°, $\lambda_{max.}$ 236 mμ (ε 5200), $\lambda_{max.}$ (HCl) 250 mμ (ε 9300), $\nu_{max.}$ 3530 (OH), 1748 and 1198 (CO_2R), and 1625 cm.$^{-1}$ (C:N) (Found: C, 49·6; H, 7·0; N, 6·5; S, 14·3. $C_9H_{15}NO_3S$ requires C, 49·7; H, 7·0; N, 6·4; S, 14·7%). The nuclear magnetic resonance spectrum (in CCl_4) was unexpectedly complex. Doublets centred at 9·04 (75%) and 8·94 τ (25%) suggested two methyl groups (attached to >CH–) in slightly different environments, possibly pseudo-axial and equatorial. This view was supported by splitting of the methyl triplets (of O·CH_2·CH_3) centred on 8·69 and 8·72 τ, in the same ratio. The corresponding methylene quadruplets also appeared to confirm this, and the methyl singlet (CH_3·C<) was split, τ 7·84 (80%) and 7·81 (20%). The OH signal was at 5·20 τ.

Ethyl 3-*Methyl*-2-*oxo*-4-*thioacetoxybutyrate* (cf. XIX; R = H).—The preceding thiazine ester (996 mg.) in aqueous 6% formic acid (60 ml.) was heated on the steam-bath for 20 min. The heavy colourless oil which separated was extracted into chloroform and washed with sodium hydrogen carbonate solution and water. Evaporation *in vacuo* afforded *ethyl* 3-*methyl*-2-*oxo*-4-*thioacetoxybutyrate*, b. p. 84°/0·2 mm., n^{15} 1·4803, $\lambda_{max.}$ 231 mμ (ε 4400), $\lambda_{max.}$ (NaOH) 247—248 and 303—306 mμ (ε 7100 and 1100, respectively), $\nu_{max.}$ 1752—1730 (CO·CO_2R), 1700 (SAc), and 3450w cm.$^{-1}$ (bonded OH) (Found: C, 49·1; H, 6·3; S, 13·3. $C_9H_{14}O_4S$ requires C, 49·5; H, 6·5; S, 14·7%) [2,4-*dinitrophenylhydrazone* (from ethanol), m. p. 113—114°, $\lambda_{max.}$ 227 and 355—356 mμ (ε 15,300 and 28,200, respectively), $\nu_{max.}$ (Nujol) 1700 (CO_2R and AcS), 1525 and 1340 cm.$^{-1}$ (NO_2) (Found: C, 45·2; H, 4·7; N, 14·1; S, 8·0. $C_{15}H_{18}N_4O_7S$ requires C, 45·2; H, 4·5; N, 14·1; S, 8·0%).

Treatment with acetic anhydride in pyridine at room temperature provided *ethyl* 2-*acetoxy*-3-*methyl*-4-*thioacetoxybut*-2-*enoate* (XIX; R = Ac), b. p. 115°/0·35 mm., n^{15} 1·4983, $\lambda_{max.}$ 226 mμ (ε 15,000), $\nu_{max.}$ 1772, 1208 (enol OAc), 1730, 1238 (CO_2Et), 1702, 1295 (SAc), and 1665 cm.$^{-1}$ (C=C) (Found: C, 50·3; H, 6·1; S, 12·1. $C_{11}H_{16}O_5S$ requires C, 50·7; H, 6·2; S, 12·3%).

Ethyl 4-*Hydroxy*-2,5-*dimethyl*-1,3-*thiazan*-4-*carboxylate* (XVII; R^1 = H, R^2 = Me).—Aluminium foil (2·2 g.), amalgamated with 3% mercuric chloride solution, was stirred for 3·6 hr. in a solution of ethyl 5,6-dihydro-4-hydroxy-2,5-dimethyl-4*H*-1,3-thiazine-4-carboxylate (1·27 g.) in ether (60 ml.) saturated with water. Evaporation of the filtered solution gave a mixture of oil and crystals which, on trituration with ether at −80°, provided the *thiazan ester* (268 mg.), m. p. 100—116°. The analytical sample (from ether) had m. p. 112—119°, $\nu_{max.}$ 3560 (OH), 3340 (NH), 1750 and 1198 cm.$^{-1}$ (CO_2R), τ (in $CHCl_3$) 9·15d and 8·63d (CH·CH_3), 8·67t and 5·68q (CH_3·CH_2·O) (Found: C, 49·6; H, 7·8; N, 6·2; S, 14·7. $C_9H_{17}NO_3S$ requires C, 49·3; H, 7·8; N, 6·4; S, 14·6%). The *oxalate* partially melted at 94—97° (decomp. >100°), $\nu_{max.}$ (in Nujol) 1760 and 1200 cm.$^{-1}$ (CO_2R) (Found: C, 42·4; H, 6·4; N, 4·0; S, 9·5. $C_{11}H_{19}NO_7S$ requires C, 42·7; H, 6·2; N, 4·4; S, 10·4%). Addition of potassium hydrogen carbonate solution to an aqueous solution of the oxalate afforded the base, m. p. 110—114°, with an infrared spectrum similar to that of authentic material. When the base was shaken in an aqueous solution of dimedone at room temperature, the acetaldehyde dimedone derivative crystallized in 52·5% yield; when 1·0 equiv. of hydrochloric acid was present, the yield was 58·5%.

Evaporation of a solution of the thiazan (1·22 g.) in ethanol which had been kept for 66 hr. at room temperature in an open flask gave an oil from which was sublimed at 75°/0·1 mm. the thiolactone (VI; R^1 = Me, R^2 = OH, X = S) (202 mg.), $\lambda_{max.}$ 246 mμ (ε 4800), infl. 260—270 mμ (ε 2900), $\lambda_{max.}$ (NaOH) 247 and 305 mμ (ε 2500 and 2600, respectively), with infrared absorption similar to that of the authentic thiolactone.

Evaporation of the mother-liquor obtained by trituration of the crude reduction product with ether at −80° afforded an oil which, after distillation, was dissolved in chloroform and washed with dilute hydrochloric acid and water. A further distillation afforded *ethyl* 2-*hydroxy*-4-*mercapto*-3-*methylbutyrate* (XX; R = H), b. p. 60°/0·2 mm., n_D^{15} 1·4840, $\lambda_{max.}$ 235—241 mμ

(ε 370), $\nu_{max.}$ (in $CHBr_3$) 3540 (OH), 2560 (SH), 1730, 1260 (CO_2R), and 1664 cm.$^{-1}$ (C=C) (Found: C, 46·8; H, 7·9; S, 18·0. $C_7H_{14}O_3S$ requires C, 47·2; H, 7·9; S, 18·0%) [OS-*diacetate*, b. p. 98°/0·15 mm., n_D^{15} 1·4740, $\lambda_{max.}$ 230—231 mμ (ε 4000), $\nu_{max.}$ 1750, 1230 (OAc), 1745, 1210 (CO_2Et), and 1695 cm.$^{-1}$ (–SAc) (Found: C, 50·6; H, 6·9; S, 11·9. $C_{11}H_{18}O_5S$ requires C, 50·4; H, 6·9; S, 12·2%)].

The same product was obtained, in poor yield, by reduction of the dihydrothiazine in acetic acid with zinc dust at room temperature.

Ethyl 5,6-*Dihydro*-2,5-*dimethyl*-2H-1,3-*thiazine*-4-*carboxylate Hydrochloride* (XXI).—Ethyl 4-hydroxy-2,5-dimethyl-1,3-thiazan-4-carboxylate (XVII; R^1 = H, R^2 = Me) (590 mg.) in anhydrous ether (65 ml.) was treated at 0° with dry hydrogen chloride. The precipitated *hydrochloride* (574 mg.) had m. p. 117—119° (decomp.) (evacuated capillary), $\nu_{max.}$ (in Nujol) 1706 and 1270 (C:C·CO_2Et), 1660 (C:N), and 2700—2400 cm.$^{-1}$ (C:NH^+) (Found: C, 45·4; H, 6·7; Cl, 15·0; N, 5·6; S, 13·3. $C_9H_{16}ClNO_2S$ requires C, 45·5; H, 6·8; Cl, 14·9; N, 5·9; S, 13·5%).

When this salt was shaken with an aqueous solution of dimedone at room temperature, acetaldehyde dimedone derivative was precipitated in 75% yield.

Ethyl 3,6-*Dihydro*-2,5-*dimethyl*-2H-1,3-*thiazine*-4-*carboxylate* (III; R^1 = R^3 = Me, R^2 = Et).—The preceding hydrochloride (XXI) (3·15 g.) was added with shaking to sodium hydrogen carbonate (1·16 g.) in water (20 ml.). The precipitate was extracted with ether and the extract was washed with water, dried, and evaporated to afford a mixture of oil and crystalline ethyl 4-hydroxy-2,5-dimethyl-1,3-thiazane-4-carboxylate (XVII; R^1 = H, R^2 = Me); the latter was removed by filtration. Distillation of the oil gave *ethyl* 3,6-*dihydro*-2,5-*dimethyl*-2H-1,3-*thiazine*-4-*carboxylate* (865 mg.), b. p. 83—85°/0·2 mm., n^{16} 1·5350, $\lambda_{max.}$ 285—286 mμ (ε 3100), $\nu_{max.}$ 3400 (NH), 1730 (CO_2Et), 1705 (hydrogen-bonded CO_2Et), 1675 and 1645 cm.$^{-1}$ (C=C and C=N), τ ($CDCl_3$) 8·7t, 5·76q (CH_3·CH_2·O), 8·42d (CH_3·CH), 7·88 (CH_3·C), 6·92, 6·50 (S·CH_2·C) [Found: C, 53·6; H, 7·9; N, 7·0; S, 15·9%; *M* (vapour-pressure method [48]), 202. $C_9H_{15}NO_2S$ requires C, 53·7; H, 7·5; N, 7·0; S, 15·9%; *M*, 201].

Treatment of the base (239 mg.) in ether (10 ml.) with hydrogen chloride at room temperature regenerated the hydrochloride, m. p. 115—117° (decomp.) (evacuated capillary), with an infrared spectrum similar to that of authentic material.

When the base was shaken with aqueous dimedone at room temperature the acetaldehyde dimedone derivative separated in 62% yield.

3,6-*Dihydro*-2-o-*hydroxyphenyl*-4,6,6-*trimethyl*-2H-1,3-*thiazine* (XIII). This compound was made by a method described [25] for the preparation of the 5,6-dihydro-2*H*-isomer; it separated from propan-1-ol as pale yellow needles, m. p. 134—135° (lit.,[25] 136°), $\lambda_{max.}$ 278 and 302 mμ (ε 3500 and 5050, respectively), $\lambda_{max.}$ (NaOH) 239 mμ (ε 8600), $\nu_{max.}$ (in Nujol) 1658 (C=N or C=C), and 752 cm.$^{-1}$ (*o*-disubstituted benzene), τ (in $CDCl_3$) 8·70 and 8·53 (CMe_2), 7·83 (CH_3), 7·48 and 7·80 (CH_2), 4·02 (CH), 3·55—2·66 (4 adjacent aromatic protons), −1·0 (bonded proton).

Reaction of the Hydrochloride (XXI) *with Benzaldehyde.*—A stream of nitrogen was bubbled for 1·3 hr. through a suspension of the hydrochloride (6·07 g.) in redistilled benzaldehyde (25 ml.) and then through a solution of 2,4-dinitrophenylhydrazine at room temperature for 1·3 hr. No dinitrophenylhydrazone was precipitated; the mixture was heated at 70—80° for 2·75 hr., during which acetaldehyde 2,4-dinitrophenylhydrazone (651 mg., 11·4%) was precipitated (identified by m. p. and spectra). After being kept overnight at 5° the mixture was mostly evaporated *in vacuo* and the residual dark oil partitioned between ether and dilute sodium hydrogen carbonate solution. The organic layer was extracted with N-hydrochloric acid, and the acid solution washed with ether, basified with sodium hydrogen carbonate, and re-extracted with ether. Evaporation of this extract gave an orange oil (3·18 g.), distillation of which afforded (*a*) *ethyl* 5,6-*dihydro*-2,5-*dimethyl*-4H-1,3-*thiazine*-4-*carboxylate* (XVIII; R^1 = R^4 = Me, R^2 = H, R^3 = CO_2Et) (348 mg.), b. p. 82—84°/0·2 mm., $\lambda_{max.}$ 235—237 mμ (ε 4800), $\lambda_{max.}$ (HCl) 249—250 mμ (ε 8500), $\nu_{max.}$ 1740, 1200 (CO_2Et), and 1640 cm.$^{-1}$ (C=N), τ (in $CHCl_3$) 9·00d (CH_3·CH), 8·68t and 5·76q (CH_3·CH_2·O), 7·83 (CH_3·C) (Found: C, 53·85; H, 7·5; N, 6·7; S, 15·7. $C_9H_{15}NO_2S$ requires C, 53·7; H, 7·5; N, 7·0; S, 15·9%) [*picrate*, m. p. 121—126°, $\lambda_{max.}$ 239 and 356—358 mμ (ε 17,000 and 15,600, respectively), $\nu_{max.}$ (in Nujol) 1730 (CO_2Et), 1566—1552 and 1338 cm.$^{-1}$ (NO_2) (Found: C, 42·0; H, 4·4; N, 12·8; S, 7·4. $C_{15}H_{18}N_4O_9S$ requires C, 41·8; H, 4·2; N, 13·0; S, 7·4%)], and (*b*) *ethyl* 5,6-*dihydro*-5-*methyl*-2-*phenyl*-4H-1,3-*thiazine*-4-*carboxylate* (XVIII; R^1 = Me, R^2 = H, R^3 = CO_2Et, R^4 = Ph) (1·18 g.), b. p.

[48] Brady, Huff, and McBain, *J. Phys. Colloid. Chem.*, 1951, **55**, 304.

157—170°/0·2 mm., $\lambda_{max.}$ 239 mμ (ε 11,400), $\lambda_{max.}$ (HCl) 263—265 mμ (ε 13,400), $\lambda_{max.}$ (NaOH) 235—237 mμ (ε 12,000), with strong end absorption, $\nu_{max.}$ 1740, 1200 (CO_2Et), 1690 (C=N), and 690 $cm.^{-1}$ (Ph) (Found: C, 64·0; H, 6·8; N, 5·4; S, 11·8. $C_{14}H_{17}NO_2S$ requires C, 63·8; H, 6·5; N, 5·3; S, 12·2%).

A similar experiment in which the ester (III; $R^1 = R^3 = Me$, $R^2 = Et$) (3·9 g.) and oxalic acid (100 mg.) were heated under nitrogen for 2 hr. at 90° gave the thiazan ester (XVII; $R^1 = H$, $R^2 = Me$) (319 mg.).

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