512. *Divinyl Sulphone and Allied Compounds.*

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The reactions of divinyl sulphone and certain other unsaturated sulphones with bromine, amines, and thiols are described. 2 : 2′-Dichlorodiethyl sulphone is a stable compound, and its various reactions are effected only after it has been converted into divinyl sulphone; it is probably not concerned in the biological action of mustard gas.

SEVERAL theories have been put forward to account for the vesicant and toxic properties of 2 : 2′-dichlorodiethyl sulphide (mustard gas) (I). That advanced by Flury and Wieland (*Z. ges. exp. Med.*, 1921, **13**, 367) postulated that (I) was oxidised in the body to 2 : 2′-dichlorodiethyl sulphone (II) and that the latter was the true toxic agent. The observation that (II) was itself vesicant and that its toxic effect, by intramuscular injection, was more rapid than that of (I) seemed to lend support to this suggestion.

Vesicant properties are also observed in certain sulphides that contain only one 2-chloroethyl group, but only those sulphides that can be converted into alk-1-enyl sulphones (by oxidation with 30% hydrogen peroxide and acetic acid, followed by loss of hydrogen chloride) exhibit such properties. For example, phenyl 2-chloroethyl sulphide (Ford-Moore, Peters, and Wakelin, this vol., p. 1754; Dawson, *J. Amer. Chem. Soc.*, 1933, **55**, 2070) and 2 : 2′-dichlorodi-*n*-propyl sulphide undergo these reactions and are vesicant; 2-chloroethyl 2′ : 2′-dichlorovinyl sulphide (III) (Mumford and Phillips, *J.*, 1929, 155) and 3 : 3′-dichlorodi-*n*-propyl sulphide (IV) (Bennett and Hock, *J.*, 1925, 2671) are non-vesicant. (III) gives 2-chloroethanesulphonic acid (not a sulphone) on oxidation; (IV) gives a sulphone that cannot give an alk-1-enyl sulphone. It seemed desirable, therefore, to study further the reactions of divinyl sulphone (V)—a substance into which (II) must be converted before it can undergo any of the reactions described in this paper—allied compounds containing only one Δ^{α}-group, and diallyl sulphone (which contains a Δ^{β}-group).

No trace of (II) has been found after intoxication with (I), probably because (II) reacts readily with amino-acids (and their esters) to give derivatives of tetrahydrothiazine 1 : 1-dioxide (Lawson and Reid, *J. Amer. Chem. Soc.*, 1925, **46**, 2821; Cashmore and McCombie, *J.*, 1923, **123**, 2884; cf. Wormall *et al.*, *Biochem. J.*, 1946, **40**, 737, who showed that the reaction takes place under biological conditions). It is probable that if (I) were oxidised in the body it would appear as a condensation product with body proteins through any free amino- (or mercapto-) groups present in the latter. The isolation of such a compound did not appear very promising but it was thought that any such (II)-protein complex might become degraded and that simpler fragments such as the condensation products with, say, alanine or tyrosine might be capable of identification and characterisation.

Subsequent to the work described in this paper, however, Wormall *et al.* (*Biochem. J.*, 1946, **40**, 734) showed that the action of (I) on proteins under physiological conditions is quite different from that of (II). Furthermore, Sugden (Ministry of Supply Communication) calculated thermodynamically that the oxidation potential in the reaction (I) ⟶ (II) is of the order of 1·4 v., which has been confirmed by treating (I) with compounds of known oxidising potential. It is doubtful whether the body is capable of producing such a potential, even in view of the fact that 2 : 2-dichlorodiethyl sulphoxide can be oxidised to (II) with a very dilute solution of hydrogen peroxide at pH 8 and 38° in the presence of a trace of ferrous salt. The theory of Flury and Wieland, though not untenable, must therefore be regarded as unlikely.

(I) and (II) exhibit an apparently anomalous reactivity towards different reagents. Thus, with ethanolic potassium iodide and thiocyanate, (I) gives the corresponding di-iodo- and dithiocyanato-sulphide with great ease. (II) requires very prolonged boiling with these reagents. On the other hand, amino-acids and thiols react much more smoothly and rapidly with (II) than with (I) (cf. Cashmore and McCombie, *loc. cit.*; Lawson and Reid, *loc. cit.*). Furthermore, (I) is rapidly and quantitatively hydrolysed by boiling water, whereas (II) is unattacked under the same conditions, though it liberates 99% of its chlorine in three hours at pH 8 and 38°.

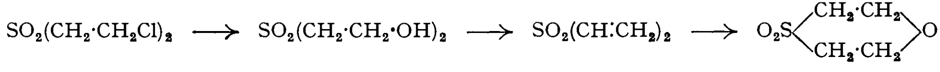
This reaction with water gives the key to the respective reactivities of the two compounds. (I), on hydrolysis (provided that the water used is in considerable excess; cf. Davies and Oxford, *J.*, **1931**, 224), gives 2 : 2′-dihydroxydiethyl sulphide. Hydrolysis of (II) gives usually divinyl sulphone (V), though some dihydroxydiethyl sulphone, together with tetrahydrothioxin 4 : 4-dioxide [from (V) by the addition of water], appears to be formed by the action of hot aqueous sodium carbonate.

Thus, when (II) undergoes a reaction that takes place readily, (V) can be formed as an intermediate. (II) is, in fact, a very unreactive substance, but under suitable conditions can lose hydrogen chloride to give the highly reactive (V). It follows that compounds that do not react with (V) (cf. Alexander and McCombie, *J.*, **1931**, 1913) will not react with (II) [or with (II) and alkali]. Also, when a substance does react with (II) and with (V), the same product will be formed in both cases. For example, neither (II) nor (V) condenses with potassium phthalimide or ethyl sodiomalonate (Alexander and McCombie, *loc. cit.*), but (V) and (II) (in presence of sodium carbonate) give identical products with many amino-acids, other amino-compounds, and thiols. The reactions of (II) and (V) with aniline seemed an exception. Alexander and McCombie (*loc. cit.*) found that (V) gave 2 : 2′-dianilinodiethyl sulphone, whereas Helfrich and Reid (*J. Amer. Chem. Soc.*, 1920, **42**, 1208) observed that (II) and aniline gave 4-phenyltetrahydrothiazine 1 : 1-dioxide. It has now been found that both products are formed simultaneously when either (II) or (V) is heated with aniline.

This study of the reactions of unsaturated sulphones has been extended to a Δ^{β}-sulphone, *viz.*, diallyl sulphone, and to other Δ^{α}-sulphones, *viz.*, 2-chloroethyl vinyl sulphone (Alexander and McCombie, *loc. cit.*), phenyl vinyl sulphone (Ford-Moore, Peters, and Wakelin, *loc. cit.*), *p*-tolyl vinyl sulphone (I.G. Farb. A.-G., Fr. P. 789,947), and ethyl vinyl sulphone. All the Δ^{α}-sulphones are very reactive, except towards bromine. Like (V), they add a hydrogen atom at the α-carbon, the rest of the molecule of the reactant attaching itself to the β-carbon atom. Halogens are added, though very slowly, across the double bond in the usual manner. Diallyl sulphone, on the other hand, decolorises bromine very rapidly.

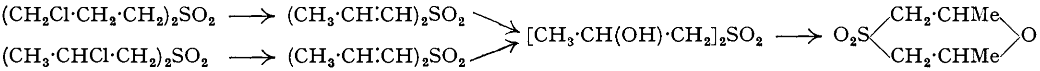
It may be noted that, whereas diallyl sulphone may be obtained from the sulphide by oxidation with hydrogen peroxide and acetic acid, divinyl sulphide (Bales and Nickelson, *J.*, 1922, **121**, 2137) cannot be oxidised to its sulphone by this reagent, though Levin (*J. pr. Chem.*, 1930, **127**, 77) obtained it by oxidation with benzoyl hydroperoxide.

Reactions with Alkali.—Both (II) and (V) with hot aqueous sodium hydroxide give tetrahydrothioxin 4 : 4-dioxide, m. p. 134° (Cashmore, *J.*, 1923, **123**, 1738, gives 129°; Alexander and McCombie, *loc. cit.*). The same product, together with other substances, is formed when (II) is heated with aqueous sodium carbonate. (II), with 1·05 moles of carbonate, gives a syrup, extraction of which with benzene yields only a small amount of tetrahydrothioxin 4 : 4-dioxide. After extraction, the syrup solidified when kept for two months *in vacuo* over sulphuric acid, to give 2 : 2-dihydroxydiethyl sulphone, also obtained by the oxidation of 2 : 2′-dihydroxydiethyl sulphide with hydrogen peroxide and acetic acid (cf. Levin, *loc. cit.*). Both the syrup and 2 : 2′-dihydroxydiethyl sulphone with warm aqueous sodium hydroxide give tetrahydrothioxin 4 : 4′-dioxide in *ca.* 80% yield. With 1 or 0·01 mole of hot aqueous sodium carbonate (V) gives tetrahydrothioxin 4 : 4-dioxide in 97% yield, no dihydroxysulphone being formed. The complete reaction series is thus :



$$SO_2(CH_2{\cdot}CH_2Cl)_2 \longrightarrow SO_2(CH_2{\cdot}CH_2{\cdot}OH)_2 \longrightarrow SO_2(CH{:}CH_2)_2 \longrightarrow O_2S{<}^{CH_2{\cdot}CH_2}_{CH_2{\cdot}CH_2}{>}O$$

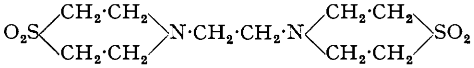
Hot aqueous sodium hydroxide converts diallyl sulphone into 2 : 6-dimethyltetrahydrothioxin 4 : 4-dioxide, which is also formed by the hydrolysis of 2 : 2′- or 3 : 3′-dichlorodi-*n*-propyl sulphone. It is possible that, under the influence of alkali, the double bonds in diallyl sulphone migrate to the Δ^{α}-positions, but it is more probable that the reaction proceeds *via* the two Δ^{α}- and Δ^{β}-propenyl sulphones which are known to give the same β-hydroxy-compound, and that the latter then loses water to give the thioxin derivative :



$$\begin{array}{l}(CH_2Cl\cdot CH_2\cdot CH_2)_2SO_2 \longrightarrow (CH_3\cdot CH{:}CH)_2SO_2 \\ (CH_3\cdot CHCl\cdot CH_2)_2SO_2 \longrightarrow (CH_3\cdot CH{:}CH)_2SO_2\end{array} \rightarrow [CH_3\cdot CH(OH)\cdot CH_2]_2SO_2 \longrightarrow O_2S\begin{array}{l}CH_2\cdot CHMe\\ CH_2\cdot CHMe\end{array}O$$

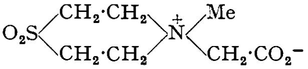
The loss of hydrogen chloride from (II) to give (V) takes place at relatively low pH. Thus, at pH 8 and 38°, 96% of the chlorine is in the ionic condition after two and 99% after three hours. At pH 7·35 (Ringer phosphate buffer), the reaction is somewhat slower : at 38°, it is 53% complete in two and 75% complete in five hours. Loss of hydrogen chloride from 2 : 2′-dichlorodiethyl sulphoxide is much slower : at pH 8 and 38°, it is less than 2% in two and about 12% in five hours. When the sulphoxide is treated with hydrogen peroxide and a trace of a ferrous salt at pH 8 and 38°, rapid oxidation takes place, to give the sulphone which can be isolated in over 70% yield as its cysteine adduct (cf. Ford-Moore, Peters, and Wakelin, *loc. cit.*). Hydrogen peroxide alone is without action on dichlorodiethyl sulphoxide : in fact, the latter can be recrystallised unchanged from the 30% reagent; the presence of acetic acid will, however, bring about its oxidation to (II).

Reactions with Amino-compounds and Amino-acids.—Lawson and Reid (*loc. cit.*) found that (II) and trimethylamine gave the diquaternary compound. With methylamine and sodium carbonate (II) gives 4-methyltetrahydrothiazine 1 : 1-dioxide. The reaction between (V) and 2-aminoethanol has already been described (Ford-Moore, Lidstone, and Waters, *J.*, 1946, 819). With ethylenediamine, the expected compound (VI) is obtained. Aniline, as already mentioned, gives a mixture.



$$O_2S\begin{array}{l}CH_2\cdot CH_2\\ CH_2\cdot CH_2\end{array}N\cdot CH_2\cdot CH_2\cdot N\begin{array}{l}CH_2\cdot CH_2\\ CH_2\cdot CH_2\end{array}SO_2$$

(VI.)



$$O_2S\begin{array}{l}CH_2\cdot CH_2\\ CH_2\cdot CH_2\end{array}\overset{+}{N}\begin{array}{l}Me\\ CH_2\cdot CO_2^-\end{array}$$

(VII.)

The reaction between (V) and a number of amino-acids has been examined, the compound formed being in all cases identical with that from (II) (and sodium carbonate). The tendency to ring-formation is very strong. Not only do the primary amino-acids, such as glycine, taurine, tyrosine, and anthranilic acid, give the expected *tetrahydrothiazine* 1 : 1-*dioxides*, but ring compounds, having a betaine structure, are also formed from secondary amino-acids. Thus, sarcosine gives the *compound* (VII) and similar *betaines* are obtained from proline, piperidine-2-carboxylic acid, and *N*-methylsulphanilic acid. Cysteine, as already mentioned, reacts through the thiol groups rather than the amino-group (Ford-Moore, Peters, and Wakelin, *loc. cit.*). The tetrahydrothiazine dioxides from the primary amino-acids, of which those from tyrosine and taurine are typical, are relatively strong acids and can be titrated to a sharp end-point with barium hydroxide. The betaines from the secondary amino-acids cannot, of course, be so titrated. The compounds from the primary acids, with the exception of the taurine adduct, are somewhat sparingly soluble in cold water and can be crystallised therefrom. Several of them separate with solvent of crystallisation which is retained rather tenaciously.

The reaction of tyrosine and α-alanine with (II) and with (V) at 38° and pH 8 (sodium hydrogen carbonate) has been investigated independently by us and by Wormall *et al.* (*loc. cit.*). With tyrosine, the reaction with (II) appeared to be complete in four and with (V) in two hours, the product being isolated in about 68% yield in each case. Alanine reacted somewhat more slowly, a 60% yield being obtained in eight hours with (II) and in six hours with (V). It seems most probable that the difference (two hours) between the times of reaction of (II) and of (V) is the time necessary for the sodium hydrogen carbonate to convert the unreactive (II) into the reactive (V).

The reaction of (V) with tyrosine requires two hours, whereas that with cysteine is complete in less than five minutes (Ford-Moore, Peters, and Wakelin, *loc. cit.*).

Reactions with Thiols.—Thiols react very readily with (V) and also with sulphones containing only one vinyl group, provided that a minute trace of a basic substance (triethylamine, diethylamine, ammonia, etc.) is present. Considerable heat is evolved in the reaction with simple thiols such as thiophenol. When thiophenol and (V) [prepared by the " calcium carbonate " method (Ford-Moore, Peters, and Wakelin, *loc. cit.*)] are mixed in a test-tube, no reaction takes place until a glass rod dipped in triethylamine is introduced into the mouth of the tube; a vigorous reaction then ensues, the temperature of the mixture rising spontaneously to >100° and the expected di(phenylthioethyl) sulphone (Alexander and McCombie, *loc. cit.*) solidifying on cooling.

Reactions with Bromine.—Bromine adds very slowly to the ethylenic linkings of divinyl, 2-chloroethyl vinyl, or *p*-tolyl vinyl sulphones, and the *products* lose hydrogen halide when treated with triethylamine in benzene. Divinyl sulphone gives two tetrabromides—1 part of one (described by Alexander and McCombie, *loc. cit.*), m. p. 138°, sparingly soluble in cold carbon tetrachloride, probably the racemic compound, and 2·5 parts of a second, m. p. 72—73°, readily soluble in cold carbon tetrachloride, probably the meso-*compound*; with triethylamine in benzene, both forms give 2 : 2′- (or 1 : 1′-)dibromodivinyl sulphone, which by further treatment with bromine affords a mixture of *hexabromodiethyl sulphone* and *tetrabromodivinyl sulphone*. Diallyl sulphone reacts very rapily with bromine to give 2 : 2′ : 3 : 3′-tetrabromodipropyl sulphone, only one tetrabromo-compound being isolated in this case.

Miscellaneous Compounds and Quaternary Derivatives of Tetrahydrothiazine 1 : 1-*Dioxide.*—Certain quaternary compounds containing the sulphone group have been prepared in the hope that they might exhibit marked toxic properties on injection; however, all these compounds had a relatively low order of toxicity.

4-Methyltetrahydrothiazine 1 : 1-dioxide was selected for investigation because it is readily prepared and forms quaternary compounds with comparative ease with most halides. By the action of ethylene chlorohydrin, chloroacetamide, allyl bromide, ethyl chloroacetate, and 2-chloroethyl carbamate, the expected *compound* was obtained. When 4-*methyl*-4-*allyltetrahydrothiazinium* 1 : 1-*dioxide bromide* was treated with bromine, the 1-2′ : 3′-*dibromo*-n-*propyl* compound was isolated. The 1-2′-*hydroxyethyl* derivative reacted with thionyl chloride, giving the corresponding 1-2′-*chloroethyl* compound (these compounds are the methochlorides of two of the quaternary compounds described by Ford-Moore, Lidstone, and Waters, *loc. cit.*).

The parent compound, tetrahydrothiazine 1 : 1-dioxide, cannot be prepared by the action of ammonia on divinyl sulphone. It was obtained by indirect means, 4-phenyltetrahydrothiazine 1 : 1-dioxide being treated with nitrous acid and the *p*-nitroso-compound so obtained hydrolysed with alkali to quinone oxime and the desired compound.

EXPERIMENTAL.

p-Tolyl 2-chloroethyl sulphone was prepared from thio-*p*-cresol by the method described by Ford-Moore, Peters, and Wakelin (*loc. cit.*) for phenyl 2-chloroethyl sulphone. Crystallised from light petroleum (b. p. 40—60°), it had m. p. 81° [Fromm and Kohn, *Ber.*, 1921, **54**, *B*, 320, give 71° (crystallised from ethanol)] (Found: C, 49·2; H, 5·1. Calc. for $C_9H_{11}O_2ClS$: C, 49·4; H, 5·1%). On treatment with triethylamine in benzene, it gave *p*-tolyl vinyl sulphone, m. p. 66° [from light petroleum (b. p. 40—60°)] (I. G. Farbenind. A.-G., *loc. cit.*, give m. p. 65—66°) (Found: C, 59·5; H, 5·5. Calc. for $C_9H_{10}O_2S$: C, 59·3; H, 5·5%).

2-Chlorodiethyl sulphone, obtained from 2-chlorodiethyl sulphide (Robinson, Ministry of Supply Communication) by oxidation with hydrogen peroxide in acetic acid, had m. p. 15° and b. p. 145—147°/8 mm. *Ethyl vinyl sulphone*, obtained from it by treatment with triethylamine in benzene, had b. p. 110—112°/8 mm. (Found: C, 39·7; H, 6·5. $C_4H_8O_2S$ requires C, 40·0; H, 6·7%).

Diallyl sulphone obtained from the sulphide by hydrogen peroxide in acetic acid, had b. p. 128°/10 mm. (Levin, *loc. cit.*, gives b. p. 109°/3 mm.) (Found: C, 49·4; H, 7·0. Calc. for $C_6H_{10}O_2S$: C, 49·3; H, 6·9%).

Reactions with Alkali.

2 : 2′-*Dihydroxydiethyl Sulphone.*—Thiodiglycol (25 g.) in glacial acetic acid (50 c.c.) was treated with 30% hydrogen peroxide. A vigorous reaction ensued which was completed by 1 hour's boiling under reflux. Volatile material was removed on a steam-bath under reduced pressure, and the residue distilled first with water (50 c.c.) and then with ethanol (50 c.c.) under reduced pressure. The syrup, when kept for 14 days *in vacuo* over sulphuric acid, solidified. It was freely soluble in water, ethanol, and acetone, and insoluble in chloroform and ethyl acetate. It was crystallised by boiling it with ethyl acetate and adding acetone till dissolution just took place. Crystallisation occurred on storing this solution at 0° for 3 days, to give the somewhat hygroscopic sulphone, m. p. 54—55° (Levin, *loc. cit.*, gives m. p. 57—58°) (Found: C, 30·4; H, 6·6. Calc. for $C_4H_{10}O_4S$: C, 31·2; H, 6·5%).

2 : 2′-Dichlorodiethyl sulphone (38 g.), sodium carbonate (23 g.), and water (75 c.c.) were heated under reflux for 1 hour and then evaporated to dryness under reduced pressure. The residue was extracted with hot ethanol and filtered, the filtrate evaporated to dryness, and the residue extracted with boiling benzene. The benzene extract on concentration gave tetrahydrothioxine 4 : 4-dioxide (2 g.), m. p. 134°. The insoluble syrup (26 g.) from the benzene extraction solidified when kept for 2 months *in vacuo* over sulphuric acid. It was purified by crystallisation from ethyl acetate and acetone and identified as dihydroxydiethyl sulphone. Both the syrup and dihydroxydiethyl sulphone (prepared from thiodiglycol) gave tetrahydrothioxine 4 : 4-dioxide in 80% yield when warmed with aqueous sodium hydroxide.

If, after 2 : 2′-dichlorodiethyl sulphone (38 g.), sodium carbonate (23 g.), and water (75 c.c.) had been boiled under reflux for 1 hour, a further 23 g. of sodium carbonate in 90 c.c. of water were added and heating was continued for a further hour, the product, on being worked up similarly, yielded tetrahydrothioxine 4 : 4-dioxide (14 g.) and a syrup (9 g.), which with hot sodium hydroxide gave a further 6 g. of tetrahydrothioxine 4 : 4-dioxide.

Diallyl sulphone (4·5 g.), sodium carbonate (0·4 g.), and water (25 c.c.) were heated under reflux for 1 hour, neutralised with hydrochloric acid, and evaporated to dryness. Tetrahydrothioxin 4 : 4-dioxide (5 g.) was obtained. No syrup appeared to be formed.

2 : 6-*Dimethyltetrahydrothioxin* 4 : 4-*Dioxide.*—3 - 3′-Dichlorodipropyl sulphone, m. p. 64—65° (Bennett and Hock, *loc. cit.*, give m. p. 65—66°) (45 g.), in ethanol (50 c.c.) was boiled with ethanolic potassium hydroxide (27 g. in 150 c.c.) for 2 hours and then filtered, and the filtrate evaporated to dryness. On distillation under reduced pressure, a fraction, b. p. 137—150°/10 mm., was obtained. The crystals that were gradually deposited were filtered off and crystallised from light petroleum (b. p. 40—60°), then having m. p. 103—104° (Hunt and Marvel, *J. Amer. Chem. Soc.*, 1935, **57**, 1691, give m. p. 102°) (Found : C, 43·6; H, 7·6. Calc. for $C_6H_{12}O_3S$: C, 43·8; H, 7·3%).

2 : 2-Dichlorodi-*n*-propyl sulphide (from 1-chloropropan-2-ol and sodium sulphide, followed by thionyl chloride) gave, on oxidation, the sulphone, m. p. 23°, b. p. 155—156°/4 mm. This sulphone (4 g.) was boiled with 20% aqueous sodium hydroxide (20 c.c.) for 3 hours; after cooling, the solid was collected and crystallised from light petroleum; it had m. p. 103—104°, not altered on admixture with the compound from 3 : 3′-dichlorodi-*n*-propyl sulphone.

Diallyl sulphone (2 g.) and 20% aqueous sodium hydroxide (10 c.c.) were boiled for 0·5 hour. The solid material, crystallised from light petroleum, had m. p. 103—104°, not altered on admixture with the compounds from 2 : 2′- and 3 : 3′-dichlorodi-*n*-propyl sulphones.

Reactions with Bromine.

1 : 1′ : 2 : 2′-*Tetrabromodiethyl Sulphone* (*Two Isomers*).—Divinyl sulphone (21 g.) in chloroform (150 c.c.) was treated with bromine (57 g.). Decolorisation was complete in about 18 hours. After removal of the solvent, the residue was crystallised from carbon tetrachloride, giving the tetrabromide (14 g.), m. p. 138° (Alexander and McCombie, *loc. cit.*, give 138°). The carbon tetrachloride mother-liquor was evaporated to dryness, and the residue crystallised three times from light petroleum (b. p. 60—80°); the resulting *isomer* (36 g.) melted at 72—73° (Found : C, 10·9; H, 1·45. $C_4H_6O_2Br_4S$ requires C, 11·0; H, 1·4%).

1 : 2-*Dibromo-2′-chlorodiethyl Sulphone.*—2-Chloroethyl vinyl sulphone (25·5 g.) in chloroform (100 c.c.) was treated with bromine (35 g.). The product, isolated as above, had m. p. 63—64° (from carbon tetrachloride) [Kretov, *J. Russ. Phys. Chem. Soc.*, 1930, **62**, 1, gives m. p. 62° (from ethanol)] (Found : C, 14·9; H, 2·25. Calc. for $C_4H_7O_2ClBr_2S$: C, 14·8; H, 2·2%).

2 : 2′- (*or* 1 : 1′-)*Dibromodivinyl Sulphone.*—1 : 1′ : 2 : 2′-Tetrabromodiethyl sulphone, m. p. 138° (10·5 g.), in warm benzene (100 c.c.), was treated with triethylamine (7 c.c.). After being kept overnight, the mixture was filtered and the filtrate evaporated to dryness. On addition of light petroleum (b. p. 40—60°), the residue crystallised. Twice recrystallised from this solvent, the *product* had m. p. 58—59° (Found : C, 17·4; H, 1·55. $C_4H_4O_2Br_2S$ requires C, 17·4; H, 1·5%).

When the isomer, m. p. 72—73°, was similarly treated, a product, m. p. 59—60°, was obtained. The m. p. was not altered on admixture with the foregoing compound.

2- (*or* 1-)*Bromodivinyl sulphone* was prepared similarly by treating 2-chloro-1′ : 2′-dibromodiethyl sulphone (11 g.) with triethylamine (23 c.c.) in benzene (200 c.c.) and had b. p. 137°/22 mm. (Found : Br, 40·5. $C_4H_5O_2BrS$ requires Br, 40·55%).

Hexabromodiethyl Sulphone and Tetrabromodivinyl Sulphone.—2 : 2′-Divinyl sulphone (4·5 g.) in carbon tetrachloride (70 c.c.) was treated with bromine (5·5 g.). Some hydrogen bromide was evolved and after 18 hours crystals had separated. These were filtered off, the filtrate was evaporated to dryness, the residue treated with warm carbon tetrachloride (25 c.c.), and the insoluble material added to the crystals already collected. Crystallised from carbon tetrachloride, in which it was sparingly soluble, and then from acetone–ethanol, *hexabromodiethyl sulphone* had m. p. 188° (decomp.) (Found : Br, 81·0. $C_4H_4O_2Br_6S$ requires Br, 80·5%). The carbon tetrachloride extract was evaporated to dryness and the residue twice crystallised from light petroleum (b. p. 60—80°), giving *tetrabromodivinyl sulphone*, m. p. 94° (Found : Br, 73·7. $C_4H_2O_2Br_4S$ requires Br, 73·7%).

2 : 2′ : 3 : 3′-*Tetrabromodi*-n-*propyl Sulphone.*—Bromine (2·5 c.c.) was added to a solution of diallyl sulphone (3·2 g.) in chloroform (25 c.c.). Decolorisation took place rapidly and, after removal of the solvent, the residue crystallised on addition of light petroleum. Twice crystallised from carbon tetrachloride, the tetrabromide had m. p. 102—103° (Levin, *loc. cit.*, gives m. p. 98—100°) (Found : Br, 68·4. Calc. for $C_6H_{10}O_2Br_4S$: Br, 68·6%).

p-*Tolyl* 1 : 2-*Dibromoethyl Sulphone.*—*p*-Tolyl vinyl sulphone reacted slowly with bromine in chloroform. The *dibromide*, after removal of the solvent, crystallised from light petroleum (b. p. 60—80°) and then had m. p. 78—79° (Found : C, 32·0; H, 2·9. $C_9H_{10}O_2Br_2S$ requires C, 32·6; H, 2·85%). This product, on treatment with triethylamine in benzene, gave p-*tolyl* 2- (or 1-)*bromovinyl sulphone*, m. p. 74—75° (from light petroleum); (Found : C, 41·75; H, 3·9. $C_9H_9O_2BrS$ requires C, 41·4; H, 3·5%); on admixture with the tetrabromide, it melted at 50—55°.

Reactions with Amino-compounds

4-*Methyltetrahydrothiazine* 1 : 1-*Dioxide.*—Divinyl sulphone (4·6 g.) in ethanol (8 c.c.) was added to a 33% ethanolic solution of methylamine (12 c.c.). Heat was developed and, after removal of the ethanol, the product (5 g.) solidified. It was distilled under reduced pressure and then had b. p. 148°/6 mm. and m. p. 86° (after crystallisation from benzene–light petroleum (Lawson and Reid, *loc. cit.*, give m. p. 82°, b. p. 174·5—175°/19 mm.). The hydrochloride was prepared by adding dry hydrogen chloride to a benzene solution of the base (Found : Cl^-, 19·25. Calc. for $C_5H_{12}O_2NClS$: Cl^-, 19·1%).

Bis(*trimethylammoniumethyl*) *Sulphone Dichloride*, $SO_2([CH_2]_2{\cdot}NMe_3Cl)_2$.—Diallyl sulphone (1·2 g.) and trimethylamine hydrochloride (2 g.) were set aside in warm ethanol (7 c.c.) containing a trace of triethylamine. The solid that had separated in 3 hours was collected and crystallised from absolute ethanol. It melted at 214° (Lawson and Reid, *loc. cit.*, give m. p. 211·5°) with evolution of gas; it then solidified and remelted with decomposition at 264—267° (Found : Cl^-, 22·7. Calc. for $C_{10}H_{28}O_2N_2Cl_2S$:

Cl^-, 22·9%). The "m. p.," 214°, is probably the temperature at which the dichloride regenerates the starting materials, 264—267° being the m. p. (decomp.) of trimethylamine hydrochloride.

2 : 2′-*Dianilinodiethyl Sulphone and* 4-*Phenyltetrahydrothiazine* 1 : 1-*Dioxide*.—(i) 2 : 2′-Dichlorodiethyl sulphone (20 g.) and aniline (61 g.) were heated on a steam-bath for 2 hours. The mixture was diluted with water and made strongly alkaline with sodium hydroxide, and the excess of aniline removed by steam-distillation, 25 g. being recovered. The organic residue from the steam-distillation was boiled with dilute hydrochloric acid. Cooling in ice caused separation of 4-phenyltetrahydrothiazin 1 : 1-dioxide (8·5 g.), m. p. 122° (from methanol) (Helfrich and Reid, *loc. cit.*, give m. p. 123·5°). The acid extract, when made alkaline, gave 2 : 2′-dianilinodiethyl sulphone as a sticky solid that crystallised during 1 hour. Recrystallised from methanol, this had m. p. 95—96° (Alexander and McCombie, *loc. cit.*, give m. p. 94—95°). With acetic anhydride, it gave a *diacetyl* derivative, m. p. 133—134° (from ethanol) (Found: C, 61·95; H, 6·3; N, 7·4. $C_{20}H_{24}O_4N_2S$ requires C, 61·85; H, 6·2; N, 7·2%).

(ii) Divinyl sulphone (6 g.) and aniline (4·7 g.), similarly treated, gave 4-phenyltetrahydrothiazine 1 : 1-dioxide (6 g.), m. p. 123°, and 2 : 2′-dianilinodiethyl sulphone (1·5 g.), m. p. 94—95°.

(iii) Divinyl sulphone (6 g.) and aniline (10·3 g.) gave the thiazine dioxide (8 g.), m. p. 94—95°, but no dianilinodiethyl sulphone.

Ethylenebis-(4-*tetrahydrothiazine* 1 : 1-*Dioxide*) (VI).—Two equivs. of divinyl sulphone were treated with one equiv. of aqueous ethylenediamine. Heat was developed and, after the reaction had ceased, the mixture was evaporated to dryness. The *product*, crystallised from water, had m. p. 211—213° (Found: C, 40·3; H, 6·85. $C_{10}H_{20}O_4N_2S_2$ requires C, 40·5; H, 6·8%). The *dihydrochloride* was extremely hygroscopic (Found: Cl^-, 18·35. $C_{10}H_{22}O_4N_2Cl_2S$ requires Cl^-, 19·2%).

Reactions with Amino-acids.

The tetrahydrothiazine dioxide derivatives were prepared from 2 : 2′-dichlorodiethyl sulphone (II) by the methods of Cashmore and McCombie, and Lawson and Reid (*locc. cit.*), *viz.*, by heating equivalent quantities of the sulphone, amino-acid, and sodium carbonate in aqueous solution.

For experiments with divinyl sulphone (V), a similar procedure was adopted, but the sodium carbonate was omitted.

The condensation product generally separated during the reaction or on cooling the mixture. That with taurine was somewhat soluble in water but could be crystallised from a small amount thereof. The following were thus obtained.

β-Phenyl-α-tetrahydro-4-thiazinylpropionic acid 1 : 1-dioxide [from phenylalanine, (II), and sodium carbonate], m. p. 174—175° (Lawson and Reid, *loc. cit.*, give m. p. 176°); [from (V)], m. p. 174—175°, not altered on admixture with the product from (II).

β-*p*-Hydroxyphenyl-α-tetrahydro-4-thiazinylpropionic acid 1 : 1-dioxide [from tyrosine, (II), and sodium carbonate], needles (from water), m. p. 230° (decomp.) [Wormall *et al.*, *loc. cit.*, give m. p. 220·5—221·5° (decomp.)] (Found: C, 50·8; H, 5·9; N, 4·5; S, 10·9. Calc. for $C_{13}H_{17}O_5NS,\frac{1}{2}H_2O$: C, 50·6; H, 5·9; N, 4·5; S, 10·4%); [from (V)] needles (from water), m. p. 230° (decomp.), not altered on admixture with the compound from (II).

The compound was prepared under conditions approaching the biological as follows. Tyrosine (3·5 g.), (II) (3·5 g.), sodium hydrogen carbonate (10 g.), and water (100 c.c.) were stirred at 38° for 4 hours, during which time the tyrosine dissolved. After filtration from a small amount of impurity, the filtrate was made just acid to Congo-red with hydrochloric acid. The product was filtered off and crystallised from water. Yield, 4 g.; m. p. 230° (decomp.).

Tyrosine (4·5 g.), (V) (2·5 g.), sodium carbonate (12 g.), and water (120 c.c.) were stirred at 38°. The reaction was complete in 2 hours, and the product was isolated by acidification. Yield, 5·5 g.; needles (from water), m. p. 230° (decomp.).

4-o-*Carboxyphenyltetrahydrothiazine* 1 : 1-*dioxide* [from anthranilic acid, (II), and sodium carbonate], fine needles (from water), m. p. 230—231° (decomp.) [Found: C, 50·0; H, 5·2%; equiv. (by titration with barium hydroxide), 268. $C_{11}H_{13}O_4NS,\frac{1}{2}H_2O$ requires C, 50·0; H, 5·3%; equiv., 264]; [from (V)] fine needles (from 50% ethanol), m. p. 231° (decomp.), not altered on admixture with the compound from (II).

4-2′-*Sulphoethyltetrahydrothiazine* 1 : 1-*dioxide* [from (II), taurine, and sodium carbonate], crystallised from a small amount of water, decomposed, without melting, at 295—300° (Found: C, 29·5; H, 5·3%; equiv., 238. $C_6H_{13}O_5NS_2$ requires C, 29·6; H, 5·4%; equiv., 243). A *silver* salt was crystallised from water (Found: Ag, 29·1; H_2O, 4·95. $C_6H_{12}O_5NS_2Ag,H_2O$ requires Ag, 29·3; H_2O, 4·9%). The acid, obtained from taurine and (V), crystallised from a small amount of water and then decomposed, without melting, at 297—300° (Found: equiv., 246).

α-Tetrahydro-4-thiazinylpropionic acid 1 : 1-dioxide [from (II), α-alanine ethyl ester hydrochloride and sodium carbonate] did not crystallise and was hydrolysed to the free acid, which was purified through the sparingly soluble copper salt and then had m. p. 187—188° (Wormall, *et al.*, *loc. cit.*, give m. p. 186°) (Found: equiv., 206. Calc. for $C_7H_{13}O_4NS$: equiv., 207).

The compound was also prepared under conditions approaching the biological as follows. (V) (5 g.) DL-α-alanine (4·5 g.), sodium hydrogen carbonate (5 g.), and water (100 c.c.) were stirred at 38° for 6 hours. The mixture was made just acid to Congo-red and treated with copper carbonate. The sparingly soluble copper salt was filtered off and decomposed with hydrogen sulphide, giving 6·5 g. of slightly impure product, m. p. 178—180°. Crystallised from 80% ethanol, it had m. p. 186—187°. No reaction took place if the sodium hydrogen carbonate was omitted.

The product was also obtained by allowing (II) (5 g.), DL-α-alanine (2·7 g.), sodium hydrogen carbonate (7 g.), and water (100 c.c.) to react at 38° for 8 hours. The product was isolated as previously described. Yield, 4 g.; m. p. 187° (from 80% ethanol).

β-Tetrahydro-4-thiazinylpropionic acid 1 : 1-dioxide [from (V) and β-alanine] did not crystallise and was converted into its *hydrochloride*, m. p. 204—206° (decomp.) (from 80% ethanol) (Found: Cl^-, 14·6. $C_7H_{14}O_4NClS$ requires Cl^-, 14·55%).

Tetrahydro-4-*thiazinylacetamidoacetic acid* 1 : 1-*dioxide* [from (V) and glycylglycine] (from 95% ethanol) had m. p. 201—202° (Found : equiv., 255. $C_8H_{14}O_3N_2S$ requires equiv., 260).

4-*Methyl*-4-*carboxymethyltetrahydrothiazine* 1 : 1-*dioxide betaine* [from sarcosine and (V)] crystallised from a small amount of water and had m. p. 240° (decomp.) (Found : C, 40·4; H, 6·3; N, 6·75. $C_7H_{13}O_4NS$ requires C, 40·6; H, 6·3; N, 6·8%). The derived *chloride* formed fine needles from dilute ethanol containing a little hydrochloric acid (Found: Cl^-, 14·45. $C_7H_{14}O_4NClS$ requires Cl^-, 14·55%).

2′-*Carboxypyrrolidine*-1′-spiro-4-*tetrahydrothiazine* 1 : 1-*dioxide betaine* [from (V) and proline] had m. p. 226° (decomp.) (175—185° on admixture with proline) [Found : H_2O (loss at 110°/5 mm.), 13·3. $C_9H_{15}O_4NS,2H_2O$ requires H_2O, 13·4%]. The derived *chloride*, crystallised from 50% ethanol, had m. p. 263—265° (decomp.) (Found : Cl^-, 13·1. $C_9H_{16}O_4NClS$ requires Cl^-, 13·2%).

2′-*Carboxypiperidine*-1′-spiro-4-*tetrahydrothiazine* 1 : 1-*dioxide betaine* [from (V) (2·6 g.) and piperidine-2-carboxylic acid tetrahydrate (5 g.) in water (25 c.c.), boiled for 3 hours and then evaporated] crystallised from ethanol and had m. p. 218—221° (decomp.) (Found : C, 48·5; H, 6·9; N, 5·5. $C_{10}H_{17}O_4NS$ requires C, 48·5; H, 6·9; N, 5·7%). The derived *chloride* was obtained by evaporation with hydrochloric acid and had m. p. 247° (decomp.) (Found : Cl^-, 12·5. $C_{10}H_{18}O_4NClS$ requires Cl^-, 12·5%).

4-p-*Sulphophenyl*-4-*methyltetrahydrothiazine* 1 : 1-*dioxide betaine* [from (V) and *N*-methylsulphanilic acid] crystallised from hot water in which it was sparingly soluble and had m. p. 264—265° (decomp.) [Found : H_2O (loss at 110°/3 mm.), 10·9%; equiv., 341. $C_{11}H_{15}O_5NS_2,2H_2O$ requires H_2O, 10·6%; equiv., 341].

β-(3 : 4-*Dihydroxyphenyl*)*tetrahydro*-4-*thiazinylpropionic acid* 1 : 1-*dioxide* [from (V) (1·2 g.), 3 : 4-dihydroxyphenylalanine (2·0 g.), water (20 c.c.), and triethylamine (1 drop); the product separated during 2 hours' boiling] crystallised from water, in which it was sparingly soluble, in felted needles, m. p. 239° (decomp.) (Found : C, 49·6; H, 5·5. $C_{13}H_{17}O_6NS$ requires C, 49·5; H, 5·4%). It is sparingly soluble in boiling ethanol and acetic acid.

β-(3 : 4-*Dimethoxyphenyl*)*tetrahydro*-4-*thiazinylpropionic Acid* 1 : 1-*Dioxide*.—(V) (1·2 g.), 3 : 4-dimethoxyphenylalanine (2·4 g.), water (20 c.c.), and triethylamine (1 drop) were heated under reflux for 2 hours. On cooling, a sticky solid separated. This was dissolved in cold sodium hydrogen carbonate, the solution was filtered, the filtrate acidified with hydrochloric acid, and the compound precipitated by the addition of sodium acetate. The *acid*, which is soluble in cold ethanol, crystallised from water and then had m. p. 172—173° (Found : C, 52·4; H, 6·3. $C_{15}H_{21}O_6NS$ requires C, 52·5; H, 6·2%).

Tetrahydrothiazine 1 : 1-*Dioxide*.—4-Phenyltetrahydrothiazine 1 : 1-dioxide (38 g.) and hydrochloric acid (150 c.c.; *d* 1·18) were treated with crushed ice till the temperature fell to 0°. A solution of sodium nitrite (12 g.) in water (40 c.c.) was added with hand-stirring, and the temperature kept below 5°. After 0·5 hour, the brown nitroso-hydrochloride was filtered off. The moist product was added to 2N-ammonia (170 c.c.), the mixture warmed to 35°, and the free base filtered off. The moist nitroso-compound was mixed with water (150 c.c.), 10% aqueous sodium hydroxide (100 c.c.) added, and the mixture heated under reflux for 1·5 hours. After cooling, the mixture was acidified to Congo-red with hydrochloric acid, the quinone oxime filtered off, and the filtrate extracted once with ether, the extract being discarded. The aqueous portion was decolorised (charcoal), made alkaline with sodium carbonate, and evaporated to dryness. The residue was extracted several times with ethanol, the ethanol distilled off, and the residue fractionated *in vacuo*, the portion, b. p. 162°/9 mm. (9 g.), being collected. After crystallisation from benzene, 8·5 g. of pure 4-*phenyltetrahydrothiazine* 1 : 1-*dioxide*, m. p. 68—69°, were obtained (Found : C, 36·2; H, 6·9; N, 10·6. $C_4H_9O_2NS$ requires C, 35·5; H, 6·7; N, 10·4%). Its *hydrochloride*, obtained by evaporation with hydrochloric acid and crystallsed from 90% ethanol, had m. p. 297° (decomp.) (Found: Cl^-, 20·6. $C_4H_{10}O_2NClS$ requires Cl^-, 20·7%). The *platinichloride* was precipitated as orange plates on addition of aqueous platinic chloride to the hydrochloride (Found : Pt, 28·45. $2C_4H_9O_2NS,H_2PtCl_6$ requires Pt, 28·7%).

Tetrahydrothiazine 1 : 1-dioxide (1 g.), ethyl chloroacetate (1 g.), and sodium carbonate (1 g.) were heated on a steam-bath for 9 hours, and the product was extracted with ethanol. After removal of the ethanol and crystallisation of the residue twice from benzene–light petroleum, ethyl tetrahydro-4-thiazinylacetate 1 : 1-dioxide was obtained, having m. p. 72°, not altered on admixture with an authentic specimen prepared from glycine ester hydrochloride, 2 : 2′-dichlorodiethyl sulphone, and sodium carbonate (Cashmore and McCombie, *loc. cit.*, give m. p. 72—73°).

Reactions with Thiols.

Di-(o-*carboxyphenylthioethyl*) *Sulphone*.—Equimolar portions of *o*-mercaptobenzoic acid and divinyl sulphone were warmed in aqueous suspension. The *product*, crystallised from ethanol, had m. p. 217—218° (Found : C, 50·1; H, 4·35. $C_{18}H_{18}O_6S_3$ requires C, 50·7; H, 4·25%).

2-Chloro-2-(*o*-carboxyphenylthio)diethyl sulphone, obtained when equimolar portions of 2-chloroethyl vinyl sulphone and *o*-mercaptobenzoic acid were warmed in aqueous suspension, and crystallised from water, melted at 164° (145° after admixture with *o*-mercaptobenzoic acid, m. p. 164°), but could not be completely purified (Found : C, 44·7; H, 4·8. $C_{11}H_{13}O_4ClS$ requires C, 42·8; H, 4·2%).

p-*Tolyl* 2-*Phenylthioethyl Sulphone*.—*p*-Tolyl vinyl sulphone and thiophenol were treated with a trace of triethylamine. Heat was developed and the product solidified on cooling. The *thio-sulphone*, crystallised from ethanol, had m. p. 139—140° (Found : C, 61·6; H, 5·7. $C_{15}H_{16}O_2S_2$ requires C, 61·6; H, 5·5%).

p-*Tolyl* 2-o-*carboxyphenylthioethyl sulphone*, similarly prepared by use of *o*-mercaptobenzoic acid, had m. p. 203—204° (from ethanol) [Found : equiv. (by titration with barium hydroxide), 333. $C_{16}H_{16}O_4S_2$ requires equiv., 336].

2-*Chloro*-2′-(2″-*amino*-2″-*carboxyethylthio*)*diethyl sulphone*, prepared from 2-chloroethyl vinyl sulphone, cysteine hydrochloride, and sodium acetate in aqueous solution, and crystallised from water, had m. p. 188—189° (decomp.) (Found : C, 30·9; H, 5·2. $C_7H_{14}O_4NClS_2$ requires C, 30·5; H, 5·1%).

2-*Phenylthiodiethyl Sulphone*.—When ethyl vinyl sulphone was mixed with thiophenol and a trace of triethylamine, heat was developed. The *product*, purified by distillation *in vacuo*, had b. p. 202—203°/2·5 mm. and then solidified and melted at 36—38° (Found : C, 52·3; H, 6·2. $C_{10}H_{14}O_2S_2$ requires C, 52·15; H, 6·1%).

2-o-*Carboxyphenylthiodiethyl sulphone*, prepared from ethyl vinyl sulphone and *o*-mercaptobenzoic acid, crystallised from ethanol and had m. p. 158—160° (Found : equiv., 275. $C_{11}H_{14}O_4S_2$ requires equiv., 273).

Phenyl 2-2'-Hydroxyethylthioethyl Sulphone.—This compound was prepared from phenyl vinyl sulphone and 2-mercaptoethanol but could not be purified and was characterised as its p-*nitrobenzoate*, m. p. 107° (from ethanol) (Found : C, 51·7; H, 4·3. $C_{17}H_{17}O_6NS_2$ requires C, 51·65; H, 4·35%).

Quaternary Compounds.

4-Methyltetrahydrothiazine 1 : 1-dioxide was warmed on a water-bath with the appropriate halogen compound. The quaternary compound was purified by washing it with absolute ethanol and crystallising it by boiling with ethanol and adding water dropwise till dissolution just took place. The following were thus prepared.

4-*Methyl*-4-*carbethoxymethyltetrahydrothiazinium* 1 : 1-*dioxide chloride* (by ethyl chloroacetate), m. p. 245—250° (decomp.) (Found : Cl^-, 12·8. $C_9H_{18}O_4NClS$ requires Cl^-, 13·05%).

4-*Methyl*-4-*carbonylmethyltetrahydrothiazinium* 1 : 1-*dioxide chloride* (by chloroacetamide), decomp. 228° without melting (Found : Cl^-, 14·5. $C_7H_{15}O_3N_2ClS$ requires Cl^-, 14·6%).

4-*Methyl*-4-2'-*hydroxyethyltetrahydrothiazinium* 1 : 1-*dioxide chloride* (by ethylene chlorohydrin), decomp. 248° without melting (Found : Cl^-, 15·3. $C_7H_{16}O_3NClS$ requires Cl^-, 15·4%).

4-*Methyl*-4-2'-*chloroethyltetrahydrothiazinium* 1 : 1-*dioxide chloride* (by the action of thionyl chloride on the foregoing compound), m. p. 223° (decomp.) (Found : C, 33·9; H, 6·0. $C_7H_{15}O_3NCl_2S$ requires C, 33·9; H, 6·1%).

4-*Methyl*-4-*allyltetrahydrothiazinium* 1 : 1-*dioxide bromide* (by allyl bromide), decomp. 275° without melting (Found: Br^-, 29·4. $C_8H_{16}O_2NBrS$ requires Br^-, 29·6%). When warmed with bromine in aqueous solution, this compound gave 4-*methyl*-4-(2' : 3'-*dibromopropyl*)*tetrahydrothiazinium* 1 : 1-*dioxide bromide*, decomp. 198° without melting (Found : Br^-, 18·35; total Br, 54·65. $C_8H_{16}O_2NBr_3S$ requires Br^-, 18·6; total Br, 55·8%).

4-*Methyl*-4-2'-*carbamyloxyethyltetrahydrothiazinium* 1 : 1-*dioxide chloride* (by 2-chloroethyl carbamate; the reaction required 24 hours' heating on a steam-bath), m. p. 224° (decomp.) (Found: Cl^-, 12·8. $C_8H_{17}O_4N_2ClS$ requires Cl^-, 13·0%).

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