# 10. *Derivatives of Oxazolid-2 : 4-dione. Part III. The Alkylation of 2-Thio-oxazolid-4-ones.**

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Alkylation of 2-thio-oxazolid-4-ones yields a mixture of the corresponding 2-thio-3-alkyloxazolid-4-ones and 2-alkylthio-oxazol-4-ones. The factors which influence the proportions of *N*- and *S*-alkylation are indicated. A number of 3-alkyloxazolid-2 : 4-diones has been prepared from the 2-thio-3-alkyloxazolid-4-ones.

In Parts I and II (preceding papers) the alkylation of the sodium and silver salts of oxazolid-2 : 4-diones has been examined and the results show that the sodium salts are alkylated in the 3-position, *i.e.*, on the *N*-atom, whilst the silver salts give a mixture of the 3-alkyl derivatives and 4-alkoxyoxazol-2-ones, the proportions depending on the temperature (lower temperatures favouring the formation of the latter) and the nature of the substituents in the 5-position. It was also shown that the 4-alkoxyoxazol-2-ones were isomerised by heat to the corresponding 3-alkyloxazolid-2 : 4-diones.

It became of interest, therefore, to examine the alkylation of 2-thio-oxazolid-4-ones, where the effect of tautomerism involving the 2- and 3-positions would be expected to be more pronounced than that of the 3- and 4-positions in oxazolid-2 : 4-diones. A second reason was the fact that 2-thio-3-alkyloxazolid-4-ones, like 2-thio-oxazolid-4-ones themselves, are readily converted into the corresponding oxazolid-2 : 4-diones by a variety of reagents, and the method affords another route to 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, which has been shown to be of value in the treatment of "petit mal" (Lennox, *J. Amer. Med. Assoc.*, 1945, **129**, 1069).

Urech (*Ber.*, 1873, **6**, 1113; 1878, **11**, 467) has shown that 2-thio-5 : 5-dimethyloxazolid-4-one (I; R = H) is formed when an aqueous solution of potassium thiocyanate, potassium cyanide, and acetone is treated with hydrochloric acid. Erlenmeyer, Kleiber, and Loebenstein (*Helv. Chim. Acta*, 1938, **21**, 1010) have similarly prepared 2-thio-5-methyl-5-ethyloxazolid-4-one from methyl ethyl ketone and converted it into 5-methyl-5-ethyloxazolid-2 : 4-dione.

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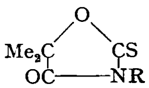
* Patents pending.

Improved conditions for the preparation of these two thio-oxazolidones by Urech's method have been developed and the method has been extended to the preparation of 2-thio-oxazolid-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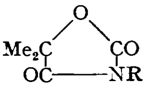
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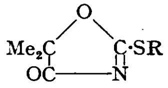
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4-one from formaldehyde, and of *2-thio-5-methyloxazolid-4-one* from acetaldehyde. The method was most successful for the 5 : 5-dimethyl derivative, which is now readily obtained in 65—75% yield, although the reaction even in this case is very slow. The condensation with methyl ethyl ketone proceeds still more slowly, even on warming, partly owing to the lower solubility of the intermediate cyanohydrin, and the yield of product is much less; and attempts to condense benzyl methyl ketone and acetophenone with cyanide and thiocyanate under these conditions failed.

The alkylation of 2-thio-5 : 5-dimethyloxazolid-4-one has been examined in alcohol, in other organic solvents, such as acetone and benzene, and in water in the presence and absence of various alkaline reagents. The best conditions for 3-alkylation have been applied to the preparation of various 2-thio-3-alkyloxazolid-4-ones and these compounds have been converted into the corresponding oxazolid-2 : 4-diones.

Ethylation of 2-thio-5 : 5-dimethyloxazolid-4-one with ethyl sulphate in ethanol in presence of one equivalent of sodium ethoxide gave an *N*-ethylation product, *2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one* (I; R = Et), and an *S*-ethylation product, *2-ethylthio-5 : 5-dimethyloxazol-4-one* (III; R = Et), which were separated by fractional distillation and crystallisation. The *N*-ethyl derivative is moderately stable to dilute mineral acid, but is hydrolysed by cold aqueous sodium hydroxide to *sodium* N-*α-hydroxy*iso*butyryl*-N-*ethylthiocarbamate* (cf. Part I). It can be determined by titration, as in the case of the 3-alkyloxazolid-2 : 4-diones (Spielman, *J. Amer. Chem. Soc.*, 1944, **66**, 1244), but the end-point is transient owing to the rapid cyclisation of the free thiocarbamic acid to re-form the thio-oxazolidone. 2-Ethylthio-5 : 5-dimethyloxazol-4-one is unstable in moist air and is rapidly hydrolysed by dilute mineral acids to 5 : 5-dimethyloxazolid-2 : 4-dione with evolution of ethanethiol; with aqueous alkali, the hydrolysis proceeds more slowly to form the alkali-metal salt of the oxazolid-dione, but with ammonia 2-imino-5 : 5-dimethyloxazolid-4-one is formed, which is identical with the product prepared by the method of Traube and Ascher (*Ber.*, 1913, **46**, 2077). Preliminary attempts to isomerise the *S*-ethyl to the *N*-ethyl compound were unsuccessful. Methylation of 2-thio-5 : 5-dimethyloxazolid-4-one also gave a mixture; the *S*-methyl derivative was not isolated, but its presence was shown by the evolution of methanethiol on acidification with dilute mineral acid and by the isolation of 5 : 5-dimethyloxazolid-2 : 4-dione from the hydrolysed product.

The ease of hydrolysis of the *S*-methyl derivative afforded a convenient method for the quantitative isolation of the *N*-methyl derivative. The total methylation product was treated with dilute hydrochloric acid, and the oxazolid-dione was separated from the *N*-methyl derivative by extraction with aqueous sodium hydrogen carbonate. This method has been applied throughout for determining the relative amounts of *S*- and *N*-alkylation products formed, the amount of *S*-alkylation being based on the weight of the recovered oxazolid-2 : 4-dione. In ethanol with methyl sulphate and sodium ethoxide, the yield of the 3-methyl derivative was 21% and with potassium ethoxide 27%, but in the absence of an alkaline reagent only *S*-methylation occurred.

In other non-aqueous solvents, such as acetone and benzene, 2-thio-5 : 5-dimethyloxazolid-4-one was methylated with methyl sulphate in presence of sodium, potassium, and barium carbonates, the yields in acetone being 31%, 44%, and 49%, respectively, and 20% with potassium carbonate in benzene; with no alkaline reagent present, only partial *S*-methylation took place. It is of interest that when ethylation is carried out in hot commercial dioxan with potassium carbonate and excess of ethyl sulphate the main reaction product is 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. Presumably, the *S*-methyl derivative initially formed is decomposed by potassium carbonate in boiling dioxan, and the resulting oxazolid-dione is then re-alkylated. *2-Thio-3 : 5-dimethyloxazolid-4-one*, *2-thio-3 : 5-dimethyl-5-ethyloxazolid-4-one* and *2-thio-5-methyl-3 : 5-diethyloxazolid-4-one* were prepared by the acetone–potassium carbonate procedure. Benzylation of 2-thio-5 : 5-dimethyloxazolid-4-one in acetone with benzyl bromide and potassium carbonate for 1½ hours gave a small yield of the

3-*benzyl* derivative, which was isolated only with difficulty owing to the presence of considerable quantities of toluene-ω-thiol and higher-boiling, related products. The indications were, however, that *S*-benzylation largely predominated. With benzyl chloride for 14 hours, a low yield of 5 : 5-dimethyl-3-benzyloxazolid-2 : 4-dione was obtained.

When methylating 2-thio-5 : 5-dimethyloxazolid-4-one in aqueous solution, it was again found that the proportion of *N*-methylation varied with the nature of the alkaline reagent; with one molecular proportion of potassium hydroxide, the yield of the *N*-methyl derivative was 18% and of *S*-methyl derivative 64% (estimated as the oxazolid-2 : 4-dione); with three molecular proportions of potassium carbonate, the yield of the *N*-methyl derivative rose to 31% with a corresponding decrease in *S*-methylation, but with sodium carbonate or potassium hydrogen carbonate, the yield of the *N*-methyl compound was only about 20%. It will be seen from the foregoing and from the experimental section that the course of methylation is influenced by a number of factors. In aqueous solution, increased alkalinity of the reagent, *e.g.*, the use of potassium carbonate in place of hydrogen carbonate, and increase in size of the cation, *e.g.*, the use of potassium carbonate instead of sodium carbonate, favour *N*-methylation. In alcohol or acetone, the effect of the basic cation is still apparent, the highest yield (49%) of *N*-methylation product being obtained by methylating the barium salt of 2-thion-5 : 5-dimethyloxazolid-4-one in acetone. When considering the effect of solvent alone, it will be seen that the proportion of *N*-methylation increased in the order : benzene $<$ water $<$ alcohol $<$ acetone.

The 2-thio-3-alkyloxazolid-4-ones were readily converted into the corresponding oxazoliddiones by treatment with chlorine or bromine water and also by acid permanganate.

## EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s and b. p.s are uncorrected.)

2-*Thio-oxazolid*-4-*one*.—Sodium cyanide (270 g., 5·5 mols.) and potassium thiocyanate (485 g., 5 mols.) were dissolved in water (550 c.c.) and formaldehyde solution (400 c.c., 5 mols.; 37%) was added with cooling and stirring. Concentrated hydrochloric acid (1,250 c.c.) was then added dropwise and the temperature kept below 10°. After filtration from the inorganic salts, the filtrate was set aside for 4 weeks and then continuously extracted with ether. The crude residue (211 g.), obtained after distilling off the ether, was crystallised from water and gave pure 2-thio-oxazolid-4-one (184 g.; 32%), m. p. 115—116° (Found: C, 30·85; H, 2·45; N, 12·4; S, 27·6. Calc. for $C_3H_3O_2NS$: C, 30·8; H, 2·6; N, 11·95; S, 27·4%). Ahlqvist (*J. pr. Chem.*, 1919, [ii], **99**, 56) gives m. p. 111—112°. The yield was raised to 40% by addition of concentrated sulphuric acid to the main filtrate (10% of the volume) and storage for 9 weeks.

By passing bromine vapour into its solution in aqueous methanol, the thio-oxazolidone gave oxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 89—91°.

2-*Thio*-5-*methyloxazolid*-4-*one*.—Sodium cyanide (54 g., 1·1 mols.) and potassium thiocyanate (97 g., 1 mol.) were dissolved in water (125 c.c.), and acetaldehyde (54 g., 1·2 mols.) was added slowly with stirring and good cooling, as much heat is evolved. Concentrated hydrochloric acid (250 c.c.) was added to the stirred mixture, the temperature being kept below 10°. The homogeneous solution was stirred for a further hour, and the inorganic salts were filtered off and washed with diluted hydrochloric acid (20 c.c.; 1 : 1 by vol.). After 1 week, the light-brown crystalline solid (32 g.; 25%) was collected, and sulphuric acid (40 c.c.) added to the filtrate, which on storage for a further 5 weeks deposited a second crop of crystals (38 g.; 29%). The united crops were crystallised from benzene, whereupon 2-*thio*-5-*methyloxazolid*-4-*one* was obtained as rosettes of colourless, prismatic needles, m. p. 93—94° (Found: C, 37·0; H, 3·8. $C_4H_5O_2NS$ requires C, 36·65; H, 3·8%). The yield on a 5-molar scale was 47%.

2-*Thio*-5 : 5-*dimethyloxazolid*-4-*one*.—Sodium cyanide (270 g., 5·5 mols.) and potassium thiocyanate (65 g.) were dissolved in water (750 c.c.), and acetone (500 c.c., *ca.* 7 mols.) was added. The mixture was stirred and cooled to 0°, and concentrated hydrochloric acid (1,250 c.c.) slowly added during about 5 hours, the temperature being kept below 10°. After 1 hour's stirring the inorganic salts were filtered off and washed with dilute hydrochloric acid (125 c.c.; 1 : 1 by vol.). Potassium thiocyanate (420 g., total of 5 mols.) in water (400 c.c.) was then added to the filtrate kept below 5°. The inorganic salts which separated were filtered off and washed with diluted hydrochloric acid, and the filtrate and washings set aside for 7 days. The first crop of material (204 g.) was filtered off and concentrated sulphuric acid (200 c.c.) added to the filtrate. After 6 weeks another crop (323 g.) separated and after 12 weeks a third crop (19 g.). The united crops were dissolved in ether, the solution filtered from insoluble impurity, the solvent removed, and the residual 2-thio-5 : 5-dimethyloxazolid-4-one (531 g., 73%) crystallised in portions from water. The yield from acetone cyanohydrin and potassium thiocyanate after about 8 weeks was 64%.

2-*Thio*-5-*methyl*-5-*ethyloxazolid*-4-*one*.—The general procedure of the previous experiments was followed with methyl ethyl ketone (265 c.c., 3 mols.), sodium cyanide (135 g., 2·75 mols.), potassium thiocyanate (242·5 g., 2·5 mols.), water (315 c.c.), and concentrated hydrochloric acid (625 c.c.). Stirring was continued for 16 hours before filtering off the inorganic salts, which were washed with a mixture of water (25 c.c.) and concentrated hydrochloric acid (25 c.c.). The united filtrates and washings were stirred at 40—45° for 8 days and then set aside for 2 days. The yellow solid (155 g.) was filtered off, washed with diluted hydrochloric acid and dried at 50°. Concentrated sulphuric acid (100 c.c.) was added to the united filtrates and washings, followed by enough water to dissolve the oil on the surface of the solution; after 6 weeks a further crop (28 g.) was obtained. The united crops were dissolved in ether, the solution was filtered, and the solvent distilled from the clear filtrate. The residue, a light-yellow solid (140 g.; 35%), on crystallisation from hot water, furnished 2-thio-5-methyl-5-ethyloxazolid-4-one, colourless needles, m. p. 106°, as described by Erlenmeyer, Kleiber, and Loebenstein (*loc. cit.*).

2-*Thio*-3 : 5-*dimethyloxazolid*-4-*one*.—2-Thio-5-methyloxazolid-4-one (65·5 g., 0·5 mol.), acetone (300 c.c.), and potassium carbonate (87 g., 0·63 mol.) were stirred for 2 hours, methyl sulphate (72 g., 0·57 mol.) was added, and the mixture boiled under reflux for 3 hours; after removal of the acetone, water (200 c.c.) and concentrated hydrochloric acid (75 c.c.) were added in turn. Extraction with carbon tetrachloride, washing the extract with aqueous ammonia (2N.) and distillation of the dried solution gave a colourless oil, b. p. 134—146°/15 mm., which solidified, and crystallisation from a mixture of ether and light petroleum (b. p. 30—40°; 1 : 1 by vol.) gave 2-*thio*-3 : 5-*dimethyloxazolid*-4-*one* as prismatic needles (27·5 g.; 38%), m. p. 74—75° (Found: C, 41·9; H, 4·85. $C_5H_7O_2NS$ requires C, 41·4; H, 4·85%). A current of chlorine was passed through a mixture of the thion compound (20 g.) in carbon tetrachloride (30 c.c.) and water (30 c.c.). Ether-extraction and distillation furnished 3 : 5-dimethyloxazolid-2 : 4-dione as an oil (12·65 g.; 71%), b. p. 116—125°/22 mm. (Found: C, 46·95; H, 5·9. Calc. for $C_5H_7O_3N$: C, 46·5; H, 5·45%).

2-*Thio*-3 : 5-*dimethyl*-5-*ethyloxazolid*-4-*one*.—2-Thio-5-methyl-5-ethyloxazolid-4-one (31·8 g., 0·2 mol.) in acetone (120 c.c.) was stirred with anhydrous potassium carbonate (34 g., 0·25 mol.) for 2 hours until neutral. Methyl sulphate (28 g., 0·22 mol.) was added dropwise during ½ hour; heat was evolved and the mixture was boiled under reflux for 1½ hours. After removal of the solvent, the residue was stirred with water (80 c.c.), concentrated hydrochloric acid (75 c.c.) was then added and the methanethiol evolved burned in a current of coal gas. Extraction of organic material with carbon tetrachloride, removal of 5-methyl-5-ethyloxazolid-2 : 4-dione with dilute ammonia (100 c.c.; 2N.), drying ($Na_2SO_4$), and fractional distillation furnished 2-*thio*-3 : 5-*dimethyl*-5-*ethyloxazolid*-4-*one* (15·95 g.; 46%) as a colourless oil, b. p. 116—122°/14 mm., which solidified when kept and then melted at 30—33°. Crystallisation from light petroleum (b. p. 40—60°) yielded colourless, prismatic needles, m. p. 34° (Found: C, 48·75; H, 6·3; N, 8·6. $C_7H_{11}O_2NS$ requires C, 48·55; H, 6·35; N, 8·1%). A current of chlorine was passed into a solution of the thion compound (13·15 g.) in carbon tetrachloride (15 c.c.) and water (15 c.c.) for 1½ hours, the temperature being kept below 5°. After neutralisation and extraction with ether, removal of solvents gave an oil (9·9 g.), which on fractionation furnished 3 : 5-dimethyl-5-ethyloxazolid-2 : 4-dione (8 g.; 67%) as a colourless oil, b. p. 100—105°/16 mm. (Found: C, 53·7; H, 7·35; N, 8·25. Calc. for $C_7H_{11}O_3N$; C, 53·5; H, 7·05; N, 8·9%).

2-*Thio*-5-*methyl*-3 : 5-*diethyloxazolid*-4-*one*.—On replacement of the methyl sulphate by ethyl sulphate (32·4 g., 0·21 mol.) in the above experiment, addition of more acetone (total 250 c.c.), and boiling under reflux for 5 hours, 2-*thio*-5-*methyl*-3 : 5-*diethyloxazolid*-4-*one* was obtained first as an oil, b. p. 129—132°/35 mm., which solidified when kept and melted at 29—32°. Crystallisation from light petroleum (b. p. 40—60°) yielded large, colourless prisms (15·4 g.; 41%), m. p. 32—33° (Found: C, 51·4; H, 6·75; N, 8·1. $C_8H_{13}O_2NS$ requires C, 51·35; H, 6·95; N, 7·5%). On hydrolytic de-sulphurisation, the thion compound (12·7 g.) gave 5-methyl-3 : 5-diethyloxazolid-2 : 4-dione as a slightly yellow oil (8·85 g.), b. p. 100—102°/15 mm. (Found: N, 7·9. Calc. for $C_8H_{13}O_3N$: N, 8·2%).

2-*Thio*-5 : 5-*dimethyl*-3-*ethyloxazolid*-4-*one and* 2-*Ethylthio*-5 : 5-*dimethyloxazol*-4-*one*.—(*a*) 2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) was dissolved in a solution of sodium ethoxide obtained from sodium (4·6 g., 0·2 mol.) and dry ethanol (100 c.c.), and ethyl sulphate (30·8 g., 0·2 mol.) was added to the clear solution. After 6 hours' boiling under reflux, the solution was fractionally distilled in a vacuum. The fraction, b. p. 80—85°/1·5 mm., was crystallised from methanol, giving 2-*thio*-5 : 5-*dimethyl*-3-*ethyloxazolid*-4-*one* as colourless, glistening plates, m. p. 62—63° (Found: C, 48·9; H, 6·7; S, 18·9. $C_7H_{11}O_2NS$ requires C, 48·6; H, 6·4; S, 18·5%). The fraction, b. p. 85—90°/1·5 mm., crystallised from dry ether to give 2-*ethylthio*-5 : 5-*dimethyloxazol*-4-*one* as colourless, vitreous prisms, m. p. 27—28° (Found: C, 48·8; H, 6·6; S, 18·5%). When shaken with dilute hydrochloric acid, the oxazolone decomposed evolving ethanethiol and ether-extraction of the liquors gave 5 : 5-dimethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 76—77°. When shaken with aqueous amonia (2N.), the oxazolone deposited 2-imino-5 : 5-dimethyloxazolid-4-one, m. p. and mixed m. p. with an authentic specimen, 245—246°. The thio-oxazolidone (17·3 g., 0·1 mol.) in carbon tetrachloride (15 c.c.) was stirred with water (15 c.c.), and chlorine passed through for ¾ hour at below 10°. Excess of chlorine was removed by a current of air, the two layers were separated, and the aqueous layer was further extracted with carbon tetrachloride. The united extracts were then washed in turn with aqueous potassium hydrogen carbonate and sodium thiosulphate and then dried, and the solvent distilled off. The residue, on crystallisation from ether, afforded 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, in 90% yield, having m. p. and mixed m. p. with an authentic specimen, 76—77°.

(*b*) 2-Thio-5 : 5-dimethyloxazolid-4-one (145 g., 1 mol.) was dissolved in acetone (1,200 c.c.); after the mixture had been stirred with anhydrous potassium carbonate (170 g., 1·2 mols.) until neutral (3 hours), ethyl sulphate (162 g., 1·05 mols.) was added slowly with vigorous stirring. The mixture soon solidified and it was necessary to break up the mass with a glass rod. The mixture was then boiled under reflux for 1 hour. The acetone was distilled off, finally under reduced pressure, water added, and the mixture stirred to hydrolyse unchanged ethyl sulphate. The mixture was acidified with concentrated hydrochloric acid (150 c.c.), and the ethanethiol evolved burned in a current of coal gas. The solution was extracted with carbon tetrachloride, and the organic layer washed with aqueous potassium carbonate and dried. The crude product after evaporation of the solvent was washed with light petroleum (b. p. 40—60°) and crystallised twice from the same solvent. The yield of 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one thus obtained was 70 g. (40%). The potassium carbonate washings were acidified and 5 : 5-dimethyloxazolid-2 : 4-dione was isolated with the aid of ether.

When the ethylation was carried out in commercial dioxan by the following procedure, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione was obtained. 2-Thio-5 : 5-dimethyloxazolid-4-one (72·5 g., 0·5 mol.) was dissolved in dioxan (300 c.c.), and ethyl sulphate (78 g., 0·51 mol.) was added with stirring. The mixture was boiled under reflux for 4½ hours at a bath temperature of 115°. Anhydrous potassium carbonate (166 g., 1·2 mols.) was added to the cooled solution, and the mixture warmed slowly to the b. p. under reflux, whereupon ethanethiol was evolved. Ethyl sulphate (78 g., 0·51 mol.) was then added dropwise at the b. p. during 1 hour, and boiling continued for 5 hours. The solvent was then distilled, finally under reduced pressure, and water (200 c.c.) and carbon tetrachloride (50 c.c.) were added. After the mixture had been stirred overnight, concentrated hydrochloric acid (150 c.c.) was added, and a further addition of water (350 c.c.) was necessary to dissolve inorganic salts. The organic layer was separated and the aqueous layer extracted 3 times with carbon tetrachloride. The combined extracts were washed with aqueous ammonia (2N.) and dried ($Na_2SO_4$). Evaporation yielded a brown oil which partly crystallised and gave 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (41·1 g.; 52%) having m. p. and mixed m. p. with an authentic specimen, 76—77°.

When the ethylation was carried out by heating equimolecular quantities of the thio-oxazolidone and ethyl sulphate for ½ hour at 100—110° (bath temperature), little reaction taking place at 80°; 60% of 5 : 5-dimethyloxazolid-2 : 4-dione and about 5% of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione were isolated after acidification with hydrochloric acid.

2-*Thio*-3 : 5 : 5-*trimethyloxazolid*-4-*one*.—2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) was dissolved in a solution of sodium ethoxide obtained from sodium (4·6 g., 0·2 mol.) and dry ethanol (100 c.c.), and treated dropwise with methyl sulphate (25·2 g., 0·2 mol.). The mixture was boiled under reflux for 1 hour, the alcohol distilled, and the residue stirred with a slight excess of dilute hydrochloric acid; methanethiol was evolved. The product was extracted with ether, the solution washed with aqueous sodium hydrogen carbonate, the solvent distilled, and the residue fractionated. The fraction, b. p. 100—105°/8 mm., was crystallised from aqueous methanol and gave 2-*thio*-3 : 5 : 5-*trimethyloxazolid*-4-*one* (21%) as colourless, glistening plates, m. p. 54—55° (Found: C, 45·9; H, 5·9; S, 19·6. $C_6H_9O_2NS$ requires C, 45·3; H, 5·7; S, 20·1%). With potassium ethoxide (0·2 mol.) in place of sodium ethoxide, the yield was 27%, and with no alkali present only partial *S*-methylation occurred.

Desulphurisation of the thio-oxazolidone with chlorine or bromine water gave an almost quantitative yield of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 45—46°. Desulphurisation with permanganate was carried out as follows. 2-Thio-3 : 5 : 5-trimethyloxazolid-4-one (31·8 g.) was suspended in water (25 c.c.), and a warm solution of potassium permanganate in sulphuric acid (2N.), saturated at 50°, added in portions with stirring until the solution exhibited a permanent pink colour. The solution was then treated with sulphur dioxide to dissolve oxides of manganese, saturated with salt, and extracted with ether. Evaporation of the dried ethereal solution, followed by cooling to −10°, gave 3 : 5 : 5-trimethyloxazolid-2 : 4-dione in almost quantitative yield.

*Methylation of* 2-*Thio*-5 : 5-*dimethyloxazolid*-4-*one in Other Solvents*.—(a) *In water*. A solution of the thio-oxazolidone (1 mol.) in an aqueous solution of the alkaline reagent (see below) was cooled in ice, and methyl sulphate (1·5 mols.) was added dropwise with vigorous stirring. Stirring was continued for 24 hours and the solution then made acid to Congo-red with hydrochloric acid. Sufficient carbon tetrachloride to dissolve the precipitated organic solid was added and stirring continued for 2 hours. The solution was then made alkaline with aqueous sodium hydrogen carbonate, and after being stirred for 1 hour the carbon tetrachloride layer was separated, washed with fresh aqueous sodium hydrogen carbonate, dried and distilled. The *N*-methylation product, 2-thio-3 : 5 : 5-trimethyloxazolid-4-one, b. p. 100—105°/8 mm., was collected. 5 : 5-Dimethyloxazolid-2 : 4-dione, formed by decomposition of the *S*-methylation product, was isolated from the acidified mother-liquors and washings by ether-extraction.

The percentages of *N*- and *S*-methylation occurring in aqueous solution with the use of various alkaline reagents are given in the following table.

| Alkaline reagent. | *N*-Methyltion, %. | *S*-Methylation, %. | Alkaline reagent. | *N*-Methylation, %. | *S*-Methylation, %. |
|---|---|---|---|---|---|
| KOH (1 mol.) ......... | 18 | 64 | $K_2CO_3$ (1·5 mols.) ...... | 28 | 60 |
| *KOH (3 mols.) ......... | 4 | — | $K_2CO_3$ (3 mols.) ...... | 31 | 56 |
| $KHCO_3$ (3 mols.) ...... | 22 | 60 | $Na_2CO_3$ (3 mols.) ...... | 20 | 65 |

* The bulk of the product was decomposed by the strong alkali.

(b) *In acetone and benzene*. A solution of the thio-oxazolidone (1 mol.) was stirred with the alkaline reagent (see below) for 2—3 hours to allow the alkali-metal salt to be formed, and methyl sulphate (1·25 mols.) added dropwise to the resulting suspension. The mixture was boiled under reflux for 3 hours, the solvent distilled, and the residue treated with dilute hydrochloric acid and worked up as for methylation in water. In acetone, a lower-boiling by-product, probably *acetone dimethyl mercaptol*, b. p. 56°/17 mm., was obtained (Found: C, 44·1; H, 8·6. $C_5H_{12}S_2$ requires C, 44·1; H, 8·8%).

The amount of *N*-methylation occurring is given in the following table:

| Solvent. | Alkaline reagent. | *N*-Methylation, %. | Solvent. | Alkaline reagent. | *N*-Methylation, %. |
|---|---|---|---|---|---|
| Acetone ...... | $Na_2CO_3$ (2 mols.) | 31 | Benzene ... | $K_2CO_3$ (2 mols.) | 20 |
| | $K_2CO_3$ (2 mols.) | 44 | | None. | Partial *S*-methylation, only. |
| | $Ba(OH)_2$–$Ba_2CO_3$ | 49 | | | |

In the experiment with barium hydroxide and barium carbonate, the solution of the thio-oxazolidone was first stirred with an excess of barium hydroxide and then filtered, and methyl sulphate was added to the filtrate in presence of excess of barium carbonate.

2-*Thio*-3-*benzyl*-5 : 5-*dimethyloxazolid*-4-*one*.—A mixture of 2-thio-5 : 5-dimethyloxazolid-4-one (48 g., 0·33 mol.) in acetone (200 c.c.) and anhydrous potassium carbonate (60 g., 0·43 mol.) was stirred for 2 hours. Benzyl bromide (65 g., 0·38 mol.) was added and the mixture boiled under reflux for 1½ hours. Acetone was distilled off, and the residue stirred with water (150 c.c.) and carbon tetrachloride (200 c.c.). The organic layer was separated, washed with water, and stirred with warm hydrochloric acid (200 c.c.; 2N.), then washed in turn with water and aqueous ammonia (2N.), dried, and distilled. The fraction, b. p. 174—185°/5 mm., on storage and cooling deposited crystals, m. p. 81—85°. Repeated crystallisation from ether furnished a small quantity of 2-*thio*-3-*benzyl*-5 : 5-*dimethyloxazolid*-4-*one*, m. p. 88—89° (Found : C, 61·2; H, 5·8. $C_{12}H_{13}O_2NS$ requires C, 61·25; H, 5·5%).

Under the following conditions of benzylation, 3-benzyl-5 : 5-dimethyloxazolid-2 : 4-dione was the only product obtained pure. 2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) in acetone (120 c.c.) was stirred with anhydrous potassium carbonate (44 g., 0·32 mol.) for 2 hours to form the potassium salt, benzyl chloride (35·5 g., 0·3 mol.) was added, and the mixture was boiled under reflux for 14 hours. After removal of the acetone, water (100 c.c.) and then concentrated hydrochloric acid (100 c.c.) were added, and the mixture was extracted with carbon tetrachloride. The extract was washed with aqueous ammonia (4N.), to remove 5 : 5-dimethyloxazolid-2 : 4-dione, and dried and the solvent distilled. The first fraction, b. p. 94—96°/30 mm., containing toluene-ω-thiol and related products, was discarded. The second fraction, a yellow oil, b. p. 164—180°/15 mm., when mixed with ether and light petroleum and cooled gave 3-benzyl-5 : 5-dimethyloxazolid-2 : 4-dione (5·15 g.), which after crystallisation from light petroleum (b. p. 60—80°) had m. p. 56—57° and did not depress the m. p. of an authentic specimen, m. p. 60—61°. Its constitution was confirmed on attempted de-sulphurisation with chlorine water; it was recovered unchanged.

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