8. *Derivatives of Oxazolid-2 : 4-dione. Part I. The Alkylation of 5 : 5-Dimethyloxazolid-2 : 4-dione.**

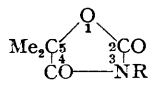
By J. S. H. Davies and W. H. Hook.

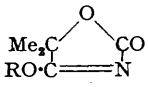
A number of *N*- and *O*-alkyl derivatives of 5 : 5-dimethyloxazolid-2 : 4-dione has been prepared. The *O*-alkyl derivatives are shown to be 4-enol ethers and have been isomerised to the corresponding *N*-alkyl derivatives. The hydrolysis products of the *N*-alkyl derivatives have been studied.

N-Alkyl derivatives of oxazolid-2 : 4-diones have been described by Ahlqvist (*J. pr. Chem.*, 1919, **99**, 77), who obtained 3-ethyloxazolid-2 : 4-dione by the hydrolytic desulphurisation of 2-thio-3 ethyloxazolid-4-one, and by Spielman (*J. Amer. Chem. Soc.*, 1944, **66**, 1244; cf. B.P. 561,183), who prepared 3-methyl derivatives of oxazolid-2 : 4-diones, having lower alkyl groups in the 5-position, by treating an aqueous alkaline solution of the appropriate oxazolid-dione with methyl sulphate. According to Spielman, methylation gave poor yields, and ethylation with

* Patents pending.

ethyl sulphate failed. The preparation of 5 : 5-*dimethyl*-3-*ethyloxazolid*-2 : 4-*dione* (I; R = Et) by a modified procedure (anhydrous conditions) was reported in a preliminary communication (*Nature*, 1947, **160**, 610) and is more fully described below. It has since been possible to show that ethylation is effected to a limited extent by Spielman's aqueous alkylation procedure when reaction is prolonged (72 hours).

(I.) 

 (II.)

By treatment of the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione with ethyl iodide Spielman (*loc. cit.*) obtained a compound, m. p. 61—62°, which he considered to be 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. In contrast to the 3-methyl derivative, his product has now been shown to be unstable to dilute aqueous mineral acid which yields the original dione, and to aqueous alkali which yields the sodium salt of the dione. With ammonia in dry ethanol, it forms an *imino*-derivative, which is also hydrolysed by boiling hydrochloric acid to the original dione. This imino-derivative is not identical with 2-*imino*-5 : 5-*dimethyloxazolid*-4-*one* prepared by condensation of ethyl α-hydroxy*iso*butyrate with guanidine (cf. Traube and Ascher, *Ber.*, 1913, **46**, 2077). Spielman's product is, therefore, now regarded as the 4-enol ethyl ether, *i.e.*, 4-*ethoxy*-5 : 5-*dimethyloxazol*-2-*one* (II; R = Et). 4-*Methoxy*- and 4-*benzyloxy*-5 : 5-*dimethyloxazol*-2-*one* have also been prepared by Spielman's method. These enol ethers slowly isomerise when heated at 180°, alone or in the presence of the alkyl halide, to the *N*-alkyl derivatives identical with the products prepared as described below. If the alkyl group of the halide differs from that of the *O*-alkyl derivative, exchange occurs. Thus, the *O*-ethyl derivative is converted by methyl iodide at 180° into the *N*-methyl derivative, and benzyl bromide similarly furnishes the *N*-benzyl derivative.

Although *O*-alkylation is the preponderating reaction between the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione and ethyl iodide at room temperature, an increasing amount of the *N*-ethyl derivative is formed as the temperature is raised. After 3 days in ether at room temperature, the product contains some 10% of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, whilst after 2 hours in boiling toluene 30% of this derivative is obtained. Work so far carried out suggests that the *O*-ethyl derivative is not necessarily an intermediate in the formation of the *N*-ethyl compound from the silver salt.

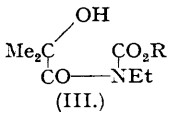
In view of the importance of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione (I; R = Me) in the treatment of " petit mal," myoclonic and akinetic epilepsies (Lennox, *J. Amer. Med. Assoc.*, 1945, **129**, 1069), improved methods for the alkylation of oxazolid-2 : 4-diones have been worked out, and new *N*-alkyl derivatives have been prepared for pharmacological investigation.

N-Alkylation of 5-substituted oxazolid-2 : 4-diones has now been found to proceed more readily and in good yield when the sodium or potassium salts are treated with an alkyl sulphate or halide under anhydrous conditions. Thus, when 5 : 5-dimethyloxazolid-2 : 4-dione in dry ethanol is treated first with sodium ethoxide and then with ethyl sulphate, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, m. p. 76—77°, is formed almost quantitatively, and this product is chemically similar to Spielman's 3-methyl derivative. Alternatively, alkylation may be carried out in excellent yield in acetone solution containing anhydrous potassium carbonate. Some *N*-alkyl derivatives are most conveniently prepared directly from ethyl α-hydroxy*iso*butyrate in one stage. The hydroxy-ester is condensed with urea in the presence of sodium ethoxide (Stoughton, *J. Amer. Chem. Soc.*, 1941, **63**, 2376) to form the sodium salt of 5 : 5-dimethyloxazolid-2 : 4-dione, and use of this solution directly for alkylation has furnished the 3-*n*- and -iso-*propyl*, 3-n- and -iso-*butyl*, 3-n- and -iso-*amyl*, 3-*allyl*, 3-2′-*methylallyl*, and 3-*benzyl* derivatives.

The above methods have been extended to the introduction of substituted alkyl groups, the 3-2′-*hydroxyethyl*, 3-2′-*ethoxyethyl*, 3-2′-*methylthioethyl*, and 3-*acetoacetoxyethyl* derivatives having been thus prepared. 5 : 5-Dimethyl-3-2′-diethylaminoethyloxazolid-2 : 4-dione was very conveniently prepared from diethylaminoethyl chloride hydrochloride by the potassium carbonate–acetone method, the free base being liberated *in situ*.

N-Alkyloxazolid-2 : 4-diones are moderately stable to mineral acids, but are rapidly hydrolysed by aqueous sodium hydroxide, a reaction which is used as a method of assay (Spielman, *loc. cit.*). This hydrolysis, however, gives rise to two products—*sodium* N-α-*hydroxy*iso*butyryl*-N-*ethylcarbamate* (III; R = Na) and 1-(*ethylcarbamyl*)iso*propyl carbonate* (IV; R = Na). Acidification of the hydrolysis mixture causes decarboxylation of the latter to the hydroxyamide, whereas it is possible to isolate the free carbamic acid, which is fairly stable and may be deter-

mined in the solution by titration. Utilising these facts, it has been observed that the proportion of lactone hydrolysis, giving rise to (III), increases with the complexity of the *N*-alkyl substituent.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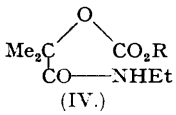
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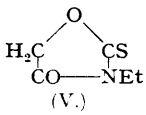
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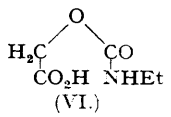
(VI.)

α-Hydroxyisobutyroethylamide, formed by decarboxylation of (IV; R = H) as above, is a low-melting solid, characterised as the 3 : 5-*dinitrobenzoate*. It is also formed when (III; R = H) decomposes on being melted. This latter decarboxylation is accompanied by partial cyclodehydration, yielding the original 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. Decarboxylation occurs to the extent of 75% when (III; R = H) is heated alone or with copper powder, but when an aqueous solution of the acid is boiled with copper powder this amount is increased to 88%; in all cases the remaining acid undergoes cyclisation. On storage in aqueous solution at room temperature, the acid slowly cyclises and 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione crystallises from the solution.

By alkaline hydrolysis of 2-thio-3-ethyloxazolid-4-one (V) and treatment of the product with bromine, Ahlqvist (*loc. cit.*) obtained a product, which he considered to be *N*-ethylcarbamylglycollic acid (carboxymethyl *N*-ethylcarbamate) (VI). Hydrolysis and desulphurisation, by the method of Ahlqvist, of 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one, the preparation of which is described in Part III (*J.*, 1950, 36) also gives (III; R = H). It seems probable, therefore, that Ahlqvist's product is *N*-ethyl-*N*-glycollylcarbamic acid and not (VI).

In a publication which has appeared since the completion of this work, Spielman (*J. Amer. Chem. Soc.*, 1948, **60**, 1021) mentions the use of methanol as a solvent for the methylation procedure, the alkaline reagent presumably being sodium hydroxide as in his earlier experiments. He mentions also an alternative alkylation procedure, in which the potassium salt of the oxazolid-dione is first formed by treating the dione in " Cellosolve " with potassium hydroxide. In the present work, alkylation proceeded most efficiently under strictly anhydrous conditions, and alkali-metal hydroxides were better replaced by alkoxides in alcoholic solution or anhydrous potassium carbonate in non-hydroxylic solvents.

Experimental.

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

O-Alkylation. 4-*Ethoxy*-5 : 5-*dimethyloxazol*-2-*one*.—In accordance with Spielman's procedure, a mixture of the dry silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione (60 g.), dry ether (400 c.c.), and ethyl iodide (50 g.) was set aside, with occasional shaking, at room temperature for 3 days. Filtration of the product and evaporation of the ether yielded a residue (22·4 g.), which was distilled. The fraction (10·4 g.), b. p. 90—91°/0·5 mm., partly solidified and was crystallised from dry ether, yielding a product (4·5 g.), m. p. 58—60°; recrystallisation raised the m. p. to 61—62°, which is that of the product described by Spielman and now considered to be 4-ethoxy-5 : 5-dimethyloxazol-2-one.

The total ether-soluble product (4·8 g.), obtained from 10 g. of silver salt as above was warmed with dilute hydrochloric acid for 15 minutes to convert the ethoxy-compound into 5 : 5-dimethyloxazolid-2 : 4-dione. The cooled mixture was made alkaline with sodium hydrogen carbonate to convert the latter into its sodium salt, and then extracted with ether. The ethereal extract yielded a crude residue (0·45 g.), which on crystallisation from ether afforded 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, identical with the product described below. Similarly, reaction of the silver salt (10 g.) with ethyl iodide in boiling toluene for 2 hours yielded a mixed product (4·5 g.), which after treatment with hydrochloric acid and sodium hydrogen carbonate afforded the crude 3-ethyl derivative (1·5 g.).

Reactions of 4-*Ethoxy*-5 : 5-*dimethyloxazol*-2-*one* (II; R = Et).—(*a*) Treatment with a slight excess of 2N-sodium hydroxide and back-titration with hydrochloric acid (phenolphthalein) gave equiv. = 155·7 (Calc., 157). Acidification of the liquors and ether-extraction yielded 5 : 5-dimethyloxazolid-2 : 4-dione. (*b*) Heating the ether alone in a sealed tube at 180° for 24 hours afforded, almost quantitatively, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. With ethyl iodide, conversion was almost complete after 18 hours at 180°, but only partial after 72 hours at 140°. (*c*) Heating the ether with methyl iodide at 180° for 18 hours yielded 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, and with benzyl bromide under similar conditions the 3-benzyl derivative (see below) was formed. (*d*) The *O*-ethyl compound (2·4 g.) in dry ethanol (20 c.c.) was treated with a stream of dry ammonia for 15 minutes. The ethanol was distilled off and the residue (2·2 g.) recrystallised from ethanol, 4-*imino*-5 : 5-*dimethyloxazolid*-2-*one* being obtained as fine colourless prisms, m. p. 270—271° (decomp.) (Found : C, 46·8; H, 6·5. $C_5H_8O_2N_2$ requires C, 46·9; H, 6·3%). When the imino-derivative was heated on a steam-bath for ½ hour with hydrochloric acid, ether-extraction of the resulting solution yielded 5 : 5-dimethyloxazolid-2 : 4-dione, m. p. 76—77°.

2-*Imino*-5 : 5-*dimethyloxazolid*-4-*one* was prepared by condensation of ethyl α-hydroxy*iso*butyrate with guanidine (cf. Traube and Ascher, *loc. cit.*). It crystallised from ethanol as colourless prisms, m. p. 245—246° (Found: C, 47·0; H, 6·4%). The mixed m. p. with the 4-imino-derivative was 200—210° (decomp.). The 2-imino-derivative was hydrolysed to 5 : 5-dimethyloxazolid-2 : 4-dione by heating it with hydrochloric acid.

4-Methoxy-5 : 5-dimethyloxazol-2-one.—The dry silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione in ethereal suspension was allowed to react with methyl iodide at room temperature for 3 days. Filtration and concentration of the ethereal solution yielded the *4-methoxy*-derivative as fine colourless needles, m. p. 153—154°, sparingly soluble in ether (Found : C, 50·15; H, 6·2. $C_6H_9O_3N$ requires C, 50·35; H, 6·3%). It was isomerised to the 3-methyl derivative by heating it at 180° for 18 hours, and with alcoholic ammonia yielded 4-imino-5 : 5-dimethyloxazolid-2-one.

4-Benzyloxy-5 : 5-dimethyloxazol-2-one.—This *ether*, prepared similarly, by use of benzyl bromide, formed colourless needles, m. p. 147—148° (Found : N, 6·7. $C_{12}H_{13}O_3N$ requires N, 6·4%). When heated at 180° for 60 hours, it furnished the 3-benzyl analogue.

N-Alkylation.—The preparation of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione by method (*a*) below is typical of the *N*-alkylation procedure employed. For the introduction of higher alkyl groups the iodides were used, and for secondary halides or 2-substituted halides the time of reaction was longer. For *products* prepared see the table.

5 : 5-Dimethyl-3-ethyloxazolid-2 : 4-dione. (*a*) To a solution of sodium (4·6 g.) in dry ethanol (100 c.c.) were added dry urea (12 g.) and ethyl α-hydroxy*iso*butyrate (26·4 g.), prepared by the method of U.S.P. 2,349,795. The reaction mixture was refluxed for 16 hours, and dissolved ammonia then removed by drawing a current of dry air through the boiling solution. The mixture was treated dropwise, with stirring, with ethyl sulphate (30·8 g.) and then refluxed for 2 hours, and the ethanol removed by distillation. The residue was treated with iced water and extracted with ether, the extract dried, and the solvent was removed. 5 : 5-Dimethyl-3-ethyloxazolid-2 : 4-dione (21·5 g., 68·5%) crystallised from aqueous methanol as flat, vitreous prisms, m. p. 76—77° (Found : C, 53·7; H, 7·1. $C_7H_{11}O_3N$ requires C, 53·5; H, 7·1%).

(*b*) 5 : 5-Dimethyloxazolid-2 : 4-dione (25·8 g.) in dry acetone (200 c.c.) was stirred for 3 hours with anhydrous potassium carbonate (30 g.). Ethyl sulphate (30·8 g.) was added to the mixture, which was refluxed for 6 hours. After filtration from inorganic material, the product (27·5 g., 87%) was isolated by removal of solvent and working up as above.

(*c*) 5 : 5-Dimethyloxazolid-2 : 4-dione (12·9 g.) in a solution of sodium hydroxide (5 g.) in water (50 c.c.) was stirred vigorously at room temperature with ethyl sulphate (15·4 g.) for 72 hours. The crystalline solid which separated was crystallised from aqueous methanol, affording 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (3·1 g.) in 20% yield.

Hydrolysis of 5 : 5-Dimethyl-3-alkyloxazolid-2 : 4-diones.—(a) *3-Ethyl derivative.* Aqueous sodium hydroxide (50 c.c.; 0·189 N.) was added to 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (1·011 g.) in alcohol (20 c.c.), and after 15 minutes the mixture was back-titrated with hydrochloric acid (12·0 c.c.; 0·249N.) using phenolphthalein (Found : equiv., 156·5. Calc. : equiv., 157). Hydrochloric acid (9·9 c.c.; 0·249N.) was then added to the neutral liquors until carbon dioxide was no longer liberated, the carbon dioxide was removed by suction, and the excess of hydrochloric acid determined by back-titration with sodium hydroxide (2·3 c.c.; 0·189N.). The amount of carbon dioxide liberated by decarboxylation was thus equivalent to 10·7 c.c. of the standard sodium hydroxide, indicating that about 31% of the oxazolid-2 : 4-dione had been hydrolysed to the carbonate, the remaining 69% having given the carbamate. When 2N-sodium hydroxide was used, the former figure was 32·6%.

3-Alkyl derivatives of 5 : 5-dimethyloxazolid-2 : 4-dione.

Derivative.	M. p.	B. p. at (mm.).	n_D^{20}.	Formula.	Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
Pr^n	46—47°	—	—	$C_8H_{13}O_3N$	56·0	7·5	56·1	7·7
Pr^i	89—90	—	—	$C_8H_{13}O_3N$	56·1	7·6	,,	,,
Bu^n	—	68—70° (0·6)	1·4455	$C_9H_{15}O_3N$	58·2	8·2	58·4	8·1
Bu^i	—	64—66 (0·7)	1·4446	$C_9H_{15}O_3N$	58·2	8·0	,,	,,
n-Amyl	—	80—81 (0·5)	1·4470	$C_{10}H_{17}O_3N$	60·6	8·3	60·3	8·6
*iso*Amyl	—	76—77 (0·7)	1·4456	$C_{10}H_{17}O_3N$	60·9	8·6	,,	,,
CH_2:CH·CH_2	—	82 (4)	1·4590	$C_8H_{11}O_3N$	56·7	6·8	56·8	6·5
CH_2:CMe·CH_2	—	85—87·5 (1·8)	1·4611	$C_9H_{13}O_3N$	58·8	7·6	58·9	7·1
C_6H_5·CH_2	60—61	—	—	$C_{12}H_{13}O_3N$	65·9	6·1	65·8	6·0
HO·CH_2·CH_2	—	119 (0·7)	1·4695	$C_7H_{11}O_4N$	48·6	6·6	48·6	6·4
EtO·CH_2·CH_2	—	76 (0·3)	1·4460	$C_9H_{15}O_4N$	54·0	7·8	53·7	7·5
MeS·CH_2·CH_2	39—40	110 (1·0)	—	$C_8H_{13}O_3NS$	47·2	6·5	47·3	6·4
Et_2N·CH_2·CH_2 *	23—24	107 (2·0)	—	$C_{11}H_{20}O_3N_2$	58·5	8·85	57·8	8·8
,, hydrochloride	190	—	—	$C_{11}H_{21}O_3N_2Cl$	50·0	8·1	49·9	8·0
,, methiodide	129—130	—	—	$C_{12}H_{23}O_3N_2I$	38·8	6·3	38·9	6·3
Et_2N·CH_2·CH(OH)·CH_2 †	34	141 (1)	—	$C_{12}H_{22}O_4N_2$	55·3	8·8	55·8	8·6
Hydrochloride	145	—	—	$C_{12}H_{23}O_4N_2Cl$	48·9	7·6	48·9	7·9
CH_3·CO·CH_2·CO·O·CH_2·CH_2 ‡	—	155 (0·7)	1·4713	$C_{11}H_{15}O_6N$	52·0	5·7	51·4	5·9

* Cf. Spielman (*loc. cit.*, 1948).

† 3-Diethylamino-2-hydroxypropyl chloride was prepared by the method of Price, Leonard, Peel, and Reitsema (*J. Amer. Chem. Soc.*, 1946, **68**, 1807).

‡ 2-Chloroethyl acetoacetate was prepared as described by Jones, Robinson, and Strachan (*J.*, 1946, 87).

The neutral liquors from 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (10 g.) treated as above with sodium hydroxide (2N.) and hydrochloric acid (2N.), after liberation of carbon dioxide, were extracted continuously with ether and yielded *α-hydroxyisobutyroethylamide* as a hygroscopic soapy solid, m. p. 25—28°, which could not be purified further owing to a tendency to lose ethylamine when heated. It gave a 3 : 5-*dinitrobenzoate*, m. p. 154° (Found : C, 48·4; H, 4·9. $C_{13}H_{15}O_7N_5$ requires C, 48·0; H, 4·6%). The aqueous mother-liquors from extraction of the amide, after acidification with hydrochloric acid and ether-extraction, yielded N-*α-hydroxyisobutyryl*-N-*ethylcarbamic acid* as colourless prisms (from ether), m. p. 122—123° (decomp.) (Found : C, 48·1; H, 7·4. $C_7H_{13}O_4N$ requires C, 48·0; 7·4%). The carbamic acid (0·535 g.) was heated at 130—140° for 15 minutes; the volume of carbon dioxide evolved was 51 c.c. (75%). When the product was heated on the steam-bath in an open flask with a cold finger inserted at the mouth, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione condensed on the cold finger. The residue, on reacting with 3 : 5-dinitrobenzoyl chloride, furnished the 3 : 5-dinitrobenzoate of α-hydroxy*iso*butyroethylamide.

(b) 3-*Methyl derivative*. Hydrolysis of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione was examined as for the 3-ethyl derivative, and the results indicated that about 40% of the hydrolysis occurred by fission of the N–C bond to yield the carbonate. α-Hydroxy*iso*butyromethylamide was readily obtained with m. p. 78—79° (cf. Spielman, *loc. cit.*) and afforded a 3 : 5-*dinitrobenzoate*, m. p. 162° (Found : C, 46·5; H, 4·3. $C_{12}H_{13}O_7N_3$ requires C, 46·3; H, 4·2%). *N*-α-Hydroxy*iso*butyryl-*N*-methylcarbamic acid melted at 115° (decomp.).

(c) 3-iso*Propyl derivative*. Hydrolysis of 5 : 5-dimethyl-3-*iso*propyloxazolid-2 : 4-dione proceeded with the liberation of only 0·15 equivalent of carbon dioxide, indicating that hydrolysis of the lactone preponderated to the extent of 85%. N-*α-Hydroxyisobutyryl*-N-iso*propylcarbamic acid* had m. p. 150—151° (decomp.) (Found : C, 51·1; H, 8·1. $C_8H_{15}O_4N$ requires C, 50·8; H, 8·0%).

Hydrolysis of 2-*Thio*-5 : 5-*dimethyl*-3-*ethyloxazolid*-4-*one* (see Part III).—Aqueous sodium hydroxide (50 c.c.; 0·2N.) was added to 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one (1 g.) in alcohol (20 c.c.). After 15 minutes, bromine vapour was drawn through the mixture until it was no longer decolorised. The solution was then made acid to Congo-red with dilute hydrochloric acid, and extracted with ether. Partial evaporation of the extract yielded *N*-α-hydroxy*iso*butyryl-*N*-ethylcarbamic acid, m. p. 122—123°, identical with the compound described above.

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