9. *Derivatives of Oxazolid-2 : 4-dione. Part II.* O- *and* N-*Alkylation of 5-Substituted Oxazolid-2 : 4-diones.**

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A number of new *N*-alkyl derivatives of 5-substituted oxazolid-2 : 4-diones has been prepared. In the reaction of the silver salts of oxazolid-2 : 4-dione and its 5-substituted derivatives with alkyl halides, 5-substitution favours *O*-alkylation.

Spielman (*J. Amer. Chem. Soc.*, 1944, **66**, 1244; 1948, **70**, 1021) has reported the preparation of a number of *N*-alkyl derivatives of oxazolid-2 : 4-diones. The formation of *O*-alkyl derivatives of 5 : 5-dimethyloxazolid-2 : 4-dione and an improved method for the *N*-alkylation of 5 : 5-dimethyloxazolid-2 : 4-dione have been reported in Part I (preceding paper). This work has now been extended in part to oxazolid-2 : 4-dione and to the 5-methyl, 5-methyl-5-ethyl, 5-benzyl-5-methyl, 5-phenyl-5-methyl, and 5 : 5-diphenyl derivatives. The *N*-alkyl derivatives described herein and in Part I have been tested for anti-convulsant activity in mice; detailed results will be published elsewhere.

The oxazolid-2 : 4-diones were prepared from the corresponding glycollic esters by the method of Stoughton (*J. Amer. Chem. Soc.*, 1941, **63**, 2376; U.S.PP. 2,349,313, 2,349,785, 2,372,861). The glycollic esters were prepared by known methods, but in some cases esterification was more efficient by the azeotropic procedure described by Clarke and Davis (*Org. Synth.*, Coll. Vol. I, p. 261) for ethyl oxalate. *Ethyl α-hydroxy-β-phenylisobutyrate*, which was prepared by a modification of Stoughton's method, has not previously been described.

N-Alkylation of 5-substituted oxazolid-2 : 4-diones by the action of the alkylating agent on an alcoholic solution of the sodium salt of the dione, as reported earlier, proceeded normally, but with oxazolid-2 : 4-dione, itself, the yields were in some cases low, probably owing to the high solubility of the products in water.

It was shown (Part I) that reaction of the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione with ethyl iodide in ether at room temperature caused mainly *O*-ethylation with about 10% of *N*-ethylation, but that in boiling toluene up to 30% of the *N*-ethyl derivative was obtained. The silver salt of oxazolid-2 : 4-dione itself, with methyl iodide, gave only the *N*-methyl derivative, 3-methyloxazolid-2 : 4-dione, although the presence of a small proportion of

* Patents pending.

O-methylation product was indicated by the formation of a trace of high-melting product, believed to be 4-imino-oxazol-2-one, when the reaction product was treated with ammonia.

In contrast, the silver salt of 5-benzyl-5-methyloxazolid-2 : 4-dione with ethyl iodide in ether at room temperature readily afforded *4-ethoxy-5-benzyl-5-methyloxazol-2-one*, and the silver salt of 5 : 5-diphenyloxazolid-2 : 4-dione with ethyl iodide in boiling benzene readily gave *4-ethoxy-5 : 5-diphenyloxazol-2-one*; a search for 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione revealed only traces. The amount of *O*- relative to *N*-alkylation in this reaction thus varies with substitution in the 5-position in the order diphenyl- > dimethyl- > unsubstituted oxazolid-2 : 4-dione.

The above-mentioned oxazolones have been isomerised to the corresponding 3-ethyloxazolid-2 : 4-diones by treatment at 180° with ethyl iodide as described in Part I.

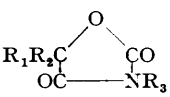
Experimental.

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

Ethyl α-Hydroxy-β-phenylisobutyrate.—A mixture of benzyl methyl ketone (300 g.) and piperidine (2·5 c.c.) was added slowly during 15 minutes to anhydrous hydrogen cyanide (150 g.), with stirring and cooling. The temperature was allowed to rise to a maximum of 30° and, after completion of addition of the ketone, was reduced to 0°, and stirring was continued for 1 hour. The mixture was then added dropwise to fuming hydrochloric acid (600 c.c.) at 0°, saturated with gaseous hydrogen chloride, stirred at 0° for 4 hours, and allowed to attain room temperature overnight. It was then filtered from precipitated solid and neutralised with aqueous sodium hydroxide (40%), the temperature being maintained below 15°. The precipitate was filtered off and dried. Crystallisation from benzene furnished *α-hydroxy-β-phenylisobutyramide* (211 g.), m. p. 83° (Found: C, 67·2; H, 7·0. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%). The acid was obtained by boiling the amide with sodium hydroxide solution (40%) for 1½ hours and was esterified by the azeotropic method of Clarke and Davis (*loc. cit.*). *Ethyl α-hydroxy-β-phenylisobutyrate* was obtained as a colourless mobile oil, b. p. 141—142°/19 mm., in 65% yield (Found: C, 69·3; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

3-Alkyloxazolid-2 : 4-diones.—The products recorded in the table were prepared as described in Part I by condensing the appropriate α-hydroxy-esters with urea in presence of sodium ethoxide and alkylating the sodium salt of the dione so obtained. They crystallised from methanol, ethanol, or ether.

Preparation of 3-alkyloxazolid-2 : 4-diones,



							Found, %.		Required, %.		Yield,
R_1.	R_2.	R_3.	M. p.	B. p.	n_D^{20}.	Formula.	C.	H.	C.	H.	%.
H	H	Bu^n	—	137—139°/ 16 mm.	1·4614	$C_7H_{11}O_3N$	53·9	7·3	53·5	7·1	66
H	H	*n*-Amyl	—	144—148/ 15 mm.	1·4605	$C_8H_{13}O_3N$	56·8	8·0	56·2	7·7	51
H	H	$CH_2{\cdot}CH{:}CH_2$	—	72/5 mm.	1·4815	$C_6H_7O_3N$	51·2	5·3	51·1	5·0	23
H	H	$CH_2{\cdot}CMe{:}CH_2$	44—45°	143/13 mm.	—	$C_7H_9O_3N$	54·4	5·9	54·2	5·85	67
H	H	$CH_2{\cdot}C_6H_5$	44—45	—	—	$C_{10}H_9O_3N$	62·9	4·8	62·8	4·8	41
H	Me	$[CH_2]_2{\cdot}CH_3$	—	73—75/ 1 mm.	1·4531	$C_7H_{11}O_3N$	53·2	6·8	53·5	7·1	43
H	Me	$[CH_2]_3{\cdot}CH_3$	—	84—87/ 1 mm.	1·4530	$C_8H_{13}O_3N$	55·8	7·3	56·1	7·7	54
H	Me	$[CH_2]_4{\cdot}CH_3$	—	100/ 1·8 mm.	1·4545	$C_9H_{15}O_3N$	58·7	8·1	58·4	8·2	40
H	Me	$CH_2{\cdot}CMe{:}CH_2$	—	128/ 11 mm.	1·4709	$C_8H_{11}O_3N$	57·1	6·7	56·8	6·6	62
H*	Me	$CH_2{\cdot}COMe$	51—52	139—141/ 2·5 mm.	—	$C_7H_9O_4N$	49·2	5·3	49·1	5·3	70
Me	Et	Et	—	77/2·5 mm.	1·4447	$C_8H_{13}O_3N$	56·1	7·7	56·1	7·7	60
Me	Et	Bu^n	—	90—91/ 3 mm.	1·4459	$C_9H_{15}O_3N$	58·4	8·3	58·4	8·2	59
Me	Et	$CH_2{\cdot}CH{:}CH_2$	—	87·5/ 1·9 mm.	1·4593	$C_9H_{13}O_3N$	58·6	7·1	58·9	7·1	62
Me	CH_2Ph	Et	71—72	—	—	$C_{13}H_{15}O_3N$	67·4	6·7	67·0	6·4	70
Me	Ph	Me	—	168—169/ 18 mm.	—	$C_{11}H_{11}O_3N$	64·0	5·5	64·4	5·4	73
Ph	Ph	Et	90	—	—	$C_{17}H_{15}O_3N$	72·8	5·1	72·6	5·3	55

* *Semicarbazone*, m. p. 193—194°, from ethanol (Found: C, 42·6; H, 5·4. $C_8H_{12}O_5N_4$ requires C, 42·1; H, 5·3%).

Reaction of the Silver Salt of Oxazolid-2 : 4-dione with Methyl Iodide.—The dry silver salt of oxazolid-2 : 4-dione (10 g.), suspended in a mixture of dry ether and methyl iodide (20 c.c.), was set aside at room temperature for 3 days. Filtration, evaporation, and crystallisation of the residue from ether

yielded 3-methyloxazolid-2 : 4-dione (0·75 g.), m. p. and mixed m. p. with an authentic specimen, 134°. Extraction of the filter cake with dry ethanol yielded a further quantity of the 3-methyl derivative. Treatment of the mother-liquors from these extractions with aqueous ammonia, and partial evaporation of the solvents, yielded a product (0·05 g.), presumably 4-*imino-oxazol*-2-*one*, m. p. 215—220° (Found: C, 36·7; H, 3·9. $C_3H_4O_2N_2$ requires C, 36·0; H, 4·0%).

4-*Ethoxy*-5-*benzyl*-5-*methyloxazol*-2-*one*.—The dry silver salt of 5-benzyl-5-methyloxazolid-2 : 4-dione (11 g.) was suspended in a mixture of dry ether (100 c.c.) and ethyl iodide (20 c.c.), the mixture set aside for 3 days and the solid filtered off. The ether, on distillation, gave a residue (6·0 g.), which on crystallisation from ethanol yielded the *oxazolone* as colourless needles, m. p. 110—111° (Found: C, 67·3; H, 6·6. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·4%).

The oxazolone (1·0 g.) in ethyl iodide (5 c.c.) was heated in a sealed tube at 180° for 20 hours. The product was dissolved in ether, the ethereal solution washed with thiosulphate solution and with sodium carbonate solution, and the solvent distilled. The residue after crystallisation from ether gave 5-benzyl-5-methyl-3-ethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 71—72°.

4-*Ethoxy*-5 : 5-*diphenyloxazol*-2-*one*.—The dry silver salt (18 g.) of 5 : 5-diphenyloxazolid-2 : 4-dione was suspended in a mixture of dry benzene (150 c.c.) and ethyl iodide (15 c.c.). The mixture was boiled under reflux for 2 hours and then filtered and the solvent distilled off from the filtrate. The residue after 3 crystallisations from ether yielded 4-*ethoxy*-5 : 5-*diphenyloxazol*-2-*one* as colourless prisms, m. p. 100—101° (Found: C, 72·5; H, 5·5. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3%). The total ethereal mother-liquors were shaken for ½ hour with warm dilute hydrochloric acid and then extracted with aqueous sodium hydrogen carbonate to remove 5 : 5-diphenyloxazolid-2 : 4-dione arising from the hydrolysis of any residual oxazolone. The ethereal solution was dried and the solvent distilled, leaving a residue (0·1 g.) from which by crystallisation from ether 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione, identical with an authentic specimen, was obtained.

The oxazolone (0·5 g.) in ethyl iodide (2 c.c.) was heated in a sealed tube at 180° for 20 hours. The product was dissolved in ether, the solution washed with aqueous sodium thiosulphate, and the solvent distilled off. Crystallisation of the residue from ether yielded 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 89—90°.

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