81. iso*Oxazolidine and Tetrahydro*-1 : 2-iso*oxazine.*

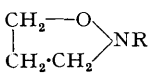
By Harold King.

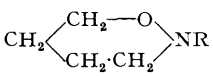
These bases arose in an attempt to prepare $\omega\omega'$-*O*-alkylenehydroxylamines. They are strong stable bases, forming neutral salts with reducing properties.

By the action of alkyl halides on *N*-hydroxyurethane in the presence of alkali, Jones and his collaborators (Jones and Oesper, *J. Amer. Chem. Soc.*, **1914**, **36**, 730; Jones and Neuffer, *ibid.*, p. 2208; Hecker, *Amer. Chem. J.*, **1913**, **50**, 457; Neuffer and Hoffmann, *J. Amer. Chem. Soc.*, **1925**, **47**, 1685) have prepared the lower *O*-alkylhydroxyurethanes, and have obtained the *O*-alkylhydroxylamines on drastic hydrolysis :

$$HO{\cdot}NH{\cdot}CO_2Et + RI + KOH \longrightarrow RO{\cdot}NH{\cdot}CO_2Et \longrightarrow RO{\cdot}NH_2$$

It has now been found that when a similar reaction is applied with trimethylene 1 : 3-dibromide and tetramethylene 1 : 4-dibromide, 1 : 3-trimethylenebisoxyurethane and 1 : 4-tetramethylenebisoxyurethane are not formed, but instead cyclisation takes place with production of N-*carbethoxy*iso*oxazolidine* (I, R = CO_2Et) and N-*carbethoxytetrahydro*-1 : 2-iso*oxazine* (II, R = CO_2Et) respectively.


(I.)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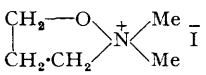
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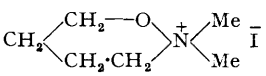
(IV.)

These heterocyclic urethanes are liquids which can be distilled under reduced pressure without decomposition, and on boiling with 16% hydrochloric acid yield *iso*oxazolidine (I, R = H) and tetrahydro*iso*oxazine (II, R = H). These substances are strongly basic oils which give neutral, crystalline salts and yield crystalline *amides* with 3 : 5-dinitrobenzoyl chloride. They behave as highly unsaturated substances to bromine water, but the possibility that they are unsaturated open-chain compounds of the type $NH_2{\cdot}O{\cdot}[CH_2]_n{\cdot}CH{:}CH_2$ is precluded by the results obtained on methylation. Both bases form monomethyl derivatives which add on methyl iodide to form N-*methyl*iso*oxazolidine methiodide* (III) and N-*methyltetrahydro*iso*oxazine methiodide* (IV). Both these methiodides decompose vigorously at their melting points, but the *methopicrates* behave normally except that they both markedly exhibit the phenomenon of thermotropy.

*iso*Oxazolidine and tetrahydro*iso*oxazine appear to be the first members to be described of these saturated ring systems. Knorr and Matthes (*Ber.*, **1901**, **34**, 3484) recorded the preparation of a series of oxazolidines with nitrogen and oxygen in the 1 : 3-position to each other by the action of aldehydes on primary and secondary ethanolamines, but these oxazolidines, unlike the *iso*oxazolidines, were very unstable bases. The nearest analogy to tetrahydro*iso*oxazine is morpholine (tetrahydroparoxazine), which also is a stable base.

Both *iso*oxazolidine and tetrahydro*iso*oxazine are readily obtained in quantity by the methods here described and it is possible that they may serve as intermediates, to advantage, in the preparation of drugs.

Experimental.

N-*Carbethoxy*iso*oxazolidine*.—Trimethylene dibromide (40·4 g.; 1 mol.), *N*-hydroxyurethane (42·0 g.; 2 mols.), and an ethyl-alcoholic solution (224 c.c.) containing potassium hydroxide (22·4 g.; 2 mols.) were boiled together on the water-bath for 6 hours. The alcohol was removed by distillation; from the residue ether extracted *carbethoxy*-iso*oxazolidine* (yield, 90%), which was fractionally distilled, the main fraction having b. p. 112°/16 mm. (Found: N, 9·9; EtO, 32·8, 33·1. $C_6H_{11}O_3N$ requires N, 9·7; EtO, 31·0%).*

When the proportions of hydroxyurethane and potassium hydroxide were halved in the above experiment, the yield was only 44·2%.

iso*Oxazolidine Hydrochloride*.—Carbethoxy*iso*oxazolidine (27·5 g.) was boiled with 16% hydrochloric acid for 2 hours. The cooled solution was extracted with ether to remove non-basic material and evaporated to dryness under reduced pressure, the last traces of moisture being removed by evaporation with alcohol. The crystalline residue was dissolved in a little warm dry ethyl alcohol; the *hydrochloride* (14·0 g.) separated in long hygroscopic needles. A further crop (1·23 g.) was obtained by addition of ether to the mother-liquor. This salt, when quickly dried at 100°, melts at 124—125° (Found: Cl, 32·2. C_3H_7ON,HCl requires Cl, 32·4%). The *hydrobromide*, thin hexagonal leaflets, also hygroscopic, was obtained in a similar way by boiling the carbethoxy-compound (26·7 g.) with constant-boiling hydrobromic acid (500 c.c.) for 3 hours (Found: N, 8·8; Br, 52·0. C_3H_7ON,HBr requires N, 9·1; Br, 51·9%). From the ethereal extract of the diluted solution, trimethylene dibromide (2·5 g.) was recovered. During the hydrolysis ammonium bromide and a little hydroxylamine hydrobromide are both formed. The *picrate*, needles, m. p. 131°, is readily soluble in water and is obtained by adding saturated sodium picrate solution to the solid hydrobromide and crystallising the product from a little water (Found: C, 36·1; H, 3·1; N, 18·5. $C_3H_7ON,C_6H_3O_7N_3$ requires C, 35·8; H, 3·3; N, 18·5%).

3 : 5-*Dinitrobenz*iso*oxazolidide*.—Dinitrobenzoyl chloride (1·15 g.) was heated with *iso*oxazolidine hydrobromide (0·77 g.) in dry pyridine (2 c.c.) for 10 minutes in boiling water. The cooled melt was treated with 3N-hydrochloric acid in excess; the solid was collected and ground successively with dilute hydrochloric acid and sodium hydrogen carbonate solution, then washed, and dried (yield, 1·2 g.). This *amide* is very soluble in the usual organic solvents, but crystallises well from methyl or ethyl alcohol. From 8 c.c. of ethyl alcohol it separated in small plates or flattened needles, m. p. 94—95° (Found: C, 45·1; H, 3·4; N, 15·6. $C_{10}H_9O_6N_3$ requires C, 44·9; H, 3·4; N, 15·7%).

Methylation of iso*Oxazolidine*.—The hydrobromide (1·54 g.) in methyl alcohol (5 c.c.) was treated with methyl iodide (2·5 c.c.) and sodium hydrogen carbonate (1·7 g.); the solution was boiled for 3 hours, concentrated slightly, and filtered. N-*Methyl*iso*oxazolidine methiodide* separated in plates (1·29 g.). On crystallisation from methyl alcohol it melts with violent decomposition at 168—170° (Found: C, 26·4; H, 5·3. $C_5H_{12}ONI$ requires C, 26·2; H, 5·3%). The *methopicrate* crystallises from 17 parts of boiling water in needles which turn orange-red on heating and have m. p. 222° (Found: C, 40·1; H, 4·2; N, 17·0. $C_{11}H_{14}O_8N_4$ requires C, 40·0; H, 4·3; N, 17·0%).

N-*Carbethoxytetrahydro*iso*oxazine*.—Tetramethylene dibromide (43·1 g.; 1 mol.), *N*-hydroxyurethane (42·0 g.; 2 mols.), and an ethyl-alcoholic solution (224 c.c.) containing potassium hydroxide (22·4 g.) were digested on the boiling water-bath for 6 hours. The cyclic *urethane* was isolated as described for its lower ring homologue; yield 27·6 g., b. p. 113—116°/12 mm. (Found: OEt, 26·8. $C_7H_{13}O_3N$ requires OEt, 28·3%).

*Tetrahydro*iso*oxazine Hydrochloride*.—The urethane (20·95 g.) was boiled with 16% hydrochloric acid for 3 hours, the solution cooled, and non-basic material removed by ether extraction. The aqueous solution was evaporated to dryness, finally with alcohol, and on solution in absolute ethyl alcohol, the residue readily crystallised (yield, 12·7 g.). The *hydrochloride* crystallised readily from 20 parts of ethyl alcohol in prismatic needles, m. p. 141—143° (Found: C, 38·8; H, 8·0; N, 11·1. C_4H_9ON,HCl requires C, 38·8; N, 8·2; N, 11·3%).

Tetrahydro*iso*oxazine and *iso*oxazolidine as hydrochlorides give no precipitate with Tanret's reagent, but both in aqueous solution decolorise large amounts of bromine water. Similar properties are exhibited by open-chain *O*-alkylhydroxylamines.

*Tetrahydro*iso*oxazine picrate* crystallises from 30 parts of boiling water in prismatic needles, m. p. 160—161° (Found: C, 38·2; H, 4·0. $C_4H_9ON,C_6H_3O_7N_3$ requires C, 38·0; H, 3·8%).

N-3 : 5-*Dinitrobenzoyltetrahydro*iso*oxazine*, prepared in the same way as its lower homologue, crystallises from 8 parts of boiling alcohol in flattened clusters of stout needles, m. p. 121—122° (Found: C, 46·5; H, 4·0. $C_{11}H_{11}O_6N_3$ requires C, 46·9; H, 3·9%).

*Methylation of Tetrahydro*iso*oxazine*.—The hydrochloride (1·24 g.) in methyl alcohol (5 c.c.) was boiled with methyl iodide (5 c.c.) and sodium bicarbonate (1·7 g.) for 2·5 hours. After removal of sodium chloride which had separated, the solution was concentrated; on addition of a little ether N-*methyltetrahydro*iso*oxazine methiodide* (1·82 g.) crystallised in plates, m. p. 176° (violent decomp.) (Found: C, 30·0; H, 5·8; N, 5·7. $C_6H_{14}ONI$ requires C, 29·6; H, 5·8; N, 5·8%). The *methopicrate* crystallises from water in long needles, m. p. 223° (decomp.). This salt turns orange at 95° and the yellow colour returns on cooling (Found: C, 41·9; H, 4·6; N, 16·4. $C_{12}H_{16}O_8N_4$ requires C, 41·8; H, 4·7; N, 16·3%).

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