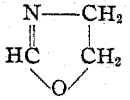
Syntheses from Ethanolamine. V. Synthesis of Δ^2-Oxazoline and of 2,2′-Δ^2-Dioxazoline

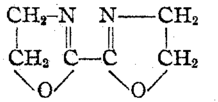
BY HENRY WENKER

As the lowest member of the series, Δ^2-oxazoline (I) is of theoretical interest. The compound has not been described hitherto; earlier attempts[1] to prepare it by dehydration of ethanol formamide resulted invariably in cleavage into carbon monoxide and ethanolamine.

The base has now been obtained by the action of alkali upon β-chloroethyl formamide; the latter was made from ethanol formamide[1,2] and thionyl chloride. Similarly, 2,2′-Δ^2-dioxazoline (II) was prepared from *s*-β,β′-dichlorodiethyl oxamide. The method in itself is not new; Gabriel and Heymann[3] obtained 2-phenyl-Δ^2-oxazoline from β-bromoethyl benzamide and alkali

I





II

Δ^2-Oxazoline is a colorless, mobile liquid which boils at 98° under atmospheric pressure and has a specific gravity of 1.075^{20}_{20}. Its odor is sweetish and somewhat pyridine-like, resembling that of the next higher 2-alkyl homologs. It is miscible with water, ethanol and ether; the aqueous solution reacts alkaline to phenolphthalein. It is less stable than the higher homologs. Boiling water hydrolyzes it to ethanol formamide. Anhydrous hydrogen chloride (in ether) forms an unstable hydrochloride which rearranges quickly to β-chloroethyl formamide, a characteristic reaction which it shares with the higher 2-alkyl homologs. Metallic sodium reacts with formation of sodium cyanide as one of the products. A picrate could not be obtained.

2,2′-Δ^2-Dioxazoline, on the other hand, is a stable, well crystallized compound. It dissolves in water with neutral reaction and forms a stable picrate. With dry hydrogen chloride it regenerates *s*-β,β′-dichlorodiethyl oxamide.

Experimental

β-Chloroethyl Formamide.—Due to its instability, this compound was not obtained in pure form. One hundred twenty-five grams of thionyl chloride was dropped into 89 g. of ethanol formamide with cooling; the charge was then heated on the water-bath for fifteen minutes and subjected to vacuum distillation. Forty-eight grams distilled between 130–155° (20 mm.); the residue then began to decompose. The distillate contained 25.0% of chlorine (theory 32.8%). Slow decomposition took place during the whole operation and made the maintenance of an adequate vacuum difficult. For the same reason, attempts at fractionating the first distillate with the aid of a column were unsuccessful. A second distillation gave 10 g. of material boiling between 137 and 140° (20 mm.) and having 28.5% chlorine; a third distillation gave 6 g. boiling at 137–138° (20 mm.) with 29.4% chlorine. The distillates represented colorless, odorless liquids miscible with water and with ethanol. Experiments in which a larger excess of thionyl chloride was used, gave smaller yields and showed an increased rate of decomposition.

The large amount of non-volatile residue apparently was caused by cleavage of β-chloroethyl formamide into carbon monoxide and β-chloroethylamine; the latter is protected by the dissolved hydrogen chloride from immediate decomposition. This explanation was supported by the following experiments. (a) Sodium hydroxide produced in a concentrated aqueous solution of the residue a liquid base which boiled up and decomposed after short standing; β-chloroethylamine shows the same spontaneous decomposition. (b) In a more dilute solution of the residue alkali produced ethylene-imine: 40 g. of residue was dissolved in a solution of 40 g. of sodium hydroxide in 350 g. of water; the clear solution was distilled, the first 20 cc. of distillate was carefully saturated, and then covered with dry sodium hydroxide, followed by distillation from a boiling water-bath. Two and two-tenths grams of ethylene-imine distilled over and was identified by its boiling point (56°).

Δ^2-Oxazoline.—Fifty-four grams of β-chloroethyl formamide, once distilled, was added to 150 g. of 50% potassium hydroxide contained in a 500-cc. distilling flask over a period of ten minutes. The mixture was shaken frequently and a temperature of 15–18° was maintained by external cooling with ice. Shaking was continued for about five minutes longer; by this time the crude oxazoline base had separated as an oily layer above the alkaline liquid. The flask was now connected with a condenser tube reaching into the bulb of a 250-cc. distilling flask; the latter was surrounded by ice. The base was distilled under a vacuum of 15 mm. from a water-bath heated to 45°. To the distillate, amounting to 25 g., 60 g. of dry potassium hydroxide was added under constant cooling with ice; the first additions had to be made in very small portions, since violent decomposition, due to overheating, occurred during one experiment at this stage. The charge was distilled *in vacuo* as before and the distillate (15 g.), which was already practically anhydrous and gave the correct nitrogen value, was covered again with 60 g. of potassium hydroxide and distilled *in vacuo*, giving 14 g. of the pure base.

Anal. Calcd. for C_3H_5NO: N, 19.7. Found: N, 19.6.

Reactions of Δ^2-Oxazoline. A. Boiling Point.—Two grams of oxazoline, heated in a test-tube over a free flame, boiled without decomposition at 98°. At the end of five minutes, the boiling point was unchanged.

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[1] Wenker, THIS JOURNAL, **57**, 1080 (1935).

[2] French Patent 638,023 (1928).

[3] Gabriel and Heymann, *Ber.*, **23**, 2493 (1890).

B. Hydrolysis with Water.—Three grams of base and 3 g. of water was heated in a test-tube. Boiling began at 94° and continued, after removing the flame, for five minutes, while the temperature rose to 108°. The colorless liquid, which still smelled of oxazoline, was heated for thirty minutes more in the boiling water-bath and then dried *in vacuo* at 100°. A colorless, odorless oil remained which contained 14.9% nitrogen as compared with 15.7% calculated for ethanol formamide. A part of the oil was heated to 100° in oxalic acid solution for one hour; ethanol now precipitated the characteristic alcohol-insoluble ethanolamine oxalate.

C. Reaction with Hydrogen Chloride.—To 3 g. of oxazoline dissolved in 10 g. of ether, 15 g. of a 10% ethereal solution of hydrogen chloride was added with ice cooling. A white crystalline powder separated at once which at room temperature soon melted to a clear colorless liquid. After removing the ether and excess of hydrogen chloride *in vacuo* at 100°, the product contained 32.1% of chlorine; calculated for β-chloroethyl formamide, 32.8%.

D. Reaction with Sodium.—A piece of sodium in 1 g. of oxazoline caused a violent reaction with evolution of gas. The residue, a yellow amorphous mass, gave a precipitate of prussian blue by the usual test for cyanides.

E. Picrate.—The alcoholic solution of the base remained clear with picric acid. Ether precipitated an oil which did not crystallize.

s-β,β-Dichlorodiethyl Oxamide.—Twenty grams of *s*-diethanol oxamide,[4] 100 g. of toluene and 42 g. of thionyl chloride was heated for thirty minutes to 60°, then for ninety minutes in a boiling water-bath. Without first dissolving, the diethanol oxamide changed to a thick white crystal sludge. After cooling, the crystals were filtered, washed subsequently with ethanol, boiling water, ethanol, and crystallized from 200 g. of boiling "cellosolve" (ethylene glycol monoethyl ether). The yield was 19 g. or 78%. The product forms white needles, insoluble in water, sparingly in hot ethanol, which melt at 203°.

Anal. Calcd. for $C_6H_{10}N_2O_2Cl_2$: Cl, 33.3. Found: Cl, 33.1.

2,2'-Δ^2-Dioxazoline.—Ten and six-tenths grams of the preceding compound in 100 cc. of *N* methyl alcoholic potassium hydroxide was boiled for one hour, the clear solution filtered from potassium chloride, evaporated on the water-bath and the crystalline residue recrystallized from 100 g. of toluene. The yield was 5.9 g. or 84%. 2,2'-Δ^2-Dioxazoline crystallizes from toluene in white, fern-like aggregates which melt at 213°. It is very soluble in water and in ethanol, almost insoluble in ether and in cold toluene.

Anal. Calcd. for $C_6H_8N_2O_2$: N, 20.0. Found: N, 19.9.

Reaction with Hydrogen Chloride.—One and four-tenths grams of dioxazoline was dissolved in methanol and 10 g. of a 10% solution of hydrogen chloride in ether was added. White crystals separated and were identified, after crystallization from "cellosolve," by melting point and mixed melting point (203°) as *s*-β,β-dichlorodiethyl oxamide.

Picrate.—Thirty-five hundredths of a gram of dioxazoline and 1.3 g. of picric acid both dissolved in hot ethanol gave a sparingly soluble picrate which crystallized in long needles and melted at 182°.

Summary

Thionyl chloride reacts with ethanol formamide and with *s*-diethanol oxamide with formation of β-chloroethyl formamide and of *s*-β,β-dichlorodiethyl oxamide. With alkali, the latter two compounds yield Δ^2-oxazoline and 2,2'-Δ^2-dioxazoline, respectively. Some characteristic reactions of the two oxazolines are described.

ELIZABETH, N. J. RECEIVED JUNE 20, 1938

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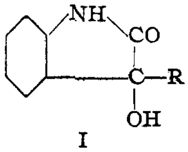
[4] Knorr, *Ber.*, **36**, 1278 (1903).

[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

Reactions of Grignard Reagents with Isatin and N-Alkyl Isatins[1]

BY FREDERICK J. MYERS[2] AND H. G. LINDWALL

The reactions of several Grignard reagents with isatin and N-methylisatin have been reported by Kohn.[3] With isatin the Grignard reagents yield the respective 3-alkyl(or aryl)-3-hydroxy-oxindoles, as would be anticipated. These products have the general formula



I

Kohn prepared the 3-methyl, 3-phenyl and 3-benzyl derivatives of I, but did not investigate the chemical characteristics of these compounds.

Structure I suggested the possibility of the preparation of 3-alkylidene oxindoles through the action of dehydrating agents; using 3-benzyl-3-hydroxyoxindole as the representative of the group, various methods of dehydration were attempted, but without success. In most cases, the compound was recovered unchanged, or, under extremely strenuous conditions, suffered changes more complex than the simple splitting off of a molecule of water.

Kohn[4] also studied the action of phenylmagne-

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(1) Presented in part at the Rochester meeting of the American Chemical Society, September, 1937.

(2) Present address: c/o Röhm and Haas Co., Bridesburg, Penna.

(3) Kohn and Ostersetzer, *Monatsh.*, **32**, 905 (1911); Kohn, *ibid.*, **31**, 747 (1910).

(4) Kohn and Ostersetzer, *ibid.*, **34**, 789 (1913).