[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

2-OXAZOLIDONES: SYNTHESIS FROM N-CARBALKOXY-β-HALOALKYLAMINES[1]

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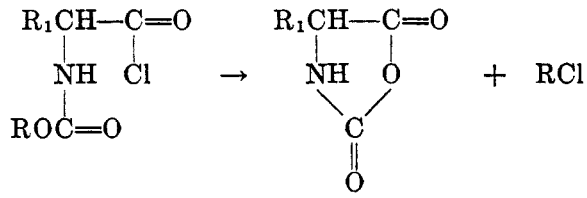
The ease with which N-carbalkoxy-α-amino acid chlorides (I) undergo ring closure to N-carboxy-α-amino acid anhydrides (2,5-oxazolidinedione derivatives) (II) with elimination of alkyl halide (1), suggested that N-carbalkoxy-β-haloalkylamines (III, X = halogen) may suffer a similar cyclization.

Indeed, it was found that at elevated temperatures (120–200°) N-carbalkoxy-β-haloalkylamines (III) split off alkyl halides yielding the corresponding 2-oxazolidones (IV). A new method for the synthesis of 2-oxazolidones is thus available [for other methods, see (2, 3)].



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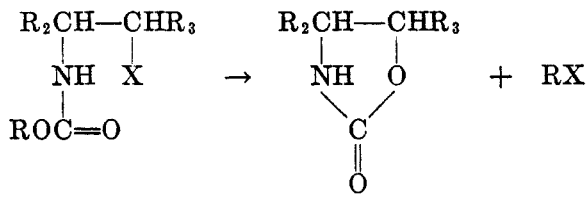

III IV

The influence of the substituents X and R on the temperature of cyclization of N-carbalkoxy-β-haloalkylamines (III, $R_2 = R_3 = H$), was studied systematically. The results are summarized in Table I, which lists the threshold temperatures at which cyclization occurred under the experimental conditions employed. On changing the halogen atom X, it was found that the temperature of cyclization decreases in the order X = Cl, Br, I. A similar decrease was observed, when R was changed from alkyl to benzyl, while in the series R = CH_3, C_2H_5, C_3H_7, C_4H_9, the threshold temperature did not change. The N-phenyl derivative of N-carbobenzoxy-β-chloroethylamine showed the same reaction, leading to N-phenyl-2-oxazolidone.

In order to elucidate the validity of the suggested method in the synthesis of

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TABLE I

CYCLIZATION OF N-CARBALKOXY-β-HALOETHYLAMINES

AMINE	M.P., °C.	B.P., °C./MM.	YIELD, %	d_4^{25}	n_D^{25}	ANALYSIS				Cyclization Temp. (°C.)
						Nitrogen		Halogen		
						Calc'd	Found	Calc'd	Found	
$ClCH_2CH_2NHCOOCH_3$	—	113/25	80	1.223	1.4534	10.2	10.2	25.8	25.5	190–200
$ClCH_2CH_2NHCOOC_2H_5$	—	121/24	87	1.156	1.4501	9.3	9.3	23.4	23.3	190–200
$ClCH_2CH_2NHCOOC_3H_7$	—	132/26	88	1.125	1.4511	8.5	8.6	21.4	20.8	190–200
$ClCH_2CH_2NHCOOC_4H_9$	—	143/26	84	1.086	1.4513	7.8	7.9	19.8	20.3	190–200
$ClCH_2CH_2NHCOOCH_2C_6H_5$	—	—	78	1.183	1.5327	6.6	6.6	16.6	16.2	170–180[a]
$BrCH_2CH_2NHCOOCH_3$	—	98/2	75	1.562	1.4822	7.7	7.8	43.9	44.0	170–180
$BrCH_2CH_2NHCOOC_2H_5$	—	118/3	82	1.412	1.4722	7.1	7.0	40.8	41.4	170–180
$BrCH_2CH_2NHCOOC_3H_7$	—	126/4	85	1.341	1.4699	6.7	7.0	38.1	38.4	170–180
$BrCH_2CH_2NHCOOC_4H_9$	24	137/3	90	1.309	1.4686	6.2	6.2	35.7	36.1	170–180
$BrCH_2CH_2NHCOOCH_2C_6H_5$	45	—	92			5.4	5.4	31.0	31.6	140–145[a]
$ICH_2CH_2NHCOOCH_3$	38	116/2	85			6.1	6.4	55.5	56.2	160–165
$ICH_2CH_2NHCOOC_2H_5$	55	—	85			5.8	5.7	52.3	53.0	160–165
$ICH_2CH_2NHCOOC_3H_7$	25	—	78			5.4	5.4	49.4	50.3	160–165
$ICH_2CH_2NHCOOC_4H_9$	48	—	80			5.2	5.4	46.8	46.0	160–165
$ICH_2CH_2NHCOOCH_2C_6H_5$	69	—	84			4.6	4.8	41.6	42.3	130–135[a]

[a] Cyclization carried out at reduced pressure (20 mm.).

2-oxazolidone derivatives, the cyclization of the following homologs of the N-carbalkoxy-β-haloethylamines was studied:

N-Carbobenzoxy-β-chloropropylamine (III, R_2 = H, R_3 = CH_3, R = $CH_2C_6H_5$, X = Cl).

N-Carbobutoxy-β-chloro-*tert*-butylamine (V).

N-Carbethoxy-β,γ-dichloropropylamine (III, R_2 = H, R_3 = CH_2Cl, R = C_2H_5, X = Cl).

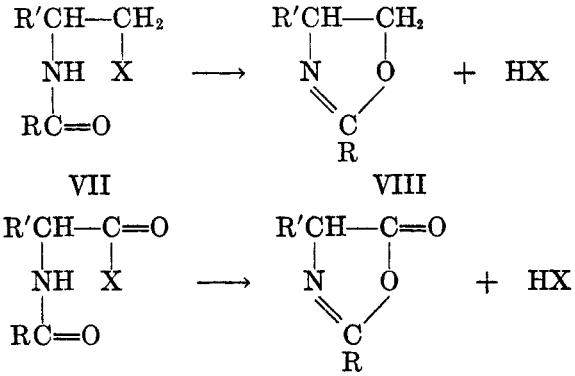
N-Carbobutoxy-β,γ-dibromopropylamine (III, R_2 = H, R_3 = CH_2Br, R = C_4H_9, X = Br).

N-Carbobenzoxy-β,γ-dibromopropylamine (III, R_2 = H, R_3 = CH_2Br, R = $CH_2C_6H_5$, X = Br).

The first substance was obtained by coupling β-chloropropylamine with benzyl chlorocarbonate; the second by the action of thionyl chloride on N-carbobutoxy-β-hydroxy-*tert*-butyl amine; the other three by addition of halogen (chlorine or bromine) to suitable N-carbalkoxy derivatives of allylamine. The first two substances at 160–180° split off benzyl chloride and butyl chloride, respectively, and gave 5-methyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_3) and 4,4-dimethyl-2-oxazolidone (VI). N-Carbethoxy-β,γ-dichloropropylamine (III, R_2 = H, R_3 = CH_2Cl, R = C_2H_5, X = Cl), decomposed to ethyl chloride and 5-chloromethyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_2Cl) previously prepared

by Thomsen (4) and Johnson and Guest (5) in a different manner. It is reasonable to assume that the bromo-compound $C_4H_6BrNO_2$ obtained from the corresponding dibromo-derivatives (with evolution of butyl bromide and benzyl bromide, respectively) is the analogous, but hitherto unknown 5-bromomethyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_2Br).

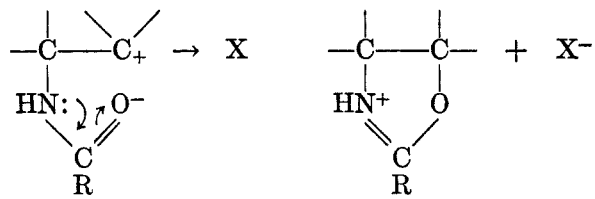
A comparison of the cyclization of these N-carbalkoxy-β-haloalkylamines (III) with that of N-acyl-β-haloalkylamines (VII) (6) shows that the former are converted into 2-oxazolidone derivatives (IV) with elimination of alkyl halides, the latter into 2-oxazolines (VIII) with liberation of hydrogen halides. An analogous difference has been observed in the case of N-carbalkoxy-α-amino acid chlorides (I) and N-acyl-α-amino acid chlorides (IX) (7, 8): the former decompose into alkyl chlorides and 2,5-oxazolidinediones (11), the latter into azlactones (X) (keto-oxazolines) and hydrogen chloride.



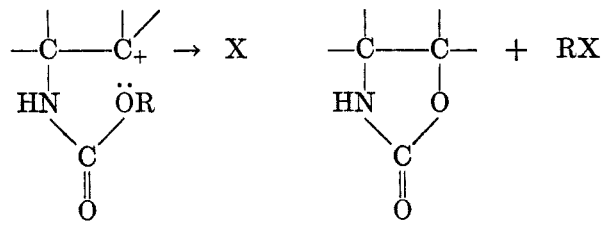
VII VIII

IX X

(a)



(b)



Schemes (a) and (b) may explain this difference in the mode of cyclization of the N-acyl and N-carbalkoxy-β-haloalkylamines. In scheme (a) it is assumed that ring closure of N-acyl-β-haloalkylamines is caused by the interaction between the electrophilic halogen-bearing carbon and the nucleophilic carbonyl-oxygen; the cyclization is accompanied by halogen anion dissociation. A mechanism

similar to (a) has been suggested by Carter (8) for azlactone hydrohalides formation from acyl-α-amino acid chlorides.

In the urethan group of carbalkoxy-β-haloalkylamines [scheme (b)] two nucleophilic oxygens (a carbonyl and an alkoxyl-oxygen) which may react with the electrophilic halogen-bearing carbon are available. A reaction between the carbonyl oxygen and the electrophilic carbon should lead by analogy with the reaction given in scheme (a) to the formation of 2-alkoxy-2-oxazoline hydrohalide. As it has been found experimentally that carbalkoxy-β-haloalkylamines are transformed into 2-oxazolidones with alkyl halide evolution, a reaction between the alkoxyl oxygen and the electrophilic carbon seems to be more plausible. The findings of Gustus, Stevens, and others (9) that acyl halides react with ethers to give esters and alkyl halides suggest that the alkoxyl oxygen of the urethan groups resembles in its nucleophilic character an ethereal oxygen.

The positive character of the halogen-bearing carbon atom is greatly enhanced in the N-acyl- and N-carbalkoxy-α-amino acid chlorides; they undergo therefore, cyclization already at relatively low temperatures (7, 8), but without change in the type of reaction. The greater ease of cyclization of the N-carbobenzoxy-compounds may be due to the pronounced ionization tendency of the benzyl group.

EXPERIMENTAL

β-Chloroethylamine hydrochloride. This amine was prepared from ethanolamine hydrochloride and thionyl chloride according to K. Ward (10).

β-Bromethylamine hydrobromide was obtained from ethanolamine and hydrobromic acid (11).

β-Iodoethylamine hydriodide. Ethanolamine (30.5 g; 0.5 mole) was added to ice-cold 50% hydriodic acid (260 g; 1.0 mole) and the mixture heated in an oil-bath at 160–180° for four hours. During this period, 120 ml. of water distilled off. On cooling, the residue solidified to a brown crystalline mass. It was twice recrystallized from an ethanol-ether mixture. Thus, 115 g. (77%) of β-iodoethylamine hydriodide was obtained; m.p. 191–192°. [Gabriel (32) reports m.p. 192–194°].

General procedure for the preparation of N-carbalkoxy-β-haloakylamines. A quantity of 0.1 mole of the β-haloalkylamine was dissolved in 50 ml. of 2 *N* sodium hydroxide solution. To the ice-cold solution, 0.1 mole of the alkyl chlorocarbonate and 25 ml. of 4 *N* sodium hydroxide solution were added simultaneously with stirring over a period of half an hour, and the stirring was continued for about 20 minutes. The N-carbalkoxy-β-haloalkylamine which separated (as an oil or as a solid) was extracted with ether. After drying with sodium sulfate, the ether was removed *in vacuo* and the residue distilled *in vacuo* or recrystallized from petroleum ether. The properties of the products are recorded in Table I. All these substances dissolve in organic solvents, but not in water.

Preparation of 2-oxazolidone from N-carbalkoxy-β-haloethylamines. Each of the N-carbalkoxy-β-haloethylamines listed in Table I was heated in an oil-bath and the lowest temperature at which liberation of the corresponding alkyl halide occurred was recorded. The alkyl halide formed was collected in a suitably cooled receiver and identified by its boiling point and specific gravity. At the end of the reaction the product, which solidified on cooling, was recrystallized from benzene. The yield of 2-oxazolidone (m.p. 90°) (2, 3) was practically quantitative.

Anal. Calc'd for $C_3H_5NO_2$: N, 16.1. Found: N, 16.0.

Cyclization experiments in solution. In preliminary experiments, it was observed that 2-oxazolidone may be obtained in practically quantitative yield also by refluxing octanol

solutions of the following N-carbalkoxy-β-haloethylamines: *N*-carbomethoxy-β-chloroethylamine, N-carbomethoxy-β-bromethylamine, and N-carbomethoxy-β-iodoethylamine. The 2-oxazolidone thus formed was precipitated from its solution by addition of petroleum ether.

N-Carbobenzoxy-N-phenyl-β-chloroethylamine. N-Phenyl-β-chloroethylamine hydrochloride was prepared from N-phenylethanolamine according to Jones (13) and condensed with benzyl chlorocarbonate. The product was an oil and could not be distilled without decomposition; however, the analysis was reasonably satisfactory.

Anal. Calc'd for $C_{16}H_{16}ClNO_2$: N, 4.8; Cl, 12.2. Found: N, 5.2; Cl, 11.9.

3-Phenyl-2-oxazolidone was prepared from the preceding substance at 165–175° under 20 mm. pressure. Benzyl chloride was evolved, and an oily residue remained which solidified upon cooling. After recrystallization from a mixture of benzene and petroleum ether, the product showed the physical properties ascribed to 3-phenyl-2-oxazolidone by Homeyer (3). Yield, 95%.

Anal. Calc'd for $C_9H_9NO_2$: N, 8.6. Found: N, 8.6.

N-Carbobenzoxy-β-chloropropylamine (III, R_2 = H, R_3 = CH_3, R = $CH_2C_6H_5$, X = Cl). β-Chloropropyl amine hydrochloride was prepared from isopropanolamine according to Jones (13). It was condensed with benzyl chlorocarbonate in the usual way. After extraction with ether and removal of the solvent *in vacuo*, an oily residue was obtained which distilled at 149–151°/5 mm. Yield, 75%. Properties: d_4^{25} 1.131; n_D^{25} 1.5202.

Anal. Calc'd for $C_{11}H_{14}ClNO_2$: Cl, 15.6; N, 6.2.
Found: Cl, 15.1; N, 6.3.

5-Methyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_3). The preceding substance was heated at 170–180° and 20 mm. Evolution of benzyl chloride ceased after one hour. The liquid residue distilled at 136–137°/5 mm. Analysis confirmed the structure of the product as 5-methyl-2-oxazolidone; yield, 90%. Properties: d_4^{25} 1.168; n_D^{25} 1.4648.

Anal. Calc'd for $C_4H_7NO_2$: N, 13.9. Found: N, 13.6.

N-Carbobutoxy-β-hydroxy-tert-butylamine was prepared with butyl chlorocarbonate in the usual way. No attempt was made to purify the oily product; yield, 90%.

Anal. Calc'd for $C_9H_{19}NO_3$: N, 7.4. Found: N, 7.2.

4,4-Dimethyl-2-oxazolidone (VI). In the course of 20 minutes, 30 g. of thionyl chloride was added at room temperature to 36 g. of N-carbobutoxy-β-hydroxy-*tert*-butylamine (14). The mixture was refluxed for a few minutes on the water-bath and the excess thionyl chloride removed *in vacuo* (60°). Distillation at 10 mm. was accompanied by vigorous evolution of gas and gave a small head fraction at 127–130° and the desired product at 152–154° (16 g.). It solidified at room temperature and was recrystallized from benzene-petroleum ether mixture.

Anal. Calc'd for $C_5H_9NO_2$: N, 12.2. Found: N, 12.2.

N-Carbethoxyallylamine was prepared according to Bergmann (15); b.p. 92°/15 mm.; yield, 93%.

N-Carbethoxy-β,γ-dichloropropylamine (III, R_2 = H, R_3 = CH_2Cl, R = C_2H_5, X = Cl). An ice-cold solution of 120 g of *N*-carbethoxy-allylamine in 150 ml. of carbon tetrachloride was saturated with gaseous chlorine. The solvent was removed *in vacuo* and the residue distilled; B.p. 166°/32 mm.; d_4^{25} 1.266; n_D^{25} 1.4755. Yield, 85%.

Anal. Calc'd for $C_6H_{11}Cl_2NO_2$: N, 7.0; Cl, 35.5.
Found: N, 7.2; Cl, 35.5.

5-Chloromethyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_2Cl). The cyclization of N-carbethoxy-β,γ-dichloropropylamine set in at 185–195°; the ethyl chloride formed was collected under ice-water and identified by its boiling point and density. The residue was recrystallized from water (charcoal) and showed the m.p. (105–106°) and other properties indicated by Thomsen (4) and Johnson and Guest (5). Yield, 80%.

Anal. Calc'd for $C_4H_6ClNO_2$: N, 10.3; Cl, 26.2.
Found: N, 10.3; Cl, 25.9.

N-Carbobutoxyallylamine. This urethan was synthesized by condensing 30 g. (0.5 mole)

of allylamine with 70 g. (0.5 mole) of butyl chlorocarbonate. It distilled without decomposition at 120–122°/22 mm.; d_4^{25} 0.955; n_D^{25} 1.4425; yield 94%.

Anal. Calc'd for $C_8H_{15}NO_2$: N, 8.9. Found: N, 8.8.

N-Carbobutoxy-β,γ-dibromopropylamine (III, R_2 = H, R_3 = CH_2Br, R = C_4H_9, X = Br). A solution of 75 g. of bromine in 50 ml. of chloroform was added to an ice-cold solution of 73 g. of N-carbobutoxy-allylamine in 100 ml. of the same solvent. The chloroform was removed *in vacuo* and the solid residue recrystallized from aqueous alcohol; m.p. 56°; yield, 82%.

Anal. Calc'd for $C_8H_{15}Br_2NO_2$: N, 4.4; Br, 50.4.
Found: N, 4.5; Br, 50.3.

5-Bromoethyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_2Br). The cyclization of N-carbobutoxy-β,γ-dibromopropylamine took place at 170–180°; butyl bromide distilled off. The solid product was recrystallized from benzene; m.p. 107°, yield, 70%.

Anal. Calc'd for $C_4H_6BrNO_2$: N, 7.8; Br, 44.4.
Found: N, 7.9; Br, 44.7.

N-Carbobenzoxy-allylamine. Allylamine (12 g.) was condensed with benzyl chlorocarbonate (42 g.). A yield of 90% was obtained.

Anal. Calc'd for $C_{11}H_{13}NO_2$: N, 7.3. Found: N, 7.6.

N-Carbobenzoxy-β,γ-dibromopropylamine (III, R_2 = H, R_3 = CH_2Br, R = $CH_2C_6H_5$, X = Br). This was prepared by bromination of the foregoing product and was recrystallized twice from aqueous alcohol. M.p. 86–87°; yield, 85%.

Anal. Calc'd for $C_{11}H_{13}Br_2NO_2$: N, 4.0; Br, 45.5.
Found: N, 4.3; Br. 45.0.

The product cyclized at 125–145° and 20 mm. with evolution of benzyl bromide. The solid residue which was recrystallized from benzene and then had m.p. 107°, was identical with the product obtained from N-carbobutoxy-β,γ-dibromopropylamine.

SUMMARY

A series of N-carbalkoxy-β-haloalkylamines has been prepared. It has been shown that at elevated temperatures, these compounds undergo cyclization with elimination of alkyl halides, yielding 2-oxazolidones.

A reaction mechanism has been suggested to explain the different mode of cyclization of N-carbalkoxy-β-haloalkylamines and N-acyl-β-haloalkylamines, a difference which is also valid for the N-carbalkoxy- and N-acyl derivatives of α-amino-acids.

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