[Contribution from Defence Research Chemical Laboratories, Canada]

CYCLIZATIONS OF β-CHLOROETHYL SUBSTITUTED AMMONOCARBONIC ACIDS[1]

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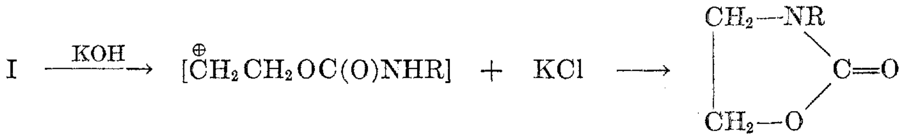
Received June 12, 1951

A consideration of carbamic acid, urea, and guanidine as mono-, di-, and tri-ammonocarbonic acids indicated that the cyclizations of their β-chloroethyl derivatives might have some properties in common, so compounds of types (I), (II), and (III) were re-examined.

$$\underset{\text{I}}{ClCH_2CH_2OC(O)NHR} \qquad \underset{\text{II}}{ClCH_2CH_2NHC(O)NHR}$$

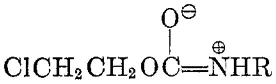
$$\underset{\text{III}}{ClCH_2CH_2NHC(NH)NHNO_2}$$

In 1885, Nemirowsky (6) prepared N-phenyl β-chloroethyl carbamate (I, R = phenyl) from β-chloroethyl chlorocarbonate and aniline. He observed this carbamate to cyclize in alkaline solution to 3-phenyl-2-oxazolidone. This reaction was employed later by Otto (8) to prepare 3-α-napthyl- and 3-β-napthyl-2-oxazolidones. The new carbamates (I) and 2-oxazolidones prepared by these procedures are given in Tables I and II respectively. The cyclization of carbamates to 2-oxazolidones is explained by the participation of a carbonium ion intermediate.



IV V

The reaction then proceeds through IV to V. N-Substituted β-chloroethyl carbamates (I) show little or no tendency to ionize in aqueous solutions, possibly due to lack of resonance stabilization of the ionic state (VI). In agreement with this, it was found that these compounds were stable to prolonged periods of



$$ClCH_2CH_2O\overset{O^{\ominus}}{\overset{|}{C}}{=}\overset{\oplus}{N}HR$$

VI

refluxing in water. Likewise refluxing for two hours in 1-octanol failed to convert these compounds to the desired 2-arylimino-1,3-dioxolanes.

N-β-chloroethyl-N′-benzylurea (II, R = benzyl) and N-β-chloroethyl-N′-phenylurea (II, R = phenyl) were prepared as described by Menne (7) and Englemann (1). Gabriel and Stelzner (2) in 1895 had shown that N-β-chloro-

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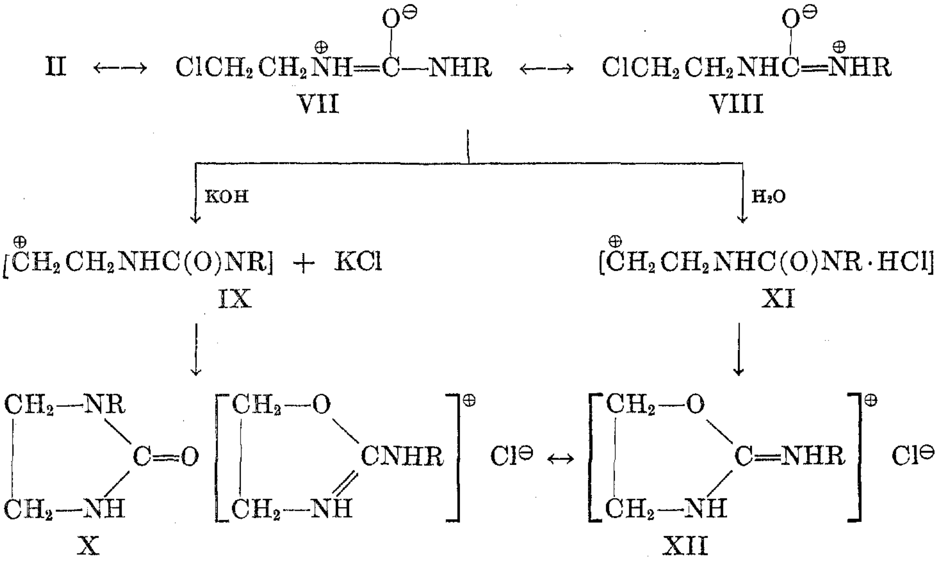
[1] Issued as DRCL Report No. 65.

ethyl-N′-phenylurea cyclizes in alkaline solution to give 1-phenyl-2-imidazolidone (XII, R = phenyl) and in water to give 2-phenylamino-2-oxazoline (XII, R = phenyl). These cyclizations are considered to involve the participation of carbonium ion intermediates IX and XI. The ionic state of an N-β-chloroethyl-N′-substituted urea possesses resonance stabilization by the participation of the electronic structures VII and VIII. Therefore the first mole-equivalent of alkali would be expected to be used in salt formation. This was found indeed to be a fact. When a little more than one mole-equivalent of alkali was added to N-β-chloroethyl-N′-benzylurea and the solution refluxed for three minutes, a clear solution was formed. This solution on cooling to room temperature or below remained clear. As soon as it was acidified, N-β-chloroethyl-N′-benzylurea was precipitated. On the other hand refluxing N-aryl β-chloroethyl carbamates with one-mole equivalent of alkali in aqueous ethanol for three minutes is sufficient to effect their cyclization to 3-aryl-2-oxazolidones.



Further evidence for N-β-chloroethyl-N′-substituted ureas (II) assuming the ionic state in water before cyclizing is their failure to cyclize to any extent in refluxing 1-pentanol. These rearrangements in water are initiated by the charge separation in the molecule. The + group approaches the chlorine[2] after which

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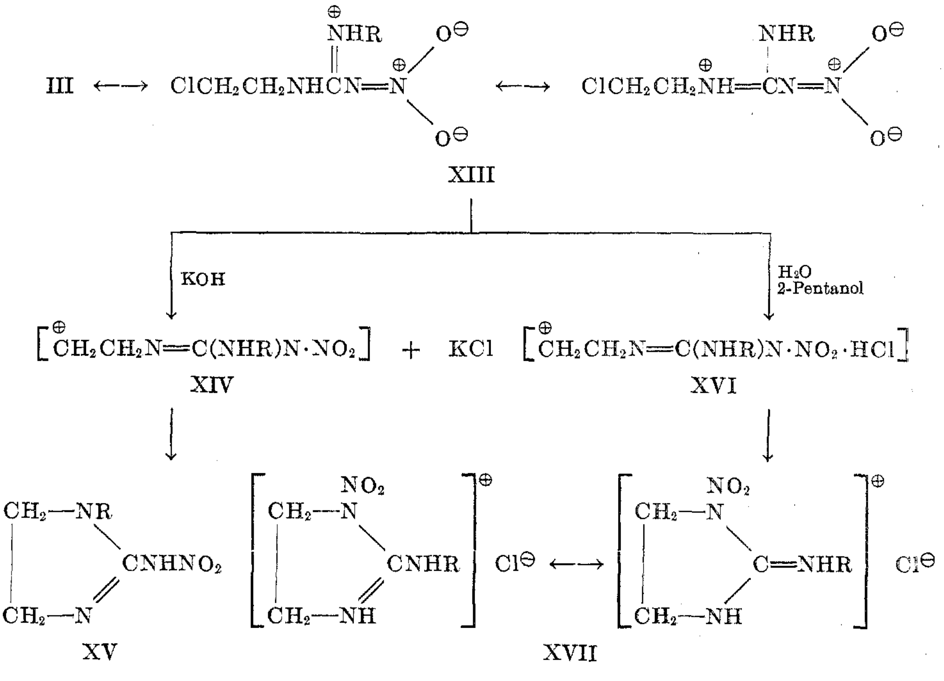
[2] If structural models of N-β-chloroethyl-N′-substituted ureas and N-β-chloroethyl-N′-nitroguanidine are made, it will be observed that the molecule is free to rotate in a manner to bring the $=\overset{\oplus}{N}HR$ group next to the chloro group. Thus the CH_2Cl bond is weakened due to attraction between the $=\overset{\oplus}{N}HR$ group and the chlorine. The electrons of the CH_2Cl bond move closer to the chlorine under the influence of the $=\overset{\oplus}{N}HR$ group. This results in an increase of negative charge on the chlorine and an increase of attraction between the chlorine and the $=\overset{\oplus}{N}HR$ group. The final result is the rearrangement to the hydrochloride salt of the cyclic product.

hydrogen chloride separates leaving a carbonium ion. The carbon carrying the sextet of electrons then combines with the available electron pair of the oxygen to give the 2-amino-2-oxazolinium chlorides (XII).

Recently (5) it has been shown by ultraviolet spectra studies that nitroguanidine and certain of its derivatives exist as a resonance hybrid of structures III and XIII. The energy of activation required to convert the hybrid into the electronic structures XIII would appear then to be less than that required for a similar conversion in the urea series. Thus on the basis of the above arguments, N-β-chloroethyl-N′-nitroguanidine (III) might be expected to cyclize in non-aqueous media or alone by supplying the conditions for the formation of a carbonium ion intermediate. It has been shown (4) that N-β-chloroethyl-N′-nitroguanidine (III) rearranges on heating in water, 2-pentanol, or alone, to 1-nitro-2-aminoimidazolinium chloride (XVII). Finally in alkaline solutions N-β-chloroethyl-N′-nitroguanidine is converted to 2-nitramino-2-imidazoline (XV, R = H) (3).



EXPERIMENTAL[3]

β-Chloroethyl chlorocarbonate. β-Chloroethyl chlorocarbonate was prepared by the following modification of the procedure described by Nemirowsky (6). Phosgene (248 g., 2.49 moles) was condensed into an 18-8 stainless steel bomb of 1 liter capacity and cooled to −20°. Ethylene chlorohydrin (190 g., 2.36 moles) was poured into the bomb and it was

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[3] All melting points were determined on a Kofler block and are corrected. All boiling points are uncorrected. The microanalyses were performed by C. W. Beazley, Skokie, Illinois.

sealed with a plug and valve. The cooling bath was removed and the bomb allowed to stand at room temperature for 24 hours with occasional shaking. Then the valve was opened carefully to bleed-off the compressed hydrogen chloride, and the contents transferred to a flask. The crude product was a reddish-brown liquid containing a fine suspension of green solid. The solid was considered to be due to the reaction of reagents with metals present in the bomb. After the green solid was removed by filtration, the filtrate was dissolved in ether (500 cc.). This ether solution was washed with 10% aqueous potassium carbonate solution (3 × 100 cc.), water (3 × 100 cc.), and dried over sodium sulfate. The ether was flashed-off and the water-white residue was distilled through a 12″ Vigreux column using a 5:1 reflux ratio. The purified yield was 171 g. (51%), bp_{756} 154.5–156.5°, $n_D^{24.4}$ 1.4438.

TABLE I

N-SUBSTITUTED β-CHLOROETHYL CARBAMATES

SUBSTITUENT	M.P., °C.	EMPIRICAL FORMULA	CARBON		HYDROGEN		X	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
Benzyl	48–49	$C_{10}H_{12}ClNO_2$	56.21	56.28	5.62	5.80	16.60[d]	16.83
α-Naphthyl[a]	100.8–101.5	$C_{13}H_{12}ClNO_2$	62.53	62.50	4.81	4.75	14.21[d]	14.20
o-Tolyl	45–46	$C_{10}H_{12}ClNO_2$	56.21	56.50	5.62	5.87	16.60[d]	16.58
m-Tolyl	—[b]	$C_{10}H_{12}ClNO_2$	56.21	56.45	5.62	5.84	16.60[d]	16.40
p-Tolyl	62.5–63.5	$C_{10}H_{12}ClNO_2$	56.21	55.99	5.62	5.70	16.60[d]	16.73
m-Anisyl	37–38[c]	$C_{10}H_{12}ClNO_3$	52.30	52.15	5.23	5.13	15.44[d]	15.40
p-Anisyl	87.3–88.3	$C_{10}H_{12}ClNO_3$	52.30	52.34	5.23	5.42	15.44[d]	15.80
p-Phenetyl	93–94	$C_{11}H_{14}ClNO_3$	54.25	54.50	5.75	5.83	14.56[d]	14.74
o-Bromophenyl	53.8–54.5	$C_9H_9BrClNO_2$	38.80	38.84	3.23	3.37	5.02[e]	5.00
p-Bromophenyl	89–89.3	$C_9H_9BrClNO_2$	38.80	39.00	3.23	3.53	5.02[e]	5.10
m-Chlorophenyl	47–48	$C_9H_9Cl_2NO_2$	46.18	45.88	3.84	3.99	30.30[d]	30.24
p-Chlorophenyl	68.6–69.3	$C_9H_9Cl_2NO_2$	46.18	46.28	3.84	3.92	30.30[d]	30.30

[a] Previously reported m.p. 100–101° (7). [b] Liquid, b.p. 125–128° at 4×10^{-4} mm.; n_D^{24} 1.5489. [c] Remained liquid until distilled, b.p. 144–148° at 1.6×10^{-3} mm.; $n_D^{24.4}$ 1.5533. [d] Chlorine. [e] Nitrogen.

N-Aryl β-chloroethyl carbamates. The N-aryl β-chloroethyl carbamates were prepared according to the procedure employed by Otto (8) for preparing N-α-naphthyl β-chloroethyl carbamate. All the compounds were obtained in practically quantitative yields and were purified by crystallization from 95% ethanol. Their properties are given in Table I.

3-Substituted-2-oxazolidones. Cyclization of the β-chloroethyl N-substituted carbamates to 3-substituted-2-oxazolidones was effected by a modification of the method described by Otto (8). To the β-chloroethyl N-substituted carbamate was added a solution of 1.2 mole-equivalents of potassium hydroxide in 70% ethanol. During the portionwise addition of the carbamate, the reaction temperature was held below 40° by external cooling. Then the reaction mixture was boiled for a few minutes, allowed to cool to room temperature, and 5 vols. of water was added. The solid products were removed, washed with water, and dried. They were purified by crystallization from 95% ethanol. When oils were obtained, they were thrown out of solution by adding 10 vols. of water to the reaction mixture. The oils were removed in a separatory-funnel and distilled *in vacuo*. The yields and properties of the 3-substituted-2-oxazolidones prepared in this manner are tabulated in Table II.

Benzyl isocyanate. ($b.p._{17}$ 103°) was prepared in 45% yield as previously (3) described.

N-β-Chloroethyl-N′-benzylurea. (m.p. 105–106°) was prepared in 90% yield as previously described (3).

Cyclization of N-β-chloroethyl-N′-benzylurea. The cyclization of N-β-chloroethyl-N′-benzylurea in boiling water has been reported (3). An attempt was made also to cyclize the urea in 1-propanol. The urea (2 g.) was refluxed in 8 cc. of 1-propanol for two hours. After the solution had cooled to room temperature it was diluted with 10 vols. of petroleum ether (b.p. 30–60°) and extracted with water. The aqueous solution on addition of a saturated aqueous picric acid solution gave a mixture of picrates, yield 170 mg. This mixture was separated by crystallization from water into 50 mg. of benzylamine picrate (m.p. 201–202°) and 50 mg. of 2-benzylamino-2-oxazolinium picrate (m.p. 185–186°). These picrates were identified by mixture melting point determinations with authentic samples. The original petroleum ether fraction on evaporation gave an oil, (yield 1.6 g.) This oil gave crystals of the original N-β-chloroethyl-N′-benzylurea, yield 0.9 g.

TABLE II

3-SUBSTITUTED-2-OXAZOLIDONES

SUBSTITUENT	YIELD,[b] %	M.P., °C.	EMPIRICAL FORMULA	CARBON		HYDROGEN		X	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
Benzyl	96.3	79.5–80.0	$C_{10}H_{11}NO_2$	67.80	67.75	6.21	6.32	7.91[f]	8.05
α-Naphthyl[a]	86.0	129.5–130	$C_{13}H_{11}NO_2$	73.21	73.44	5.16	5.28	6.57[f]	6.41
o-Tolyl	55.0	—[c]	$C_{10}H_{11}NO_2$	67.80	67.89	6.21	6.18	7.91[f]	8.03
m-Tolyl	78.4	94.3–95	$C_{10}H_{11}NO_2$	67.80	67.96	6.21	6.37	7.91[f]	8.00
p-Tolyl	64.8	90.5–91	$C_{10}H_{11}NO_2$	67.80	67.96	6.21	6.28	7.91[f]	7.75
m-Anisyl	72.0	77–77.6	$C_{10}H_{11}NO_3$	62.17	62.05	5.71	5.80	7.25[f]	7.12
p-Anisyl	93.0	109–110	$C_{10}H_{11}NO_3$	62.17	62.33	5.71	5.83	7.25[f]	7.09
p-Phenetyl	92.0	94–95	$C_{11}H_{13}NO_3$	63.78	64.00	6.28	6.47	6.76[f]	6.53
o-Bromophenyl	76.0	—[d]	$C_9H_8BrNO_2$	44.60	44.71	3.30	3.38	33.02[g]	33.46
p-Bromophenyl	96.0	139.8–140.6	$C_9H_8BrNO_2$	44.60	44.80	3.30	3.38	33.02[g]	33.26
m-Chlorophenyl	76.3	53–53.5	$C_9H_8ClNO_2$	54.70	54.89	4.05	4.20	17.96[e]	18.06
p-Chlorophenyl	93.3	120.9–121.5	$C_9H_8ClNO_2$	54.70	54.51	4.05	4.03	17.96[e]	18.06

[a] Previously reported m.p. 125° (7). [b] Refined yields reported. [c] Liquid, b.p. 125–130° at 1 × 10^{-3} mm.; $n_D^{24.3}$ 1.5495. [d] Liquid, b.p. 142–147° at 1 × 10^{-2} mm.; $n_D^{24.5}$ 1.5841. [e] Chlorine. [f] Nitrogen. [g] Bromine.

Attempted cyclization of N-p-anisyl β-chloroethyl carbamate to 2-p-anisylimino-1,3-dioxolanes. β-Chloroethyl N-p-anisyl carbamate (1.0 g., 0.0043 mole) was refluxed for two hours in 20 cc. of 1-octanol. After most of the 1-octanol was removed *in vacuo*, the solid residue (m.p. 87–88°) was removed by filtration, yield 90%. This material was identified as the original N-p-anisyl β-chloroethyl carbamate by a mixture melting point determination. A similar experiment using water in place of 1-octanol gave an 88% recovery of the original material.

1-Phenyl-2-imidazolidone. N-β-Chloroethyl-N′-phenylurea (m.p. 123–123.5°) was prepared in 84.1% yield by the addition of phenyl isocyanate to β-chloroethylamine (9) in benzene. This procedure is similar to methods described by Menne (7) and Englemann (1). For cyclization 3 g. (0.015 mole) of the urea was added to a cold solution of 1.68 g. (0.03 mole) of potassium hydroxide in 15 cc. of 70% aqueous ethanol. This solution was refluxed for five minutes, then cooled to room temperature, and drowned with 5 vols. of water. After the resulting mixture was cooled to 4°, the crystals were removed and washed with water. The melting point was 162–163°, yield 2.16 g. (86.8%). Previously reported m.p. 160–161° (2).

SUMMARY

The relationship of the cyclizations of β-chloroethyl substituted carbamates, ureas, and nitroguanidines is discussed. A number of new N-substituted β-chloroethyl carbamates and 3-substituted-2-oxazolidones are described.

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