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OXAZOLINE RING-OPENING

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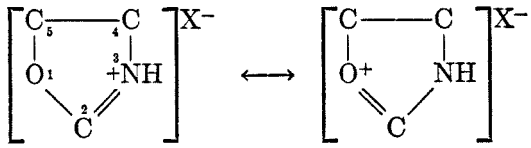
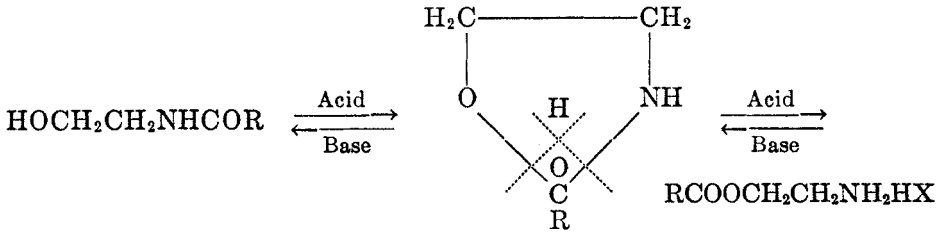
The alkyl- or aryl-substituted oxazoline ring is normally opened between positions 2 and 3 by acid hydrolysis as well as by the action of acid anhydrides followed by water (1). Hydrogen sulfide opens the ring between positions 1 and 2 (2) and between positions 1 and 5 (3), and alkaline hydrolysis also involves either or both of these positions (4, 2). The rearrangement of hydrohalide salts causes rupture between positions 1 and 5 (2, 5). The present report deals with the reactions of organic acids and acid chlorides and attempts to correlate these findings with the foregoing observations.

Goldberg and Kelly have recently suggested that the place of opening may be influenced by the predominant form of an oxonium-ammonium ion equilibrium as well as by external factors (2). This resonance concept provides a reasonable explanation for the vulnerability of the ionic form to nucleophilic attack at positions 2 and 5 which are analogous to the positions adjacent to electropositive oxygen and nitrogen centers in the benzopyrrylium (6) and dihydroisoquinoline systems (7) which also behave as carbonium ions.

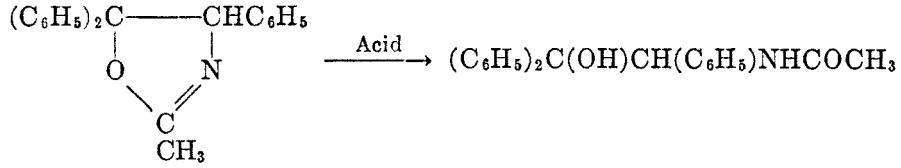


This formulation easily leads to a rational mechanism for the reactions mentioned above. The salts are stable as long as the anion is below the energy state necessary to add to position 5. Unlike the reversible addition to position 2, addition at 5 breaks the ring to give the stable chloroethylamide. However, a hydroxyl or sulfhydryl group at 2 can lose a proton to either the oxygen or nitrogen with ring opening between 1 and 2 or between 2 and 3. This hypothetical hydroxyoxazolidine was first proposed to explain the O → N transfer of an acyl group in a β-aminoethyl ester (8). The subsequent rearrangement to the

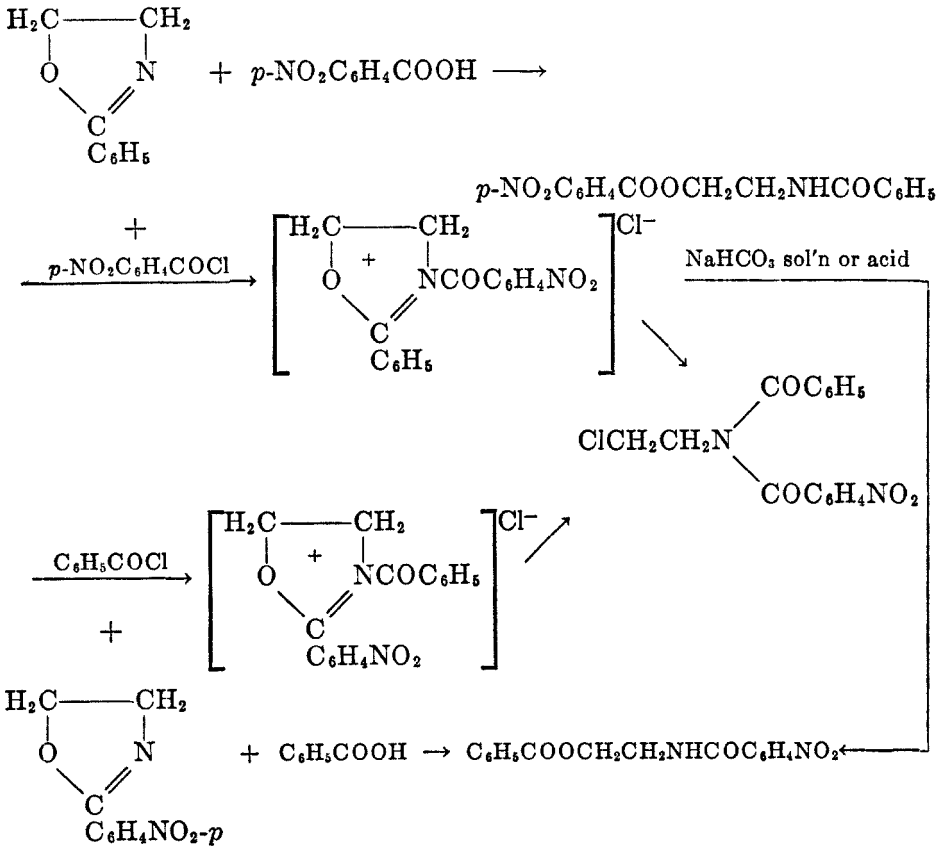


amide involves transfer of a proton to oxygen and this might take place with or without intercession of solvent, but that such is not necessary was demonstrated by conducting one such isomerization in anhydrous triethylamine.

Since the solvent need not participate in this proton transfer it is inferred that the electronic state of the unstable hydroxyoxazolidine ring induced by substituents and solvent is the primary determinant of direction of ring opening. Acid hydrolysis of the oxazoline ring may involve this same rearrangement but in the reverse direction. However, at least one example of anomalous behavior on acid hydrolysis appears in the literature (9). 2-Methyl-4,5,5-triphenyloxazoline yielded 2-acetamido-1,1,2-triphenylethanol.



In this case the phenyl groups at position 5 could have stabilized the charge on the carbonium ion at this point (10) so that hydroxylation occurred here rather than at position 2. That there may be competition between these centers is indicated by the results of two experiments in which the sulfhydryl ion in alkaline medium was the hydrolytic agent. In the first case 2-phenyloxazoline



yielded the thioamide (2-mercaptoöxazolidine intermediate) (2), and in the other 2-phenyl-4-carboxymethyloxazoline gave the cysteine derivative in very small yield (3). Probably the thioamide was here also the main product. Hydrolysis of the oxazoline ring in alkaline medium could similarly take place by two mechanisms.

Results of the action of acid chlorides are shown in the chart and involve the same type rearrangement as the hydrohalide salts with the exception that whereas the acid is removed in alkaline solution, the N-acyloxazoline salt undergoes hydroxylic ring-opening between positions 2 and 3 as was reported for acid anhydrides and water (1). The salts probably have only a transient existence and were not isolated. Again assuming the primary formation of a 2-hydroxyoxazolidine, it would appear that ring opening in this manner in alkaline solution is at variance with the other evidence cited above, but it may be significant that both the acetylated nitrogen and the free nitrogen in acid solution have lost basicity and this factor rather than the *p*H of the solvent may determine direction of ring opening.

Thioacids react in an unexceptional manner to give thiol esters and a synthesis of cystine using this method has been described (3). Other examples are given in the experimental section as are structure proofs based on alkaline hydrolysis of the esters.

EXPERIMENTAL

2-(p-Nitrophenyl)oxazoline. Ethanolamine reacted with *p*-nitrobenzoylchloride in sodium bicarbonate solution to give N-(β-hydroxyethyl)-*p*-nitrobenzamide, m.p. 130–132°. The previously reported value is 132–133° (11). By the action of thionyl chloride this was converted to a crystalline compound, probably the sulfinyl chloride, which rearranged in dioxane to give the oxazoline salt. This salt was decomposed with sodium carbonate solution to give the oxazoline. Purified from alchol it melted at 178–179°. The literature gives the melting point 178–178.5° (12).

N-(β-Chloroethyl)-N-benzoyl-p-nitrobenzamide. A mixture of 0.83 g. of benzoyl chloride and 0.113 g. of 2-(*p*-nitrophenyl)oxazoline was heated on the steam-bath for 3 min. The product was recrystallized from alcohol; wt. 0.152 g. (77%), m.p. 129–130.5°.

Anal. Calc'd for $C_{16}H_{13}ClN_2O_4$: C, 57.75; H, 3,93; Cl, 10.66.
Found: C, 57.87; H, 3.92; Cl, 10.62.

This compound was also obtained by the addition of *p*-nitrobenzoyl chloride to 2-phenyloxazoline. The identities were checked by a mixture melting point.

β-Benzamidoethyl p-nitrobenzoate. A mixture of 0.55 g. of *p*-nitrobenzoic acid and 0.45 g. of 2-phenyloxazoline was heated on the steam-bath for 50 min. The crystalline product was triturated with sodium bicarbonate solution to remove excess acid, then recrystallized from alcohol, wt. 0.55 g., m.p. 143–148°. After purification it melted at 148.5–150°.

Anal. Calc'd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49.
Found: C, 61.04; H, 4.58.

This compound readily dissolved in 2 *N* NaOH. Acidification and separation of the hydrolysis products gave an 86% recovery of *p*-nitrobenzoic acid and a 93% recovery of β-hydroxyethylbenzamide.

β-(p-Nitrobenzamido)ethyl benzoate. A mixture of 0.10 g. of 2-(*p*-nitrophenyl)oxazoline and 0.12 g. of benzoic acid was heated for 15 min. at 130°. The melt crystallized on cooling.

It was triturated with acid and sodium bicarbonate solutions and then purified from alcohol. Weight, 0.09 g.; m.p. 145–146° which was lowered on admixture with the above isomer.

Anal. Calc'd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49.
Found: C, 61.27; H, 4.60.

To a chilled suspension of 0.197 g. of 2-phenyloxazoline, 0.4 g. of sodium bicarbonate, 1 ml. of water, and 0.3 ml. of dioxane was added 0.5 g. of *p*-nitrobenzoyl chloride. After stirring for 20 min. in the ice-bath, during which time carbon dioxide was evolved, the suspension was diluted with water and the solid product recovered, extracted with sodium bicarbonate solution, and purified from alcohol; weight 0.42 g. (58%), m.p. 144–146°. A mixture melting point showed it to be identical with the above described compound.

The same compound was recovered when sodium bicarbonate was omitted, but the yield was lower probably due to removal of oxazoline as the hydrochloride. In the presence of sodium hydroxide hydrolysis of the acid chloride took precedence over the condensation.

β-Benzamidoethyl thiolbenzoate. Thiobenzoic acid was made by the method of Kym (13). A mixture of 0.181 g. of 2-phenyloxazoline and 0.17 g. of thiobenzoic acid reacted exothermally and the product crystallized on cooling, wt. 0.3 g. (86%). It was purified by adding petroleum ether to an alcohol solution, m.p. 92–93°.

Anal. Calc'd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30.
Found: C, 67.31; H, 5.33.

This compound was hydrolyzed by heating a few minutes in alcoholic sodium hydroxide. After acidification and oxidation with potassium iodide solution the product crystallized. It was washed with sodium carbonate solution and recrystallized from alcohol; m.p. 131–133°. It was identified as *bis*-(β-benzamidoethyl)disulfide by comparison with an authentic sample prepared as follows: ethylenimine prepared according to Wenker (14) was converted to mercaptoethylamine by the method of Mills and Bogert (15). After oxidation to the disulfide by means of iodine, benzoylation yielded the above compound, m.p. 131.5–132.5°. The value 132° has been reported (16).

β-Benzamidoethyl p-chlorothiolbenzoate was similarly made. It was purified from alcohol and melted at 140–141°.

Anal. Calc'd for $C_{16}H_{14}ClNO_2S$: C, 60.09; H, 4.41.
Found: C, 59.99; H, 4.55.

β-(p-Nitrobenzamido)ethyl thiolbenzoate. A mixture of 2-*p*-nitrophenyloxazoline and thiobenzoic acid in equivalent amounts was heated briefly on the steam-bath. The product was obtained in 78% yield after purification from alcohol; m.p. 156–157° with a slight sinter at 152°.

Anal. Calc'd for $C_{16}H_{14}N_2O_4$: C, 58.17; H, 4.27.
Found: C, 57.96; H, 4.50.

2-(3-Chloro-1-amino-n-propyl) p-nitrobenzoate hydrochloride (5), 0.10 g., was suspended in dry (over KOH) triethylamine. On manipulation the solid became oily and in about 5 minutes recrystallized. Excess amine was removed under reduced pressure and excess 3 *N* HCl was added to the solid. The solid was washed with water; weight 0.070 g., m.p. 95–96°. After recrystallization from ethyl acetate-benzene it melted at 102–104° and the melting point was not depressed on mixing it with another sample of *N-(3-chloro-2-hydroxy-n-propyl)-p-nitrobenzamide.*

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SUMMARY

Rather meager observations of oxazoline ring-openings have been rationalized with a carbonium ion structure having a charge distribution between positions 2 and 5. Reactions with organic acids, thioacids, and acid chlorides are reported.

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