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OXAZOLINES

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β-Hydroxyalkylamides have been converted to oxazolines by such agents as heat, sulfuric acid, phosphorus pentoxide, phosphorus pentachloride, and thionyl chloride. Bergmann, *et al.*, developed the use of thionyl chloride but did not take into account the rearrangement of oxazoline hydrochlorides into β-chloroalkylamides (1, 2). This rearrangement is known and has been correlated with the similar degradation of imino-ether hydrochlorides to alkyl chlorides and amides (3, 4). The accidental discovery in this laboratory that the compound described as 2-phenyl-4-carboxymethyloxazoline hydrochloride (1) is methyl α-benzoylamino-β-chloropropionate led to a re-examination of this reaction to see whether ring closure involves the chlorosulfinate or the chloro derivative, the amide group or a derivative thereof, and whether thionyl chloride is necessary as a condensing medium.

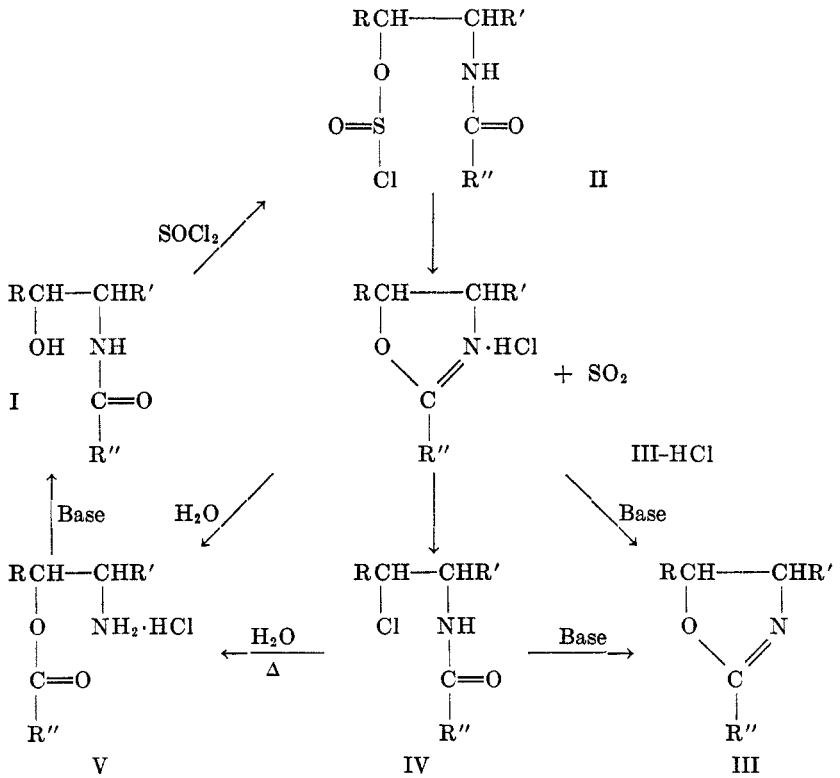
β-Chloroalkylamides seem inert to thionyl chloride and are therefore eliminated as intermediates in the formation of oxazolines. Recovered as end product, the β-chloroalkylamides can arise either from direct replacement of hydroxyl by chlorine or by transformation of the oxazoline salt. Although simple primary and secondary alcohols give stable chlorosulfinates (5), the presence of amide hydrochloride might lead to replacement by chlorine in a manner analogous to the catalytic effect of amine salts (6). But in no case has a β-chloroalkylamide been recovered when the reaction mixture is kept cold, whereas it appears to be the only product when refluxing thionyl chloride is used. That the oxazoline is the intermediate in all but one of the cases cited in the experimental section was shown by isolating either the oxazoline or its hydrolysis product, the β-aminoalkylester hydrochloride. In the exceptional case, the product formed from β-hydroxyethylformamide and thionyl chloride is a crystalline solid showing the combined weight of the reactants. Oxazoline was not proved to be one of its components on decomposition with alkali, but on heating it yielded β-chloroethylformamide as reported by Wenker for the product obtained with thionyl chloride on the steam-bath (7).

Leffler and Adams used refluxing thionyl chloride to get "dihydrochlorides" of amine-substituted oxazolines which were not characterized but were decomposed in sodium hydroxide to yield the oxazolines (8). A repetition of one of the preparations showed that the oxazoline resulted from ring closure of the β-chloroalkylamide rather than from oxazoline salt decomposition.

The chart shows the relationships involved and is known to be valid in its entirety for at least one of the systems examined. The chlorosulfinate (II) was identified by its reaction products. It reverted to the original β-hydroxyalkylamide on hydrolysis and condensed with the latter to give a sulfite ester. The chlorosulfinate expelled sulfur dioxide on heating, to give the oxazoline hydro-

chloride (III-HCl), which rearranged to the amide (IV) on further heating. Thus, thionyl chloride did not participate in oxazoline formation. It is possible that the oxazoline salt is formed in all cases but is not attainable if the energy required to form it is more than that needed in its rearrangement to the β-chloroalkylamide (IV).

The possibility of confusing III-HCl and IV is made evident by their physical and chemical similarity. The melting piont of III-HCl may not be observable as more than a slight sinter as it passes into and melts as IV. Both are transformed into the same compound in aqueous solutions. Hydrolysis of the oxazoline salt may take place more easily than the transformation of IV to V (probably *via* III-HCl), and under alkaline conditions base liberation is more rapid than ring closure of IV to III, but the differences are ones of degree and the mistaken identity in the Bergmann papers (1) seems to be the origin of the idea that oxazoline salts are only slowly hydrolyzed by boiling water (8). Some salts are rapidly hydrolyzed at room temperature, but no example was found in which hydrolysis



took more than two-minutes heating on the steam-bath. Since hydrolysis and formation of the β-haloalkylamide involve anionic attack on positions two and five, a high concentration of halide ion should favor the formation of the β-haloalkylamide. Thus, Gabriel and Heymann (9) obtained a high yield of β-chloroethylbenzamide by the action of hydrochloric acid on 2-phenyloxazoline

hydrochloride, whereas the action of hot water on this salt is primarily one of hydrolysis with the amide as secondary product. Under these conditions the existence of the β-chlorobenzamide is, of course, transitory.

EXPERIMENTAL

PART 1: R = H, R′ = $COOCH_3$ or COOH, R″ = C_6H_5

*Transformation of N-benzoyl-*DL*-serine methyl ester (I) to methyl α-benzoylamino-β-chloropropionate (IV).*[1] The starting material was prepared according to Bergmann and Miekeley (1) and the oily ester or an ethereal solution of the ester treated cold with a 4- to 8-fold excess of thionyl chloride. The crystalline product was a complex salt containing sulfur dioxide in the approximate ratio of 1 mole of sulfur dioxide to 2.1 moles of base. It sintered at about 57°, resolidified and melted at 108–112°. The salt seemed stable cold but at room temperature and more rapidly on warming, it lost sulfur dioxide and also its water solubility to give methyl α-benzoylamino-β-chloropropionate (IV). That the sulfur dioxide was bound alone with hydrogen chloride in a salt and not in the intermediate chlorosulfinate was indicated by the high yield of O-benzoylserine methyl ester hydrochloride (V) on hydrolysis (see below), and by the fact that a mixture of hydrogen chloride and sulfur dioxide bubbled through an ethereal solution of 2-phenyl-4-carboxymethyloxazoline (III) gave a similar salt containing less sulfur dioxide; it decomposed on heating to give sulfur dioxide in a ratio of 1 mole to 3.4 moles of methyl α-benzoylamino-β-chloropropionate (IV).

Methyl α-benzoylamino-β-chloropropionate (IV), m.p. 114–116°, was obtained in 86% yield when the reaction was run at the reflux temperature of ether for one hour. It was purified by adding water to a solution in hot alcohol. Bergmann and Miekeley (1) reported 113–114° as the melting point of 2-phenyl-4-carboxymethyloxazoline hydrochloride, and the value 117° has been given (10).

Anal. Calc'd for $C_{11}H_{12}ClNO_3$: C, 54.67; H, 5.00.
Found: C, 54.62; H, 4.86.

On heating in water this compound gave O-benzoylserine methyl ester hydrochloride (V) in 79% yield. It (IV) was unaffected by standing in ether-thionyl chloride (equal vols.) for two hours.

O-Benzoylserine methyl ester hydrochloride (V), m.p. 137–138° (gas), was formed in 73% yield when the complex salt described above was dissolved in water. It was purified by dissolving in alcohol, then adding ether. Bergmann, *et al.*, (1) reported 130–132°.

Anal. Calc'd for $C_{11}H_{14}ClNO_4$: C, 50.87; H, 5.43.
Found: C, 50.89; H, 5.57.

2-Phenyl-4-carboxymethyloxazoline (III) was obtained in 72% yield when the complex salt described above was decomposed in sodium carbonate solution. It distilled at 133–135° (2 mm.), f.p. 29.5°, n^{23}_D 1.5501. The values 130–132° (0.4 mm.), and $n^{20.5}_D$ 1.5504 have been reported (1).

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40.
Found: C, 64.39; H, 5.42.

O-Benzoylserine. 2-Phenyl-4-carboxymethyloxazoline (III) dissolved in 2 *N* sodium hydroxide to give a crystalline, acetone-insoluble sodium salt. A solution of the salt with an equivalent amount of hydrochloric acid gave 2-phenyl-4-carboxyoxazoline (III), m.p. 159–161°; previously reported (1) m.p. 159–160°. It was purified by dissolving in acetone and concentrating the hot solution. This substance hydrolyzed at room temperature in 95% alcohol solution to give O-benzoylserine (V) in 96% yield, m.p. 145–145.5° (dec.), purified from water. The value 149–150° has been given (1).

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[1] Since all compounds were DL-forms, this designation will be omitted henceforth.

Anal. Calc'd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30.
Found: C, 57.60; H, 5.30.

O-Benzoylserine in sodium carbonate solution rearranged to *N-benzoylserine* in 91% yield.

α-Benzoylamino-β-chloropropionic acid (IV). When dry hydrogen chloride was passed into a solution of 2-phenyl-4-carboxyoxazoline (III) in dry dioxane a crystalline salt formed which dissolved on heating on the steam-bath for ten minutes. Removal of the solvent and addition of water gave crystalline α-benzoylamino-β-chloropropionic acid, m.p. 145–147°, in 86% yield.

Anal. Calc'd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43.
Found: C, 53.00; H, 4.55.

This compound gives an 83% yield of O-benzoylserine (V) by first heating with water and then treating the hydrochloride solution with pyridine.

α-Benzoylaminoacrylic acid. Both α-benzoylamino-β-chloropropionic acid (IV) and its methyl ester gave α-benzoylaminoacrylic acid on treatment with 2 *N* sodium hydroxide at room temperature. The product was recovered on acidification and was purified by adding water to a solution in hot alcohol, m.p. 153–155° (gas and orange color); yield 72% from the ester. The previously reported melting point (11) was 137–138°.

Anal. Calc'd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74.
Found: C, 62.58; H, 4.71.

This compound in alcohol solution absorbed hydrogen in the presence of Adams catalyst to give DL-*benzoylalanine*, m.p. 163–165°. The melting point was not depressed on mixing it with an authentic sample.

Anal. Calc'd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74.
Found: C, 62.06; H, 5.86.

α-Benzoylamino-β-chloropropionic acid (IV) was converted to 2-phenyl-4-carboxyoxazoline (III) in approximately 50% yield by holding it in a sodium bicarbonate solution at 40° for 22 hours, then carefully liberating the product with hydrochloric acid.

PART 2: R = R′ = R″ = H

The product of the addition of twice the theoretical amount of thionyl chloride to hydroxyethylformamide (temperature not over 18°) was a crystalline solid. It was brought to constant weight after drawing the excess thionyl chloride off at 10 mm. while chilling in an ice-bath. This weight corresponded to approximately 94% of that required for the union of 1 mole of hydroxyethylformamide and 1 mole of thionyl chloride. The reverse addition did not give a solid due perhaps to the loss of hydrogen chloride. Attempts to decompose the compound in such a way as to get oxazoline were unsuccessful. A small amount of material boiling in the right range was isolated but gave poor analytical values. The solid, layered with dry ether, and put on the steam-bath, melted in a few minutes. After six hours it was distilled several times to give a 35% yield of β-chloroethylformamide, b.p. 118.5–121° (10 mm.), n_D^{25} 1.4845. This compound did not appear to be as unstable as previously reported, but in like manner gave poor analytical values (7).

Anal. Calc'd for C_3H_6ClNO: C, 33.50; H, 5.62; Cl, 32.97.
Found: C, 32.61; H, 5.47; Cl, 31.56.

PART 3: R = R′ = H; R″ = C_6H_5

Ethanolamine was benzoylated in sodium bicarbonate solution at 15°. The product was taken into chloroform, recovered, and distilled at 179–189° (1 mm.). The crude product (85% yield) was recrystallized by dissolving in warm ethyl acetate, then adding dry ether; m.p. 61–63°, 64% yield. It was previously reported (12) distilling at 185–187° (1 mm.), m.p. 60–61°.

2-Phenyloxazoline hydrochloride (III-HCl). β-Hydroxyethylbenzamide (2.0 g.) was added portionwise to 4 ml. of chilled thionyl chloride at not over 13°. The solution was kept

in the ice-bath for one hour; excess thionyl chloride was then removed under reduced pressure and the crystalline product brought to constant weight (2.3 g.) while keeping cold. The theoretical weight for the oxazoline hydrochloride is 2.22 g. The salt melted at 101–103° with a slight sinter at 77°. It was decomposed with sodium carbonate solution, the base removed with ether and the carbonate solution analyzed for sulfite and chloride ions. The ratio of the moles of sulfur dioxide to that of starting material was 0.03 to 1.0. Chloride was found in small excess, 105 % of theory. As reported (4) the oxazoline hydrochloride is stable in solution at room temperature. Recrystallization was effected by adding acetone to an aqueous solution; m.p. 75–76°. The value previously given (4) is 80–81°, and it is possible the lower melting point and low analytical value are due to loss of hydrogen chloride. The phenomenon of slight sintering at the melting point with transformation into *β-chloroethylbenzamide*, m.p. 101–103°, (see above) was observed solely with the crude reaction product.

Anal. Calc'd for $C_9H_{10}ClNO$: Cl, 19.31. Found: Cl, 18.46.

β-Aminoethyl benzoate hydrochloride (V), 0.133 g., m.p. 142–145°, and *β-chloroethylbenzamide (IV)*, 0.025 g., m.p. 99–101°, were recovered when 0.20 g. of 2-phenyloxazoline hydrochloride in aqueous solution was held on the steam-bath for two minutes. The identities were established after further purification by mixed melting points. The isolation of the latter compound shows that rearrangement can precede hydrolysis.

β-Chloroethylbenzamide (IV) was obtained by rearrangement of the oxazoline hydrochloride on the steam-bath. After purification from alcohol it was obtained in 88% yield, m.p. 102–103.5°. The literature gives values of 106–108° (4) and 102–103° (3).

Anal. Calc'd for C_9H_{10} ClNO: Cl, 19.31. Found: Cl, 19.78.

β-Aminoethyl benzoate hydrochloride (V). β-Chloroethylbenzamide (IV) 0.20 g., was covered with water and put on the steam-bath. The solid melted and the oil dissolved in the water in ten minutes. The water was removed and the crystalline product recovered from acetone in which it is insoluble. Yield, 0.193 g. (88%); m.p. 143–145°. The compound was purified by adding acetone to a solution in hot alcohol. The melting point was unchanged. The previoulsy reported (4) melting point is 129–130°.

Anal. Calc'd for $C_9H_{12}ClNO$: Cl, 17.58. Found: Cl, 17.54.

β-Aminoethyl benzoate hydrochloride (V) on rearrangement in a slight excess of sodium hydroxide solution gave β-hydroxyethylbenzamide (I) in 61% of theory.

PART 4: R = $ClCH_2$; R′ = H; R″ = p-$NO_2C_6H_4$

3-Chloro-2-hydroxy-*n*-propylamine hydrochloride, m.p. 100–103°, was obtained in 15% yield, based on epichlorohydrin, by the method of Gabriel and Hohle (13). Reaction with *p*-nitrobenzoyl chloride in a benzene-layered sodium bicarbonate solution gave N-(3-chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide. Purified by adding benzene to a hot ethyl acetate solution, it melted 103–106°; yield 74%. The reported value (8) is 110–111°.

Anal. Calc'd for $C_{10}H_{11}ClN_2O_4$: C, 46.43; H, 4.29.

Found: C, 46.69; H, 4.49.

2-(3-Chloro-1-p-nitrobenzoylamino-n-propyl) chlorosulfinate (II). N-(3-Chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide (I) 2.0 g., was added to 3.0 ml. of thionyl chloride at not over 8°. Crystals rapidly formed. After standing in the ice-bath for 40 min., excess thionyl chloride was removed under reduced pressure and the product brought to constant weight while still in the ice-bath. The weight of the product was 2.65 g. with 2.64 g. theoretical for the chlorosulfinate. Decomposition with cold water yielded 1.81 g. (90%) of starting material, m.p. 100–103°, identity confirmed by a mixed melting point. Analysis of the aqueous mother liquor for chloride gave silver chloride in 96% of theory.

Di-2-(3-chloro-1-p-nitrobenzoylamino-n-propyl) sulfinate. In a similar run the chlorosulfinate was dissolved in a little dry dioxane and an equivalent amount of N-(3-chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide added. Removal of the solvent gave an oil which crystallized. The compound was purified by dissolving in pyridine (not over 100°) and then adding alcohol. The yield was 30%; m.p. 167–168° (gas).

Anal. Calc'd for $C_{20}H_{20}Cl_2N_4O_9S$: C, 42.64; H, 3.58; Cl, 12.59; S, 5.69.
Found: C, 42.90; H, 3.94; Cl, 12.24; S, 5.8.

2-(3-Chloro-1-amino-n-propyl) p-nitrobenzoate hydrochloride (V). The chlorosulfinate (II), 0.657 g., in a test tube connected with a sodium carbonate absorption solution was placed in steam for 4 min. It partly melted and the tube was swept with nitrogen. The loss of weight was 0.116 g. with 0.121 theory for loss of sulfur dioxide in ring closure to the oxazoline hydrochloride. Titration of the sodium carbonate solution with 0.1 *N* iodine solution showed sulfite ion in 86% of theory. The carbonate solution also gave chloride in molal quantity equivalent to 2% of the starting material. Eight ml. of water was added to the organic residue and the suspension warmed 2 min. on the steam-bath. After cooling, undissolved solid was filtered; yield, 0.145 g., m.p. 95–100°. This is impure N-(2,3-dichloro-*n*-propyl)-*p*-nitrobenzamide (IV) in 27% of theory. The remainder of the material, 2-(3-chloro-1-amino-*n*-propyl) *p*-nitrobenzoate hydrochloride (V), recovered from water and washed in acetone, melted at 184–186°; yield, 0.415 g. (73%). It was purified from alcohol and melted at 185–187° (gas).

Anal. Calc'd for $C_{10}H_{12}Cl_2N_2O_4$: C, 40.69; H, 4.10; Cl, 24.03.
Found: C, 40.90; H, 4.30; Cl, 23.70.

The benzoate (V) dissolved in water and treated with sodium bicarbonate solution threw down an oil which soon crystallized. It was purified to give N-(3-chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide (I) in 57% yield.

2-p-Nitrophenyl-5-chloromethyloxazoline (III). In another experiment the thionyl chloride suspension of the chlorosulfinate (II) was held on the steam-bath for 5 min., during which time the solid dissolved giving a clear solution. The thionyl chloride was removed under reduced pressure and the product crystallized easily when rubbed with a little dry ether. It weighed 2.14 g. with 2.15 g. being theoretical for the oxazoline hydrochloride, m.p. 127–129°. This salt is not very soluble in water and the base could be liberated by titrating with 2 *N* sodium hydroxide using phenolphthalein indicator. The impure oxazoline, m.p. 111–114°, recovered in 95% yield, was purified from alcohol; m.p. 116–117°, slight sinter at 113°. The literature (8) gives m.p. 117–118°.

Anal. Calc'd for $C_{10}H_9ClN_2O_3$: Cl, 14.73. Found: Cl, 14.68.

After standing in the air for several days, the oxazoline hydrochloride was found to have lost some hydrogen chloride to give the oxazoline, easily separated by reason of its acetone solubility.

N-*(2,3-Dichloro-n-propyl)-p-nitrobenzamide (IV)* resulted when the oxazoline hydrochloride alone or in thionyl chloride was rearranged by heating. Purified by adding water to a hot alcohol solution it melted at 122–123.5°. A mixture melting point with the oxazoline hydrochloride, m.p. 127–129°, showed a sharp depression, mixture m.p. 115–125°.

Anal. Calc'd for $C_{10}H_{10}Cl_2N_2O_3$: C, 43.34; H, 3.64.
Found: C, 43.52; H, 3.78.

The transformation of this compound (IV) into 2-(3-chloro-1-amino-*n*-propyl) *p*-nitrobenzoate (V) could not be effected by heating it in aqueous suspension for 24 hours on the steam-bath. In suspension in 2 *N* sodium methoxide it (IV) slowly cyclized to 2-*p*-nitrophenyl-5-chloromethyloxazoline (III).

PART 5: R = $HCl(C_2H_5)_2NCH_2$; R′ = H; R″ = *p*-$NO_2C_6H_4$

N-(3-Diethylamino-2-hydroxy-n-propyl)-p-nitrobenzamide hydrochloride was made by heating N-(3-chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide with diethyl amine, twice theory, in a sealed tube on the steam-bath for one hour. The product was treated with excess absolute alcoholic hydrogen chloride to make the salt which was purified from absolute ethanol. Yield 75%; m.p. 162–163.5°. The reported melting point (8) is 163–164.5°.

2-(3-Diethylamino-1-amino-n-propyl) p-nitrobenzoate dihydrochloride (V). N-(3-Diethylamino-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide hydrochloride (I), 0.30 g., with 1.0 ml. thionyl chloride gave a solution at room temperature. At the end of 20 minutes excess

thionyl chloride was removed under reduced pressure and 2 ml. of water added to the oil to give a solution. After removing the water under reduced pressure and adding acetone, a crystalline product was obtained which was purified by slowly adding acetone, to its solution in a little water. Yield, 0.065 g. (20%); m.p. 194–195° (gas).

Anal. Calc'd for $C_{14}H_{23}Cl_2N_3O_4$: Cl, 19.25. Found: Cl, 19.42.

N-(3-Diethylamino-2-chloro-n-propyl)-p-nitrobenzamide hydrochloride (IV) was obtained in 87% yield by rearrangement of 2-*p*-nitrophenyl-5-diethylaminomethyloxazoline dihydrochloride (III-HCl) on the steam-bath. It was also obtained in good yield by the action of hot thionyl chloride on N-(3-diethylamino-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide (I). This compound (IV) has been designated the oxazoline dihydrochloride but was not characterized (8). It was purified by adding ethyl acetate to a solution in hot alcohol, m.p. 112.5–114.5°.

Anal. Calc'd for $C_{14}H_{21}Cl_2N_3O_3 \cdot H_2O$: Cl, ionic, 9.63; Cl, total, 19.26.
Found: Cl, ionic, 11.04; Cl, total, 19.39.

The high ionic chlorine is probably due to partial splitting off of the bound chlorine. The attempt to convert this compound to the ester (V) was inconclusive.

The oxazoline dihydrochloride (III-HCl) mentioned above was made by adding dry hydrogen chloride to a dry ethereal solution of the base. This base (III) was made as previously described (8) and melted at 55–57° [L. and A. (8) reported m.p. 57–57.5°] after purification from petroleum ether.

The *ease of hydrolysis* of the oxazoline dihydrochloride is illustrated by the following experiment: 2-*p*-nitrophenyl-5-diethylaminomethyloxazoline (III), 0.50 g., was slowly titrated with 1.0 *N* HCl. At one equivalent of acid (1.8 ml.) the solid was in complete solution, *p*H 7 by Accutint paper. Further addition of acid to two equivalents (3.6 cc.) was accompanied by an increase of *p*H to a value of 1 at the end. The water was immediately removed under reduced pressure at room temperature. Addition of absolute ethanol gave crystals of 2-(3-diethylamino-1-amino-*n*-propyl) *p*-nitrobenzoate dihydrochloride (V), 0.645 g. (97% crude), m.p. 185–190° (gas). Purified as described above, it melted at 194–195° (gas).

This compound (V) was dissolved in sodium bicarbonate solution, allowed to stand ten minutes, then acidified to give N-(3-diethylamino-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide hydrochloride (I) in 76% yield.

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SUMMARY

The formation of oxazolines by the action of thionyl chloride on β-hydroxyalkylamides appears to go by way of the chlorosulfinate. Erroneous interpretations in this series are believed due to the similarity in behavior of oxazoline salts and β-haloalkylamides.

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