that azulene is bicyclic. Permanganate oxidation yielded substances characterized as phthalic acid, acetone, acetic acid, and carbon dioxide. Azulene has been shown to behave as an unsaturated compound. In conformity with these facts a benzfulvene structure has been tentatively assigned to it.

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GAMMA-CHLOROPROPYL URETHANS AND A SYNTHESIS OF THE 1,3-OXAZINE RING

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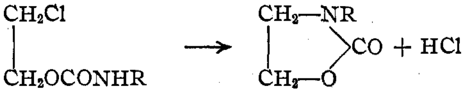
Of the numerous possible halogen-substituted propyl carbamates only 2 are described in the literature, namely, β,γ-dichloropropyl and β,β'-dichloro*iso*propyl carbamate.[1] The latter has come into therapeutic use as a hypnotic[2] and appears on the market under the name "Aleudrin." Homologs of γ-chloropropyl carbamate, namely, γ-chloro-α-ethylpropyl and γ-chloro-α-propylpropyl carbamate have been reported by Puyal and Montagne.[3]

Two methods have been used in the preparation of these urethans: (1) treatment of the substituted alcohol with phosgene and conversion of the resulting chlorocarbonate into the urethan by ammonia, (2) treatment of the alcohol with urea chloride.

For the preparation of the corresponding carbanilates, or phenylurethans, another method is available which consists in the simple addition of phenyl isocyanate to the alcohol. This method was used by Johnson and Langley[4] for the preparation of a number of dihalogen propyl and *iso*propyl carbanilates.

An interesting observation reported by Otto, and later extended by Johnson and Langley, is the fact that β-halogen alkyl carbanilates when treated with alkali lose halogen acid with ring closure to form oxazoles.



The only instance where a γ-halogen alkyl carbanilate has been subjected to this treatment with alkali was the γ-chloro-β-bromopropyl carbanilate where a β-halogen was also present.[4] In this case it was the β- and not the γ-halogen that reacted.

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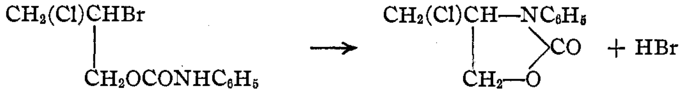
[1] Otto, *J. prakt. Chem.*, [2] **44,** 20 (1891).

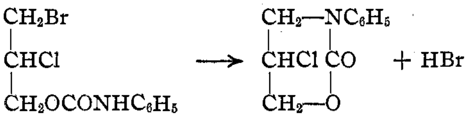
[2] Ger. pat., 271,737, 1911; U. S. pat., 1,108,676, **1914.**

[3] Puyal and Montagne, *Bull. soc. chim.*, **27,** 857 (1920).

[4] Johnson and Langley, *Am. Chem. J.*, **44,** 352 (1910).



The instance cited above is all the evidence we have for any assumption that a γ-halogen would fail to react in the same manner or that it would react less readily than a β-halogen present in the same molecule. In other words, there is no reason to suppose that the 6-membered oxazine is less readily formed than the 5-membered oxazole. Bromine is known to be more reactive in such reactions than chlorine. Although Johnson and Langley prepared the isomeric β-chloro-γ-bromopropyl carbanilate they did not attempt to prepare an oxazole from it. Considering the greater reactivity of bromine and the ease with which a γ-chlorine reacts in the absence of a β-halogen, as will be shown later, it is not improbable that the isomer would have yielded a 6-membered oxazine.

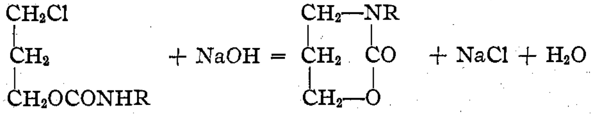


Our experiments show that γ-chloropropyl alcohol reacts readily with phosgene to form a chlorocarbonate, and from the latter the simple treatment with ammonia or a primary amine gives the corresponding urethan or N-substituted urethan. Treatment with alkali then removes hydrochloric acid and the ring closes to form a 1,3-oxazine. The reactions may be represented as follows.

I $Cl(CH_2)_3OH + ClCOCl = Cl(CH_2)_3OCOCl + HCl$

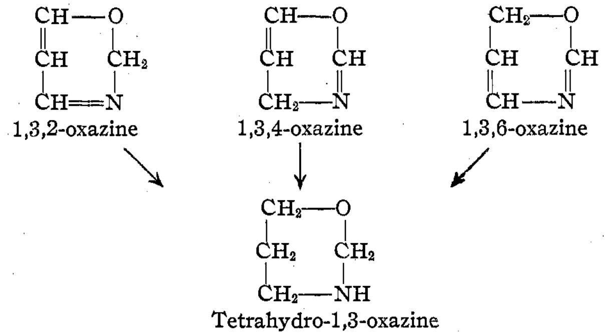
II $Cl(CH_2)_3OCOCl + 2RNH_2 = Cl(CH_2)_3OCONHR + RNH_2HCl$

III



Reaction III applies, however, only to the N-substituted urethans. Without a substituent group on the nitrogen, saponification of the ester takes place. With aqueous alkali, ammonia is liberated, and with sodium ethylate in absolute alcohol a separation of sodium cyanate occurs, and unless an excess of alkali is used, the chlorine remains intact. On the other hand, the N-phenyl and N-tolyl urethans were found to react smoothly with aqueous alkali, and good yields of the oxazines were obtained.

According to the accepted nomenclature of ring systems, the parent substance, 1,3-oxazine, would exist in 3 modifications, depending upon the location of the two double bonds, the position of the methylene carbon being designated by the third number. All 3 would give the same tetrahydro derivative.



Experimental Part

The γ-chloropropyl alcohol, which served as the starting point in this work, was the commercial "trimethylene chlorohydrin." It was redistilled with a fractionating column, and the portion collected between 160° and 170° was used in these experiments.

β-Chloropropyl Chlorocarbonate.—A flask containing 600 g. of a 20% solution of phosgene in toluene was well cooled by immersion in ice water, and 110 g. of γ-chloropropyl alcohol slowly added. An evolution of hydrogen chloride began in a very short time and continued for several hours. The mixture was allowed to stand for 24 hours, and then the toluene and excess of phosgene were distilled through a fractionating column. The fraction collected between 165° and 175° was redistilled, yielding 79 g. of a product boiling at 175–176° at 736 mm. It had a pungent, irritating odor similar to that of ethyl chlorocarbonate, though less pronounced on account of the higher boiling point. The substance is insoluble in water, toward which it is quite stable, but reacts rapidly with alcohol, and violently with ammonia.

Analyses.[5] Subs., 0.1689, 0.1979: AgCl, 0.2945, 0.3439. Calc. for $C_4H_6O_2Cl_2$: Cl, 45.2. Found: 43.2, 43.0.

γ-Chloropropyl Carbamate.—This was prepared by two methods, of which the second gave by far the better yield.

1. A mixture of 52 g. of γ-chloropropyl alcohol and 123 g. of urea nitrate (2 moles) was heated in an oil-bath at 130–135°. A slight but steady evolution of gas occurred, indicating decomposition of the urea nitrate. Heating was continued for 3 hours. The product consisted of 2 layers, the lower of which solidified on cooling (ammonium nitrate). The viscous upper layer was transferred to a distilling flask and distilled under diminished pressure. The urethane came over between 135° and 140° at 8 mm., and solidified in the receiver. By recrystallization from hot water it was obtained in white scaly crystals with pearly luster, melting at 62°. The substance is readily soluble in ether and in alcohol, and difficultly soluble in cold water. The yield was 12 g. or 16%.

Analyses. Subs., 0.2, 0.2: NH_3, 9.20, 9.10 cc. of 0.1 *N* acid. Calc. for $C_4H_8NO_2Cl$: N, 6.35. Found: 6.44, 6.37.

2. Ten g. of chloropropyl chlorocarbonate was slowly dropped into the calculated amount (2 moles) of 10% ammonia solution. The reaction was so vigorous that cooling with ice was necessary. The urethan separated in white scaly crystals which were filtered, washed and recrystallized from hot water. The melting point was 62° as in the

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[5] The presence of a small amount of chloropropyl carbonate was afterwards demonstrated in this preparation.

preceding preparation. The yield, however, was much better, amounting to 8 g. or 71%.

Attempts to prepare an oxazine from the above urethan by removal of hydrochloric acid and ring closure were unsuccessful. When the urethan was dissolved in alcohol and the calculated amount (1 mole) of *N* sodium hydroxide solution added, an evolution of ammonia took place on slight warming, indicating hydrolysis instead of ring closure. A solution of the urethan in absolute alcohol was then treated with the exact equivalent of sodium dissolved in absolute alcohol. A separation of small granular crystals was noticed shortly and these became more abundant on warming. The crystals were separated by filtration and washed with absolute alcohol. Since they failed to give the chloride test, they were examined further and identified as sodium cyanate. (Calc. for NaOCN: Na, 35.4. Found: 35.8.) Treatment with a solution of aniline hydrochloride gave a separation of phenylurea, melting at 147°.

γ-Chloropropyl Allophanate.—The recent method of Dains and Wertheim[6] was applied to this preparation and found to be very satisfactory; 16.7 g. of chloropropyl chlorocarbonate and 12.6 g. of urea (2.1 moles) were warmed together for 3 hours on a steam-heated sand-bath, using an air condenser. The mixture first melted, then gradually solidified. After the mass was cooled, it was broken up in a mortar, washed with water and recrystallized from hot alcohol. The product consisted of fine, white, scaly crystals melting at 166°. It is nearly insoluble in water, but moderately soluble in boiling alcohol. The yield was 14.2 g. or 75%.

Analyses. Subs., 0.2, 0.2: NH_3, 22.4, 22.5 cc. of 0.1 *N* acid. Calc. for $C_5H_9N_2O_2Cl$: N, 15.52. Found: 15.68, 15.75.

γ-Chloropropyl Carbanilate.—Twenty g. of chloropropyl chlorocarbonate and 20 g. of freshly distilled aniline, both diluted with 3 volumes of absolute ether, were slowly mixed in a flask surrounded by ice water. A copious separation of aniline hydrochloride occurred, which after completion of the reaction was removed by shaking with water. The ethereal layer after evaporation of the ether could not be induced to crystallize, even in a freezing mixture. It was, therefore, purified by distillation in a vacuum. The greater portion distilled between 160° and 170° at 5 mm., leaving practically no residue. The distillate consisted of a colorless, thick sirup. When cooled in a freezing mixture it suddenly solidified, with a rise in temperature of 20°. On recrystallization from alcohol it was obtained in long, flat prisms melting at 38°. It is insoluble in water, but extremely soluble in alcohol and in ether.

Analyses. Subs., 0.2, 0.2: NH_3, 9.95, 9.95 cc. of 0.1 *N* acid. Calc. for $C_{10}H_{12}NO_2$-Cl: N, 6.56. Found: 6.96, 6.96.

2. A mixture of 9.45 g. of chloropropyl alcohol and 11.9 g. of freshly distilled phenyl isocyanate was placed in an oil-bath, and the temperature was gradually raised to 150° during the course of 3 hours. The product solidified in a freezing mixture but melted again at room temperature. It was, therefore, distilled in a vacuum and the fraction boiling at 160–170° at 5 mm. collected as in the previous preparation. The distillate was an oil which readily solidified when the walls of the container were scratched with a glass rod. After it was dried on a porous plate and then recrystallized from alcohol it melted at 38°.

2-Keto-3-phenyl-tetrahydro-1,3-oxazine.—γ-Chloropropyl carbanilate (4.27 g.) was dissolved in 20 cc. of alcohol, and the theoretical amount (20.0 cc.) of *N* sodium hydroxide solution added. This dilution of the alcoholic solution caused the carbanilate to separate as an oil which, however, dissolved again completely on warming. The solution was gently refluxed for 2 hours, when it was practically neutral to litmus and no separation occurred on cooling. Evaporation of the solution left an oil and a mass of

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[6] Dains and Wertheim, This Journal, **42,** 2304 (1920).

sodium chloride crystals. The oil was allowed to solidify and then the sodium chloride washed out with water. On recrystallizing from alcohol, the substance was obtained in large thick prisms melting at 96°. It is moderately soluble in water and readily soluble in alcohol. The yield was 84%.

Analyses. Subs., 0.2, 0.2: NH_3, 11.40, 11.45 cc. 0.1 *N* acid. Calc. for $C_{10}H_{11}NO_2$: N, 7.91. Found: 7.98, 8.01.

The removal of hydrochloric acid as noted in the above experiment might conceivably occur in two ways. (1) The chlorine might carry with it a hydrogen from the adjacent carbon, leaving a double bond between the β and γ carbons. The product would then be allyl carbanilate. (2) The chlorine might unite with the hydrogen on the nitrogen of the anilide group, leaving a closed ring structure. The first possibility is ruled out by the failure of the product to add bromine in the cold, and the fact that allyl carbanilate is reported to melt at 70°. The only alternative then is the closed ring.

γ-Chloropropyl-*o*-methyl Carbanilate.—Twenty g. of chloropropyl chlorocarbonate and 24 g. of freshly distilled *o*-toluidine, both diluted with absolute ether, were slowly mixed and cooled. The toluidine hydrochloride which separated was removed by shaking the mixture with water. The ethereal layer was evaporated to a sirup and then distilled in a vacuum. The fraction collected between 170° and 175° at 5 mm. was a thick oil which solidified on cooling. After recrystallization from alcohol, it consisted of small needles melting at 49°. The yield was 20 g.

Analyses. Subs., 0.2, 0.2: NH_3, 6.44, 6.37 cc. 0.1 *N* acid. Calc. for $C_{11}H_{14}NO_2Cl$: N, 6.16. Found: 6.44, 6.37.

2-Keto-3-*o*-tolyl-tetrahydro-1,3-oxazine.—This was prepared exactly in the same manner as was the phenyl derivative described above, by removal of hydrochloric acid from γ-chloropropyl-*o*-methyl carbanilate. The product was obtained in large, flat prisms melting at 89°. The yield was 60%.

Analyses. Subs., 0.2, 0.2: NH_3, 10.45, 10.55 cc. of 0.1 *N* acid. Calc. for $C_{11}H_{13}NO_2$: N, 7,33. Found: 7.31, 7.38.

Summary

1. γ-Chloropropyl alcohol reacts readily with phosgene to form a chlorocarbonate, and the latter with ammonia and with aniline to form the carbamate and the carbanilate, respectively.

2. Removal of hydrochloric acid from γ-chloropropyl carbanilate and *o*-methyl carbanilate results in the formation of the 6-membered 1,3-oxazine ring. This reaction is analogous to that studied by Otto and by Johnson and Langley in which the β-halogen carbanilates lose hydrochloric acid and form the 5-membered 1,3-oxazole ring.

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