Typical examples of the reactions of alcoholic solutions of halogenated ethers with zinc are given. The action of zinc has been found to be entirely selective in the removal of two atoms of the halogen or the halogen acid from a given ether. The mechanisms of these reactions have been studied. Beta hydrogen atoms are removed by zinc more readily than beta halogen atoms, but alpha halogen atoms are much more reactive than alpha hydrogen atoms.

The removal of two atoms of a halogen from halogenated ethers in alcohol solution results in the quantitative formation of vinyl ethers but, under the same conditions, the removal of the halogen acid from halogenated ethers containing one less halogen atom in each case does not result in the formation of the same vinyl ethers, as had been expected, but of the corresponding acetals. Various tests indicated that the acetal formation was due to the alcohol addition to the unsaturated ether after the removal of the halogen acid by the direct action of zinc on the saturated ether. The assumption is made, in explaining these facts, that the removal of the halogen acid leaves the double bond of the vinyl ether in a polarized condition that is more favorable to the addition of other polar molecules, such as alcohol, than if the vinyl ether were prepared by the removal of two halogen atoms.

PRINCETON, N. J.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ISOXAZOLINE OXIDES

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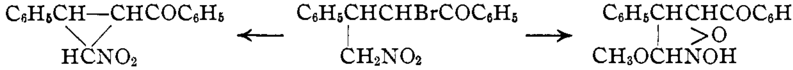
In the first paper of this series[1] it was shown that the reaction between methyl alcoholic potassium acetate and an α-bromo-γ-nitro-ketone which had no hydrocarbon residue in the γ position resulted mainly in the formation of two substances. One of these substances was the expected nitrocyclopropane derivative; the other was regarded as a methyl alcohol addition product of an isoxazoline oxide.



$$\begin{array}{ccccc} \mathrm{C_6H_5CH{-}CHCOC_6H_5} & & \mathrm{C_6H_5CHCHBrCOC_6H_5} & & \mathrm{C_6H_5CHCHCOC_6H_5} \\ \diagdown\ \diagup & \longleftarrow & | & \longrightarrow & |\quad >\mathrm{O} \\ \mathrm{HCNO_2} & & \mathrm{CH_2NO_2} & & \mathrm{CH_3OCHNOH} \end{array}$$

Most of the properties of the second product that were known at the time were expressed satisfactorily by the isoxazolidine formula, but it was not easy to account for the action of bases which readily degraded the substance into methyl alcohol, formic acid, phenylacetic acid and benzonitrile. This peculiar and unexpected reaction led to the present investigation. In order to avoid some of the difficulties encountered in the interpretation of the results of the earlier work it seemed advisable to employ, in place of

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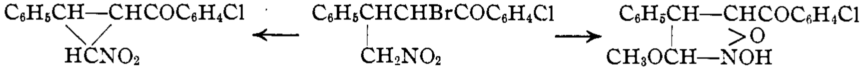
[1] Kohler, THIS JOURNAL, **46**, 503 (1924).

the diphenyl compound there used, a substance in which one of the phenyl groups is marked by a substituent. The *p*-chlorophenyl compound (I) served this purpose well; it is readily prepared and, like its chlorine-free analog, it gives with potassium acetate two products of which one is a cyclopropane derivative.



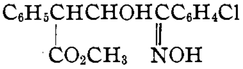
II I III

The second product of this reaction is evidently constituted like the corresponding compound that was obtained from the chlorine-free analog, for like this it forms a green copper derivative when its ethereal solution is shaken with aqueous copper acetate, and like it also, it is degraded by concentrated alkalies into methyl alcohol, formic acid, phenylacetic acid and *p*-chlorobenzonitrile. This substance, however, cannot possibly have the structure represented by Formula III. With acetic anhydride or acetyl chloride it forms, in succession, a mono- and a diacetate. The diacetate can be hydrolyzed to a second mono-acetate and this, in turn, to the original compound. The diacetate, therefore, is formed without rearrangement and the substance must have two active hydrogen atoms—a conclusion that is quite inconsistent with Formula III.

It is not easy to see how methyl alcoholic potassium acetate can transform the bromoketone into a substance containing two active hydrogen atoms, and the behavior of corresponding ketones which have phenyl groups in the γ position gives no clue to the process. Moreover, most reagents transform the substance into oils or into products whose relation to it is remote. By cautious treatment with weak bases, however, it is possible to replace methoxyl with hydroxyl—apparently without disturbing the rest of the molecule, for the hydroxyl compound still has the peculiar power of forming a copper derivative. This hydroxyl compound is an acid from which the methoxyl compound can be regenerated by the ordinary methods of esterification. The parent substance is, therefore, a methyl ester and this, almost of necessity, is an open-chain compound.

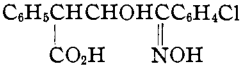
When the acid that is obtained by hydrolyzing the methoxyl compound with bases is digested with mineral acids it loses its nitrogen in the form of hydroxylamine. The result is a new acid which presumably is formed without disturbance of the rest of the molecule, because from it hydroxyl amine in a faintly alkaline solution regenerates the nitrogenous acid. This acid, therefore, contains an oximido group.

The transformations which have been described—hydrolysis to an acid, hydrolysis to a carbonyl compound and conversion into a diacetate—indicate that the substance is an open-chain compound containing a carbomethoxy, an hydroxyl and an oximido group. Assuming that the carbon chain is the same as that of the bromonitroketone, and taking account of the fact that *p*-chlorobenzonitrile is one of the degradation products, this analysis leads to Formula IV for the methoxyl compound and to Formulas V and VI for the products of hydrolysis.



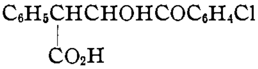
$$\begin{array}{l} C_6H_5CHCHOHCC_6H_4Cl \\ \quad | \qquad\qquad\quad \| \\ \quad CO_2CH_3 \quad NOH \end{array}$$

IV



$$\begin{array}{l} C_6H_5CHCHOHCC_6H_4Cl \\ \quad | \qquad\qquad\quad \| \\ \quad CO_2H \quad NOH \end{array}$$

V



$$\begin{array}{l} C_6H_5CHCHOHCOC_6H_4Cl \\ \quad | \\ \quad CO_2H \end{array}$$

VI

All these formulas have been confirmed by synthesis. Addition of hydrogen cyanide to benzal-*p*-chloro-acetophenone gave a nitrile of which the structure was known from the method of preparation (VII). This was hydrolyzed to the corresponding acid (VIII) which was then brominated. The structure of this bromo compound likewise follows from its method of preparation (IX). When the bromoketonic acid was warmed with dil. sodium carbonate solution it gave, along with other products, the ketolic acid (VI) and this was converted into the oximido acid (V) and the oximido ester (IV) in the manner already described.

$$\underset{\text{VII}}{C_6H_5CH(CN)CH_2COC_6H_4Cl} \longrightarrow \underset{\text{VIII}}{C_6H_5CH(CO_2H)CH_2COC_6H_4Cl} \longrightarrow \underset{\text{IX}}{C_6H_5CH(CO_2H)CHBrCOC_6H_4Cl}$$

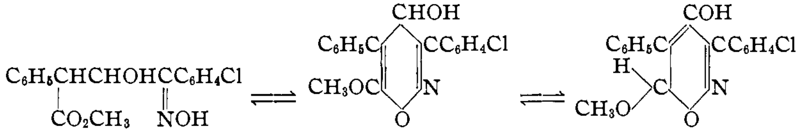
This synthesis leaves no doubt as to the structure of the oximido ester, but it gives no indication of the manner in which a mild reagent like methyl alcoholic potassium acetate converts the bromoketone into a substance that is so different from it as is the bromo ester. The process is accompanied by the formation of other products: two isomeric cyclopropane derivatives and a considerable quantity of an oil that gives the characteristic color reactions of hydroxamic acids and, on long standing, usually deposits an orthoxazine derivative. All attempts to isolate an isoxazoline oxide from the oil or to prepare such an oxide directly from the bromo compound were unsuccessful. Pyridine, which readily forms an oxide from α-bromo-γ-nitroketones that have a phenyl group in the γ position, here produces only highly colored oils. Ammonia and amines likewise eliminate hydrogen bromide but form either cyclopropanes or amorphous, acidic products. Aqueous alkalies convert most of the bromoketone into cyclopropanes but give in addition a considerable quantity of a hydroxamic acid. These results tell little about the mechanism by which the oximido ester is formed.

Most of the properties of the ester could be predicted from its structure, and therefore need no special comment here. Its ability to form a copper compound was perplexing until Feigl and his collaborators[2] announced the discovery that this is a general property of α-hydroxy-oximes. Our results confirm their conclusions in every way: the oximido acid, its ester and the corresponding amide form these extremely insoluble copper compounds; the various acetates do not.

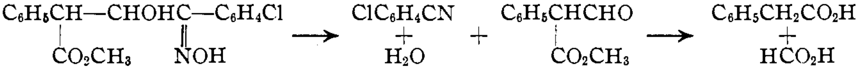
The oximido and ketolic esters are as easily acylated as the ketoses but

[2] Feigl, Sicher and Singer, *Ber.*, **58**, 2294 (1925).

they resist alkylation. With dimethyl sulfate and alkali the oximido ester gives a solid product but this, like the ester itself, contains only one methoxyl group. The composition and molecular weight of this product indicate that it is formed from the ester by loss of water and the fact that it reverts quantitatively to the oximido acid when potassium hydroxide is added to its solution in methyl alcohol confirms this relation. Since the substance forms a benzoate without losing the methoxyl group it is probably one of the modifications of an orthoxazine derivative.



The degradation of the oximido ester by alkalies which was so puzzling when the first paper was published is now readily explained. It is well known that many of the oximes which are formed by the action of alkalies on isoxazoles readily undergo cleavage and form nitriles.[3] A somewhat similar cleavage was reported by Werner and Piguet[4] who state that benzoin oxime, when treated with benzene sulfone chloride and pyridine or alkali, is smoothly cleaved into benzaldehyde and benzonitrile. We have found that the benzene sulfone chloride is not essential although it appears to facilitate the cleavage. By a corresponding reaction the oximido ester would give as primary products methylformylphenyl acetate and *p*-chlorobenzonitrile but since the aldehyde ester is likewise unstable in the presence of bases, the final products would be those actually obtained.



$$\underset{CO_2CH_3}{C_6H_5CH}-\underset{NOH}{\overset{}{CHOHC}}-C_6H_4Cl \longrightarrow \underset{H_2O}{\overset{ClC_6H_4CN}{+}} + \underset{CO_2CH_3}{C_6H_5CHCHO} \longrightarrow \underset{HCO_2H}{\overset{C_6H_5CH_2CO_2H}{+}}$$

Experimental Part

The bromonitroketone used in the investigation was made by adding nitromethane to benzal-*p*-chloro-acetophenone, and brominating the product. It was known that when the mixture of stereoisomeric bromine compounds that is obtained in this way is treated with methyl alcoholic potassium acetate it gives, along with two isomeric cyclopropane derivatives, a substance that has the composition of the oximido ester.[5]

The procedure for getting this substance in quantity was as follows.

I

Fifty g. of the mixture of bromine compounds was poured into a solution of 50 g. of fused potassium acetate in 100 cc. of methyl alcohol which had been made at the boiling point and then chilled to room temperature. The thick mass was shaken briskly with occasional cooling if the reaction became too vigorous, until the bromine com-

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[3] Claisen, *Ber.*, **24**, 3904 (1891); **36**, 3672 (1903).

[4] Werner and Piguet, *Ber.*, **37**, 4309 (1904).

[5] Smith, Dissertation, Harvard University, 1920.

pound had disappeared. It was then brought to the boiling point and immediately cooled again in a freezing mixture. After 30 minutes the solid deposit was collected on a suction filter and thoroughly washed with cold methyl alcohol. Most of the cyclopropane remained on the filter, mixed with potassium bromide.

The filtrate was poured into water and the mixture thoroughly extracted with ether. The ethereal solution was freed from most of the acetic acid by extraction with sodium carbonate solution, then shaken mechanically for 24 hours with a large excess of saturated aqueous copper acetate. The precipitate of copper derivative was collected on a filter and thoroughly washed with water and hot methyl alcohol in order to remove a small quantity of cyclopropane derivative that commonly precipitated along with the copper compound. By pumping off the ether in the filtrate, decanting the clear aqueous layer and diluting the residual oil with methyl alcohol, it was usually possible to secure a small additional quantity of copper derivative.

The combined precipitates of copper compound were introduced into a separatory funnel along with a small quantity of ether and shaken with successive portions of a 1:3 hydrochloric acid until all of the copper derivative was decomposed. This procedure gave a nearly colorless ester which was washed with a mixture of ether and petroleum ether and recrystallized from methyl alcohol; yield, 7 g., or about 18%.

Anal. Calcd. for $C_{17}H_{16}O_4NCl$: C, 61.2; H, 4.8. Found: C, 61.0; H, 5.0.

Methyl α-Phenyl-β-hydroxy-γ-oximido-γ-[*p*-chlorophenyl]butyrate, III.—The ester is very slightly soluble in ether, and moderately so in boiling methyl alcohol and boiling acetone. It crystallizes in small prisms melting at 165°. Above the melting point it decomposes, *p*-chlorobenzonitrile sublimes in long colorless needles and the remainder of the molecule turns into an insoluble amorphous solid, which is evidently due to polymerization. Caustic alkalies impart a deep red color to its ethereal solution, but this soon fades; at room temperature the principal product is the corresponding acid; at higher temperatures the substance is cleaved into phenylacetic and formic acids and *p*-chlorobenzonitrile.

THE COPPER DERIVATIVE.—This is precipitated as a dark green, amorphous solid when an ethereal solution of the ester is shaken with aqueous copper acetate. As it is insoluble in water as well as in all common organic solvents it cannot be recrystallized. Specimens obtained by washing the precipitate with water and hot methyl alcohol and then thoroughly drying them showed a copper content of 15.8% instead of 15.4% as calculated; m. p., about 222°, with decomposition.

A SECOND COPPER DERIVATIVE.—A second copper derivative is formed when a suspension of the green amorphous precipitate in ether is shaken with dil. hydrochloric acid. The green powder is slowly changed into a light blue-green, crystalline solid which is very readily soluble in methyl alcohol. From its methyl alcoholic solution, ether precipitates it in fine needles that melt with decomposition at 168–170° and contain 9.5% of copper. Further treatment with acids converts the compound into the oximido ester.

Hydrolysis to the Oximido Acid, V.—One g. of the ester suspended in 2 cc. of ether was shaken with 10 cc. of a 2% solution of sodium hydroxide. The ethereal layer immediately turned red, the aqueous layer yellow. The ethereal layer retained its color until the last of the solid had disappeared, then became colorless. On evaporation it left a small quantity of *p*-chlorobenzonitrile.

The aqueous layer was thoroughly extracted with ether, then covered with ether and acidified with dil. hydrochloric acid. By vigorous shaking, the resulting milky white precipitate was quickly dissolved in the ether in order to avoid hydrolysis of the oximido group. The ethereal solution was dried, concentrated and diluted with petroleum ether; it deposited a solid that, after recrystallization from methyl alcohol, melted at 174°.

Anal. Calcd. for $C_{16}H_{14}O_4NCl$: C, 60.1; H, 4.5. Found: C, 59.9; H, 4.6.

α-Phenyl-β-hydroxy-γ-oximido-γ-[*p*-chlorophenyl]butyric Acid, V.—The acid is readily soluble in ether, moderately soluble in methyl alcohol, insoluble in petroleum ether. It crystallizes in small colorless prisms. When its ethereal solution is shaken with aqueous copper acetate it deposits an insoluble blue copper compound.

Hydrolysis to the Ketolic Acid, VI.—A very fine suspension of the oximido acid was prepared by dissolving 0.5 g. in 10 cc. of 2% sodium hydroxide solution, pouring this into 100 cc. of water and adding dil. hydrochloric acid until the solution barely showed a reaction with Congo red paper. The cloudy solution gradually deposited clusters of white needles. These were washed, dried and recrystallized from ether-petroleum ether mixture.

Anal. Calcd. for $C_{16}H_{13}O_4NCl$: C, 63.1; H, 4.3. Found: C, 62.8; H, 4.5.

α-Phenyl-β-hydroxy-γ-oxo-γ-[*p*-chlorophenyl]butyric Acid, VI.—The acid is readily soluble in all common organic solvents except petroleum ether. It crystallizes in fine needles and melts at 139–140°. It is, as would be expected, unstable in alkaline solution. Thus its colorless solution in sodium hydroxide turns yellow when warmed, the acid loses water and carbon dioxide, and the solution deposits benzal-*p*-chloro-acetophenone. Its solution in sodium carbonate likewise turns yellow and deposits a colorless, indifferent crystalline solid which, doubtless, is an hydroxyketone. The acid also has the reducing power characteristic of α-hydroxyketones, being readily oxidized both by permanganate and by ammoniacal silver nitrate solution.

II. Synthesis of the Oximido Ester and its Hydrolysis Products

α-Phenyl-β-[*p*-chlorobenzoyl]propionitrile, VII.—A solution of 13.5 g. of potassium cyanide in 37 cc. of water was slowly dropped into a solution of 21 g. of benzal-*p*-chloro-acetophenone in 300 cc. of alcohol and 5.6 g. of acetic acid. The mixture was stirred mechanically and kept at a temperature of 35–40° for eight hours during which all of the unsaturated ketone disappeared. The mixture was then chilled and filtered, the solid washed with water and alcohol and recrystallized from alcohol. The pure nitrile crystallizes in fine, white needles; m. p., 121°.

Anal. Calcd. for $C_{16}H_{12}ONCl$: C, 71.2; H, 4.5. Found: C, 71.0; H, 4.6.

Methyl α-Phenyl-β-[*p*-chlorobenzoyl]propionate.—As it usually is easier to change secondary nitriles into esters and hydrolyze these, than to go directly from nitrile to acid, the nitrile was suspended in twice its weight of absolute methyl alcohol, and the mixture saturated with dry hydrogen chloride. The nitrile dissolved and in the course of eight days the orange solution deposited nearly its own weight of methyl ester. This was recrystallized from methyl alcohol and thus obtained in colorless flakes; m. p., 111.5°.

Anal. Calcd. for $C_{17}H_{15}O_3Cl$: C, 67.4; H, 5.0. Found: C, 67.2; H, 5.1.

α-Phenyl-β-[*p*-chlorobenzoyl]propionic Acid, VIII.—The methyl ester was heated on a steam-bath with an excess of a 10% solution of potassium hydroxide in methyl alcohol until a sample of the solution remained clear when poured into water. The entire solution was then diluted with water and acidified. It deposited almost pure acid. This was recrystallized from methyl alcohol, forming colorless plates melting at 152°.

Anal. Calcd. for $C_{16}H_{13}O_3Cl$: C, 66.5; H, 4.5. Found: C, 66.3; H, 4.7.

α-Phenyl-β-bromo-β-[*p*-chlorobenzoyl]propionic Acid, IX.—The ketonic acid was brominated with the greatest ease. Thus when bromine was dropped slowly into a suspension of the acid in eight times its weight of boiling chloroform, the bromine disappeared at once, the acid dissolved gradually and the bromo acid crystallized from the solution immediately after all of the bromine had been added. It was washed and recrystallized from methyl alcohol; it gave long, colorless needles; m. p., 216°.

Anal. Calcd. for $C_{16}H_{12}O_3BrCl$: C, 52.3; H, 3.3. Found: C, 52.1; H, 3.5.

Replacement of Bromine by Hydroxyl.—Ten g. of the bromo acid was dissolved in 100 cc. of 1% aqueous sodium hydroxide. The solution turned yellow and gradually became turbid. After 18 hours it was extracted with ether which removed 0.5 g. of benzal-*p*-chloro-acetophenone. The aqueous layer was acidified and the acid isolated in the usual manner. The crude acid melted at 115° but on recrystallization from an ether-petroleum ether mixture the melting point gradually rose to 139–140° and it remained the same after the acid had been mixed with the product obtained by hydrolyzing the oximido ester.

Formation of the Oximido Acid.—A solution of 0.5 g. of the ketolic acid in 10 cc. of 5% sodium hydroxide solution was treated with 5 g. of hydroxylamine hydrochloride, then warmed on a steam-bath for five minutes. The clear yellow solution was diluted with water, acidified and extracted with ether. On evaporation the ethereal solution deposited 0.35 g. of a substance that melted at 174°, and proved to be the same acid that had been obtained by hydrolysis of the oximido ester.

Esterification of the Oximido Acid.—A solution of the oximido acid in five times its weight of methyl alcohol was saturated with dry hydrogen chloride and set aside for three days. It was then evaporated under diminished pressure. The solid residue, after recrystallization from methyl alcohol, melted at 167°. Since this was also the melting point of a mixture of this synthetic product and the substance obtained by the action of potassium acetate on the bromoketone, the proof that the latter is the oximido ester (IV) is complete.

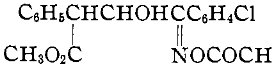
Esterification of the Ketolic Acid.—The oximido ester was also made by first esterifying the ketolic acid and then introducing the oximido group. For this purpose it was first shaken with an excess of saturated sodium carbonate solution which turned it into a sodium salt that separated in lustrous plates. The salt was washed with ice water, then dissolved in a large volume of water and changed into the silver salt by addition of silver nitrate. The vacuum-dried and finely powdered silver salt was boiled with methyl iodide in absolute ether. It gave an excellent yield of methyl ester.

Anal. Calcd. for $C_{17}H_{15}O_4Cl$: C, 64.0; H, 4.8. Found: C, 64.0; H, 4.7.

Methyl α-Phenyl-β-hydroxy-γ-oxo-γ-[*p*-chlorophenyl]butyrate.—The ketolic ester crystallizes in colorless plates and melts at 105°. Like the esters of most other ketolic acids it is hydrolyzed by bases with great rapidity. In order to turn it into the oximido ester it was necessary, therefore, to operate in a neutral solution. A mixture composed of 0.5 g. of the ester, 0.25 g. of hydroxylamine hydrochloride, 0.5 g. of precipitated calcium carbonate and 15 cc. of methyl alcohol was boiled for ten minutes, then cooled and filtered. From the filtrate, after dilution and acidification, ether extracted 0.5 g. of oximido ester—an excellent yield.

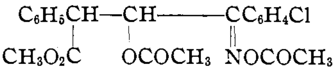
III. The Acyl Derivatives of the Oximido Ester

The oximido ester forms, in succession, a mono- and a diacetate. Both are easily hydrolyzed to the ester by methyl alcoholic hydrochloric acid. Both are also easily hydrolyzed by dilute aqueous ammonia, but the hydrolysis of the diacetate is only partial and the product is an isomeric monoacetate. Since the acyl derivatives of oximes are easily hydrolyzed as well as easily formed, the relation between the three acetates is represented by the following formulas.



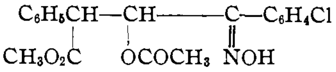
$\mathrm{C_6H_5}\underset{\mathrm{CH_3O_2C}}{\underset{|}{\mathrm{CH}}}\mathrm{CHOH}\underset{\mathrm{NOCOCH_3}}{\underset{\|}{\mathrm{C}}}\mathrm{C_6H_4Cl}$

X



$\mathrm{C_6H_5}\underset{\mathrm{CH_3O_2C}}{\underset{|}{\mathrm{CH}}}-\underset{\mathrm{OCOCH_3}}{\underset{|}{\mathrm{CH}}}\text{———}\underset{\mathrm{NOCOCH_3}}{\underset{\|}{\mathrm{C}}}\mathrm{C_6H_4Cl}$

XI



$$\begin{array}{ccc} C_6H_5CH & -CH & -C-C_6H_4Cl \\ | & | & \| \\ CH_3O_2C & OCOCH_3 & NOH \end{array}$$

XII

The Mono-acetate, X.—When the finely powdered oximido ester was added to twice its weight of acetic anhydride, it dissolved and in a few minutes the solution contained nothing that was capable of forming a copper derivative. The solution was poured into twice its volume of 30% acetic acid, which dissolved it and rapidly destroyed the excess of anhydride, then diluted with water and extracted with ether. The extract was washed with sodium carbonate solution, dried, concentrated and diluted with petroleum ether. The acetate separated in small, colorless prisms which, after crystallization from an ether-petroleum ether mixture, melted at 105°.

Anal. Calcd. for $C_{19}H_{18}O_5NCl$: C, 60.7; H, 4.8. Found: C, 60.6; H, 5.0.

The Corresponding Benzoate.—The corresponding benzoate was made by the Schotten-Baumann reaction and purified by recrystallization from acetone and ether; it gave stout needles; m. p., 134–135°.

Anal. Calcd. for $C_{24}H_{20}O_5NCl$: C, 65.8; H, 4.6. Found: C, 65.8; H, 4.9.

Hydrolysis of the Acetate.—When a solution of the mono-acetate in methyl alcohol containing a little hydrochloric acid was tested at intervals with copper acetate it soon gave the characteristic copper derivative of the oximido ester. After 48 hours the test was negative. Ether then extracted the ketolic ester in almost the calculated quantity.

α-Phenyl-β-hydroxy-γ-oximido-γ-[*p*-chlorophenyl]butyramide, $C_6H_5CH(CONH)_2$-CHOHC(NOH)C_6H_4Cl.—When an ethereal solution of the mono-acetate or of the oximido ester itself is shaken with 6 *N* aqueous ammonia, it gradually deposits the amide in long, fine needles. After recrystallization from acetone, from which it separates in clumps of stout needles, the amide melts at 171°. Like the oximido ester it forms an insoluble copper derivative.

Anal. Calcd. for $C_{18}H_{17}O_4N_2Cl$: C, 60.5; H, 4.8. Found: C, 60.1; H, 4.6.

Acetate of the Ketolic Ester, $C_6H_5CH(CO_2CH_3)CH(OCOCH_3)COC_6H_4Cl$.—In order to compare the relative ease with which the hydroxyl and oximido groups are acetylated we also subjected the ketolic ester to the action of acetic anhydride. We found that the acetylation of the ketolic ester is much more difficult than that of the oximido ester. The acetate can be made by boiling the ester with five times its weight of acetic anhydride for 30 minutes and then evaporating the excess of anhydride in a vacuum. By recrystallization from an ether-petroleum ether mixture the acetate was obtained in colorless needles; m. p., 84–85°.

Anal. Calcd. for $C_{19}H_{18}O_5Cl$: C, 63.2; H, 4.7. Found: C, 62.8; H, 4.9.

The Diacetate, XI.—The diacetate is most easily made by dissolving the oximido ester or either of its mono-acetyl derivatives in five times its weight of acetyl chloride and allowing the solution to evaporate slowly. No other product is formed. The substance is sparingly soluble in ether, readily soluble in methyl alcohol and in acetone and crystallizes in large, colorless plates; m. p., 122°.

Anal. Calcd. for $C_{21}H_{20}O_6NCl$: C, 60.4; H, 4.9; Cl, 8.5. Found: C, 60.4; H, 5.0; Cl, 8.6.

Hydrolysis to the Mono-acetate, XII.—With methyl alcoholic hydrochloric acid the diacetate behaves exactly like the mono-acetate, but with aqueous ammonia its behavior is different. A saturated ethereal solution was shaken for 24 hours with a large excess of 6 *N* ammonium hydroxide. The ethereal layer was washed until free from ammonia, dried, concentrated and mixed with petroleum ether. This precipitated a fine powder which changed to large, colorless needles when recrystallized slowly from ether-petroleum ether; m. p., 151°.

Anal. Calcd. for $C_{19}H_{18}O_5NCl$: C, 60.7; H, 4.8. Found: C, 61.1; H, 5.1.

Benzoylation, $C_6H_5CH(CO_2CH_3)CH(OCOCH_3)C(NOCOC_6H_5)C_6H_4Cl$.—A solution of 1 g. of the second mono-acetate in 10 cc. of ether was shaken with an equal weight of benzoyl chloride and 8 cc. of 8% sodium carbonate solution for two hours. The ethereal layer yielded a powdery solid; m. p., 128°.

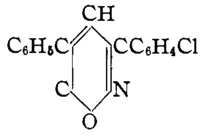
Anal. Calcd. for $C_{26}H_{22}O_6NCl$: C, 65.6; H, 4.6. Found: C, 66.3; H, 4.8.

THE DIBENZOATE.—Although benzoylation by the Schotten-Baumann method stops with the introduction of one benzoyl group, it is possible to make a dibenzoate of the oximido ester by using pyridine. Thus, when a solution of 1 g. of the ester and 4 g. of benzoyl chloride in 10 g. of pyridine was warmed on a steam-bath for 30 minutes and then manipulated in the usual manner, it gave 1 g. of the dibenzoate. This crystallized from methyl alcohol in needles. The melting point, 135°, is the same as that of the monobenzoate, but a mixture of the two melts much lower.

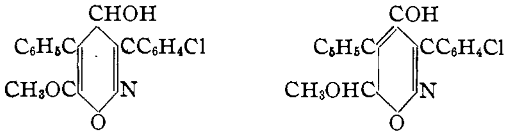
Anal. Calcd. for $C_{31}H_{24}O_6NCl$: C, 68.7; H, 4.5. Found: C, 68.7; H, 4.7.

IV. The Oxazine Derivatives

Two *o*-oxazine derivatives appeared in the course of the investigation. One of these (XIII) is formed as a by-product in the reaction between potassium acetate and the bromonitroketone. It crystallizes slowly from the oils left after removal of the cyclopropane derivatives and the oximido esters. It is completely insensitive to acids and but little affected by dilute bases, but forms a water-soluble sodium compound when digested with sodium alcoholate or concd. sodium hydroxide solution. The formula is based mainly on its relation to an analogous diphenyl compound for which the *o*-oxazine formula has been established by synthesis.



XIII



XIV

The second *o*-oxazine derivative is formed by the action of dimethyl sulfate and dilute alkali on the oximido ester. The structure is not quite certain, but it is difficult to find any other formula with which to represent a substance that has this composition, forms a benzoyl derivative and is changed to the oximido acid by bases, to the ketolic ester by acids.

5-Phenyl-3-[*p*-chlorophenyl]-6-oxo-orthoxazine, XIII.—The substance crystallizes in flat needles melting at 164°. It is very soluble in methyl alcohol and in chloroform and readily soluble in acetone. It very readily reduces permanganate both in water and in acetone. Sodium alcoholate converts it into a solid sodium compound which is insoluble in alcohol, soluble in water, and which reverts to the orthoxazine when acidified.

Anal. Calcd. for $C_{16}H_{10}O_2NCl$: C, 67.7; H, 3.5. Found: C, 67.4; H, 3.5.

5-Phenyl-3-[*p*-chlorophenyl]-4-hydroxy-6-methoxy-orthoxazine, XIV.—To a boiling solution containing 5 g. of the oximido ester and 5 g. of dimethyl sulfate in 10 cc. of ether, 40 cc. of 10% aqueous sodium hydroxide was added drop by drop. A crystalline solid appeared in the ethereal layer. After boiling the mixture for 20 minutes, this solid was removed, washed, dried and purified by repeated recrystallization from methyl alcohol; it gave thin plates melting at 184°. The yield was 2.5 g. and the only other product was the oximido acid which was isolated by acidifying the alkaline solution and extracting with ether.

Anal. Calcd. for $C_{17}H_{14}O_3NCl$: C, 64.7; H, 4.5. Found: C, 64.0; H, 4.8.

A molecular-weight determination in methyl alcohol gave 343 instead of 313 as calculated and a methoxyl determination by the Zeisel method showed the presence of one methoxyl group.

BENZOYLATION.—Using pyridine as the condensing agent, benzoylation resulted in a solid product which crystallized from acetone in large clumps of needles; m. p., 215–216°.

Anal. Calcd. for $C_{24}H_{18}O_4NCl$: C, 68.6; H, 4.3. Found: C, 68.3; H, 4.7.

HYDROLYSIS.—A solution of 1 g. of the oxyazine in 10 cc. of a 1% solution of sodium methylate was boiled for 30 minutes, then diluted, acidified and extracted with ether. The ethereal solution yielded about 0.5 g. of the oximido acid. A solution of the same substance in 10 cc. of methyl alcohol to which 3 cc. of concd. hydrochloric acid had been added was set aside for 48 hours, then evaporated under diminished pressure. It gradually deposited about 0.5 g. of the ketolic ester.

Summary

1. An α-bromo-γ-nitroketone, when treated with methyl alcoholic potassium acetate, gave four products: two isomeric cyclopropane derivatives, an oximido-hydroxy ester, and an oxyazine derivative. There are good reasons for believing that this represents the general behavior of those α-bromo-γ-nitroketones that have no other substituents in the γ position.

2. The oximido-hydroxy ester, the corresponding acid and the ketolic acid were synthesized in a different manner. They contain three reactive groups, are sensitive both to acids and bases and undergo a great variety of reactions.

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