[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Reactions of Certain Gamma Ketonic Acids. IV. The Ketonic Esters

BY E. P. KOHLER AND W. D. PETERSON

In the investigation of diastereomeric ketonic acids it is necessary at times to employ esters. We have therefore prepared the esters of the two bromo acids which were described in earlier papers[1] and have converted them into the corresponding unsaturated esters. And because we found these esters too low melting to serve our purpose we have also made the corresponding derivatives of phenyl *p*-chlorobenzoyl propionic acid.

In the case of the bromo esters we investigated the possibility of securing oxido compounds by a reaction that is not uncommon in simpler α-halo ketones.[2] We found no indication of such a reaction; all bases—sodium methylate, sodium carbonate in methyl alcohol, sodium acetate in methyl alcohol or in acetic acid, pyridine by itself or in glacial acetic acid—converted the bromo esters directly into two unsaturated esters:

$C_6H_5CHCHBrCOC_4H_4Cl$ (CO$_2$CH$_3$) → $C_6H_5C{=}CHCOC_6H_4Cl$ (CO$_2$CH$_3$)

I II

The cis and trans esters that are obtained in this manner are readily isomerized but because both are available for comparison, it is possible, nevertheless, to establish their configuration with certainty. We therefore employed them for examining the relative reliability of the various means which are available for determining the configuration of unsaturated ketonic acids. To this end we compared four different ways in which these substances can be related to cyclic compounds, namely: (1) converting the esters into orthoxazines, (2) adding methylmagnesium iodide to the carbonyl group of the esters and converting the resulting γ-hydroxyl compounds into γ-lactones, (3) forming the cyclic esters of the acids, (4) forming the cyclic acetates of the acids.

Originally[3] the configuration of the unsaturated ketonic compounds was based solely on the first of these methods, the one known acid and ester being regarded as cis compounds because they formed orthoxazines.

(1) Kohler and Kimball, THIS JOURNAL, **56**, 729 (1934); Kohler, Peterson and Bickel, *ibid.*, **56**, 2000 (1934).

(2) For literature see Kohler and Brown, *ibid.*, **55**, 4299 (1933).

(3) Kohler, *ibid.*, **50**, 221 (1928).

$HCCOC_6H_4Cl$ ‖ $C_6H_5CCO_2CH_3$ → CC_6H_4Cl / HC, N / C_6H_5C, O / CO

II III

Now that both esters are available for comparison it is clear that in the form in which this method was used—treating the ester with hydroxylamine hydrochloride and sodium acetate—this method is completely unreliable, both esters being largely converted into the orthoxazine. But when the esters are treated with hydroxylamine hydrochloride in pyridine, then the cis ester alone forms an orthoxazine; the trans ester is converted into an oximido ester which can be hydrolyzed to the corresponding acid and regenerated from the acid without forming a trace of the cyclic compound.

$H{-}C{-}CC_6H_4Cl$ ‖ NOH ‖ $CH_3O_2C{-}C{-}C_6H_5$ ⇌ $H{-}C{-}CC_6H_4Cl$ ‖ NOH ‖ $HO_2C{-}C{-}C_6H_5$

IV V

In the present case this method is completely reliable when it is applied in this manner, and it would be equally decisive if but one of the isomers were in hand. Its extension to other cases, however, is full of uncertainty because if but one isomer were available its failure to form an orthoxazine might be due solely to the stability of an antioxime. The second method is free from this uncertainty.

By operating in the inverse of the usual manner it is possible to add methylmagnesium iodide to the carbonyl group of these ketonic esters and leave the ester group intact. In this manner both esters are converted largely into γ-hydroxy esters.

CH_3 / $H{-}C{-}C{-}C_6H_4Cl$ / OH / ‖ $C_6H_5C{-}CO_2CH_3$

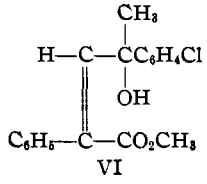
VI

CH_3 / $H{-}C{-}C{-}C_6H_4Cl$ / OH / ‖ $CH_3O_2C{-}C{-}C_6H_5$

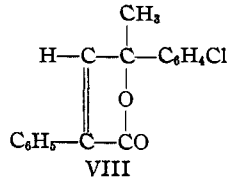
VII

As is to be expected, the product from the cis ester forms a lactone with the utmost ease; indeed, unless all operations from the addition of

the reagent to the isolation of the ester are carried out at low temperatures, the lactone is almost the only product



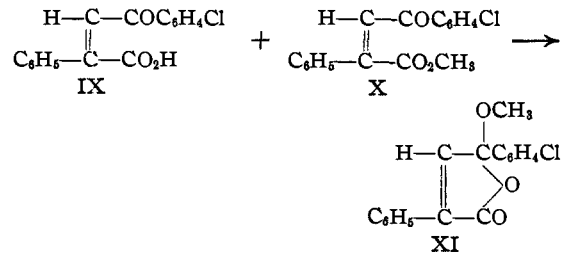
VI



VIII

The product from the trans ester, on the contrary, is completely stable; it can be hydrolyzed to the hydroxy acid and then regenerated from the acid without loss. In the present case, therefore, this method also is reliable and it would be equally so if but one of the isomers were available. This method, moreover, is equally applicable to acids—is, in fact, much more easily applied to the acids than to the esters. When the cis acid was added to excess of the Grignard reagent in the usual manner it was converted completely into the γ-lactone VIII. The trans acid, on similar treatment, formed the hydroxy acid corresponding to the ester VII and a small quantity of some polymeric product; diligent search failed to discover a trace of the lactone.

The third method appears to be equally as reliable as the two preceding but it probably cannot be applied as generally. Both acids can be esterified through the silver salts or with diazomethane without undergoing isomerization. The trans acid also gives only trans ester when it is esterified with a dilute solution of sulfuric acid in methyl alcohol, but the cis acid on similar treatment forms a mixture of open-chained and cyclic esters in which the latter greatly predominates

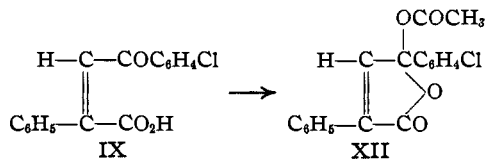


IX X

XI

The distinction between the open-chained and cyclic esters presents no difficulty because the open-chained ester is reduced, catalytically, to the stable saturated ester while the corresponding reduction product of the cyclic ester is hydrolyzed with such extreme ease that only the acid could be isolated.

The fourth method resembles the third. A solution of acetic anhydride in glacial acetic acid rapidly converts the cis acid into a cyclic acetate



IX XII

This method is the easiest and quickest of the four but unfortunately the same reagent also slowly isomerizes the trans acid and therefore finally converts this acid also into the cyclic compound. In the present case this is immaterial because the difference in the rates is too great to permit confusion but in cases in which but one isomer is known this method might easily lead to error.

Having established the configuration of the unsaturated esters by relating them to cyclic compounds by a quite unusual number and variety of reactions, we examined the possibility of determining whether or not each ester loses hydrogen bromide in but one way and forms a single unsaturated ester. Here it was necessary first of all to devise operating conditions in which the unsaturated esters are sufficiently stable because each of them readily passes into an equilibrium mixture of which the composition varies with the solvent and the temperature, but in which the cis ester always is in great excess.

We found that each ester could be heated for hours on a steam-bath with dry pyridine without undergoing inversion and that the addition of dry hydrogen bromide to the pyridine did not promote isomerization. Each ester also could be heated safely with glacial acetic acid, and while the addition of sodium acetate induced inversion, the isomerization was very much slower than the elimination of hydrogen bromide from the bromo esters. These combinations therefore appeared to be safe, but when we employed them for eliminating hydrogen bromide from the bromo esters the results were utterly contradictory.

Thus pyridine by itself removed hydrogen bromide slowly from both bromo esters at the ordinary temperature. The product from the ester of the higher melting bromo acid was almost pure trans ester but the product from the isomeric bromo ester was a mixture containing more trans than cis ester. And when the esters were digested on a steam-bath with sodium acetate in glacial acetic acid, each of them gave a mixture in which the trans ester preponderated.

The significant fact in these perplexing results is the preponderance of trans ester in all cases in which both unsaturated esters are formed from a single bromo compound. These mixtures cannot be due to isomerization of the unsaturated esters because the equilibrium mixture of these esters always contains more cis than trans ester. The excess of the less stable trans ester in the products therefore suggested that the bromo esters themselves might undergo isomerization more rapidly than they lost hydrogen bromide—a possibility that seemed easy to confirm or disprove. The experiments with pyridine and with sodium acetate were accordingly repeated but with the difference that at intervals samples were removed for examination.

In all samples taken from the solution of the ester of higher melting acid in pyridine, only trans ester and unchanged bromo ester were found; if they contained any isomeric bromo ester the quantity was too small to isolate. In the case of the corresponding solution of the isomeric bromo ester, however, the very first sample which was withdrawn when the reaction had gone less than one-fourth of the way to completion contained—besides cis ester, a little trans ester and a small quantity of the unchanged bromo ester—mainly the ester of the higher melting bromo acid. Even at this early stage, therefore, the original bromo ester had been largely isomerized. All subsequent samples accordingly showed very nearly constant quantities of cis and steadily increasing quantities of trans ester.

The solutions in acetic acid containing sodium acetate—a combination in which all the changes are slower—presented a different picture but the results were equally consistent. The first samples—withdrawn when the reaction had gone about one fifth of the way—contained both bromo esters and also both unsaturated esters. The proportion of the two bromo esters was nearly the same in both solutions, the ester of the higher melting acid preponderating greatly. This proportion remained very nearly constant throughout the reaction. The relative quantities of the unsaturated esters, on the contrary, were quite different in the two solutions. The first sample withdrawn from the solution made from the ester of the higher melting bromo acid contained mainly trans ester, while that withdrawn from the solution made from the isomeric bromo ester contained mainly cis ester. In the first solution the proportion of trans to cis ester fell off slightly as the reaction progressed and in the second solution the same proportion increased steadily until the reaction was complete.

With these facts available, the confused results become orderly. Evidently each bromo ester loses hydrogen bromide in but one way, the ester of the higher melting acid forming only the trans unsaturated ester and that of the isomeric bromo ester only the cis ester. In all reactions in which both of these unsaturated esters are formed from a single bromo ester the results are due to isomerization. In these cases the composition of the mixture depends upon two processes which differ greatly in speed and which are opposite in effect, namely, the inversion of the bromo ester and the isomerization of the unsaturated ester. The inversion of the bromoesters is relatively fast, tends toward an equilibrium in which the ester of the higher melting acid preponderates, and therefore favors the formation of trans ester. The relatively slow and consequently less effective isomerization of the unsaturated esters tends toward an equilibrium in which the cis ester preponderates.

In so far as they have been ascertained the stereochemical relations of these various ketonic acid derivatives present a singularly consistent picture. Bromination of the saturated acid or its methyl ester results in a mixture of diastereomers in which the higher melting acid or its ester preponderates greatly. Inversion of either of these diastereomers appears to produce very nearly the same mixture that is formed by bromination. Each bromo acid forms but one bromo acetate and but one β-lactone, and each bromo ester forms but one unsaturated ester. And the bromo acid which gives rise to the ester from which the trans ester is formed also gives rise to the β-lactone from which alone it is possible to get the trans acid—an unusual persistence of a spatial type.

Experimental Part

The two diastereomeric β-bromo esters can be obtained by brominating the corresponding ketonic ester and separating the resulting mixture of bromo esters, but it is much easier to brominate the ketonic acid, separate the mixture of bromo acids by the method devised for the chlorine-free analog[1b] and esterify the bromo acids.

α - Phenyl - β - bromo - β - [p - chlorobenzoyl] - propionic Acid.—The two diastereomeric bromo acids melt at 216° and 183°. The higher melting acid has been de-

scribed in an earlier paper.[4] The lower melting isomer crystallizes in plates and melts at 183°.

Anal. Calcd. for $C_{16}H_{12}O_3ClBr$: C, 52.3; H, 3.3. Found: C, 52.3; H, 3.5.

The Bromo Esters I.—The two isomeric acid were esterified with methyl alcohol and sulfuric acid, and since the higher melting acid formed the lower melting ester, each of the acids was also esterified with diazomethane. The ester from the higher melting acid crystallizes in thin needles and melts at 133°, that from the lower melting acid crystallizes in plates or flattened needles and melts at 145°.

Anal. Calcd. for $C_{17}H_{14}O_3ClBr$: C, 53.5; H, 3.7. Found: (133°) C, 53.2; H, 3.8; (145°) C, 53.2; H, 3.6.

Elimination of Hydrogen Bromide: The Unsaturated Esters II.—When bases like sodium acetate and pyridine are added to solutions of the esters in methyl alcohol or glacial acetic acid, they almost immediately generate the deep yellow color of the trans ester in the previously colorless solutions. At the boiling point of the solvent the elimination of hydrogen bromide is complete in a few hours. The result is a mixture of cis and trans esters in proportions that vary with the conditions. The mixture can be separated by systematic fractional crystallization from methyl alcohol.

The cis ester forms almost colorless solutions. It crystallizes in very pale yellow needles and melts at 93°. The trans ester crystallizes in golden-yellow plates and melts at 109°.

Anal. Calcd. for $C_{17}H_{13}O_3Cl$: C, 67.9; H, 4.4. Found: (93°) C, 67.7; H, 4.4; (109°) C, 67.8; H, 4.5.

Addition Reactions.—Both esters were reduced at the same rate, catalytically, to the saturated ketonic ester. Both esters also added bromine with equal ease in carbon disulfide and the same dibromide was obtained from both. It crystallized from ether in diamond-shaped plates and it melted at 136°. When its ethereal solution was shaken with aqueous potassium iodide the product was pure cis ester.

Anal. Calcd. for $C_{17}H_{13}O_3ClBr_2$: C, 43.9; H, 2.8. Found: C, 44.4; H, 2.9.

Reaction with Hydroxylamine.—Hydroxylamine hydrochloride and sodium acetate in methyl alcohol rapidly converted both esters into an orthoxazine. With hydroxylamine hydrochloride alone, the trans ester gave a small quantity of oxime but the principal product likewise was the orthoxazine. Hydroxylamine hydrochloride in pyridine, however, formed orthoxazine only from the cis ester.

The Orthoxazine III.—A solution of 2 g. of the cis ester and an equal weight of hydroxylamine hydrochloride in 10 g. of dry pyridine was left to itself for twelve hours, then evaporated as completely as possible in a draught. The residue was dissolved in ether and the ethereal solution was extracted repeatedly with dilute hydrochloric acid until free from pyridine, then dried and concentrated. It deposited first a solid which was identified as the orthoxazine by comparison with a sample in hand, then an oil which, doubtless, was an unstable oximido ester because it passed almost completely into the orthoxazine during the manipulations. The only other product was a small quantity of some polymeric material.

The Oximido Ester IV.—The trans ester, treated precisely like the cis ester with hydroxylamine hydrochloride in pyridine, formed in addition to a small quantity of polymer two products melting, respectively, at 130 and 105°. Most of the higher melting compound, constituting at least 90% of the entire product, was easily purified but the isolation of the lower melting compound required prolonged fractional crystallization from ether and petroleum ether.

Anal. Calcd. for $C_{17}H_{14}O_3NCl$: C, 64.8; H, 4.6. Found: (130°) C, 64.7; H, 4.7; (105°) C, 65.3; H, 4.7.

The higher melting compound crystallizes in prisms, the lower melting in flat needles; both are extremely soluble in all common solvents except petroleum ether. They are doubtless the syn and anti forms of the trans oximido ester, because they are hydrolyzed to the same oximido acid when they are boiled for a short time with methyl alcoholic potassium hydroxide.

The Trans Oximido Acid V.—The acid was formed quantitatively by the hydrolysis of both oximido esters. It crystallizes from acetic acid and water in transparent leaflets and it melts with decomposition at about 220°. When it is esterified with methyl alcohol and sulfuric acid it forms the oximido ester melting at 130°.

Anal. Calcd. for $C_{16}H_{12}O_3Cl$: C, 63.7; H, 4.0. Found: C, 63.5; H, 4.3.

Addition of Methylmagnesium Iodide.—The procedure was the same for both esters: an ethereal solution containing 8.5 g. of methylmagnesium iodide was added very slowly to a solution of 10 g. of the unsaturated ester in ether and benzene that was kept in a freezing mixture throughout the operation. The resulting magnesium compounds were precipitated as completely as possible by addition of petroleum ether, collected on a filter, thoroughly washed with petroleum ether and decomposed with iced acid in the presence of ether.

The Unsaturated Hydroxy Ester VI.—The principal product obtained from the cis ester crystallized in flattened needles and melted at 107°. It was isolated by crystallizing the mixture of products, first from ether and petroleum ether and finally from methyl alcohol.

Anal. Calcd. for $C_{18}H_{17}O_3Cl$: C, 68.2; H, 5.4. Found: C, 68.0; H, 5.6.

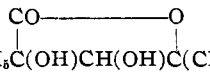
The structure of the ester was established by oxidizing it with permanganate in acetone. It gave but two products: phenylglyoxylic ester—identified by hydrolyzing it to the acid and converting this into the phenylhydrazone—and *p*-chloroacetophenone—identified by condensation with benzaldehyde. The configuration of the ester was established by hydrolysis with cold methyl alcoholic potassium hydroxide and subsequent acidification. The product was the crotolactone VIII—proving that the benzoyl and carboxyl groups are in cis positions.

α-Phenyl-γ-methyl-γ-[*p*-chlorophenyl]-croto Lactone VIII.—The second product obtained from the cis ester crystallized in very thin needles and melted at 94°.

Anal. Calcd. for $C_{17}H_{13}O_3Cl$: C, 71.7; H, 4.6. Found: C, 71.6; H, 4.8.

(4) Kohler and Shohan, THIS JOURNAL, **48**, 2430 (1926).

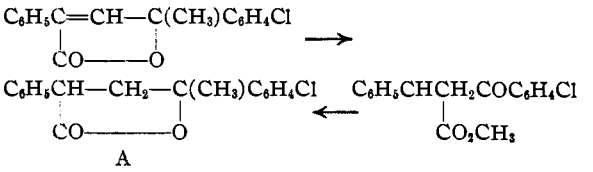
The structure of this product was established both by oxidation and by reduction. When it was oxidized with permanganate in acetone it was converted into a comparatively stable dihydroxy lactone as required by Thiele's rule for crotolactones of this type.



$C_6H_5C(OH)CH(OH)C(CH_3)C_6H_4Cl$, **α-Phenyl-α,β-dihydroxy-γ-methyl-γ-[*p*-chlorophenyl]butyro Lactone.**—The dihydroxy lactone crystallized from ether in shining needles and melted at 182°. On further oxidation it likewise was converted into phenylglyoxylic acid and *p*-chloroacetophenone.

Anal. Calcd. for $C_{17}H_{15}O_4Cl$: C, 64.0; H, 4.8. Found: C, 64.0; H, 5.50.

A more explicit proof of the structure of the crotolactone is supplied by its reduction to a saturated lactone which was synthesized from the saturated ester



Reduction of the unsaturated lactone gave but one of the two diameric butyrolactones represented by A—a substance that crystallized in needles and melted at 105°. The reaction between the saturated ester and methylmagnesium iodide gave a mixture of lactones and esters which was entirely converted into lactones by treatment with methyl alcoholic sodium hydroxide followed by acidification. The result was a mixture which by crystallization from methyl alcohol was separated into the lactone melting at 105° and a diamer that crystallized in lustrous prisms and melted at 120°.

Anal. Calcd. for $C_{17}H_{15}O_2Cl$: C, 71.2; H, 5.2. Found: (105°) C, 71.2; H, 5.4; (120°) C, 71.1; H, 5.2.

The Trans Hydroxy Ester VII.—The principal product of the reaction between methylmagnesium iodide and the trans unsaturated ester was an isomeric hydroxy ester which crystallized in thick transparent plates and melted at 105°.

Anal. Calcd. for $C_{18}H_{17}O_3Cl$: C, 68.2; H, 5.4. Found: C, 68.3; H, 5.5.

This ester was likewise oxidized to phenylglyoxylic ester and *p*-chloroacetophenone, but unlike its isomer it yielded a stable hydroxy acid when it was hydrolyzed with methyl alcoholic sodium hydroxide. It therefore is a trans compound.

The Trans Hydroxy Acid.—The acid that is formed by hydrolyzing the hydroxy ester crystallizes from ether in nuggets composed of minute plates. It shows no tendency to undergo isomerization and it can be re-esterified with methyl alcohol and sulfuric acid without forming any of the crotolactone.

Anal. Calcd. for $C_{17}H_{15}O_3Cl$: C, 67.4; H, 5.0. Found: C, 67.4; H, 5.2.

Addition of Methylmagnesium Iodide to the Acids.—Both the cis and the trans acids were added in the usual manner to a large excess of the Grignard reagent. In each case there was some polymerization but besides this the cis acid gave only the crotolactone melting at 94°—yield 92%—and the trans acid only the hydroxy acid melting at 134°—yield 88%.

Hydrolysis of the Esters. Cis α-Phenyl-γ-[*p*-chlorobenzoyl]-acrylic Acid IX.—Both esters are rapidly hydrolyzed by methyl alcoholic sodium hydroxide and by hydrochloric acid in glacial acetic acid but owing to the ease with which the trans acid is inverted, only the cis acid can be obtained in this manner. The acid is most easily purified by crystallization from benzene, from which it separates with solvent that is lost in the air. From ether and petroleum ether it crystallizes in two forms—the one separating in colorless silky needles that melt at 103°, resolidify and then melt again at 132°, and the other separating in stout needles that are faintly yellow in color and melt at 132°. In view of the ease with which the cis acid forms cyclic derivatives one of these modifications may have a cyclic structure but we found no evidence that this is the case.

Anal. Calcd. for $C_{16}H_{11}O_3Cl$: C, 67.0; H, 3.8. Found: C, 67.0; H, 4.0.

Trans α-Phenyl-β-[*p*-chlorobenzoyl]-acrylic Acid.—The trans acid, like the analogous chlorine-free compound, was obtained only from the bromo acids and their lactones. To a hot solution of 10 g. of sodium bicarbonate in 40 g. of glacial acetic acid were added in succession 10 g. of acetic anhydride and 10 g. of the lactone from the higher melting bromo acid. The mixture was heated on a steam-bath for ninety minutes, then evaporated as completely as possible in a draught. The residue was dissolved in ether and water. From the ethereal layer, which contained besides the trans acid only the cyclic acetate of the cis acid, sodium bicarbonate extracted 2.1 g. of trans acid. The β-lactone of the lower melting bromo acid, on similar treatment, gave only 0.3 g. of trans acid.

The acid crystallizes from ether and petroleum ether in very pale yellow plates and it melts at 135°. Its solutions in all solvents are intensely yellow. When its solutions in alkalies or in glacial acetic acid are warmed for a short time they become colorless, the trans acid being inverted completely into its cis isomer.

Anal. Calcd. for $C_{16}H_{11}O_3Cl$: C, 67.0; H, 3.8. Found: C, 66.8; H, 4.0.

The Cyclic Acetate XII.—For reasons presented in the introduction this acetate is the principal product of the action of sodium acetate on the β-lactones in acetic acid and acetic anhydride. It is formed rapidly when the cis acid is digested with acetic acid and acetic anhydride, and it is also formed very slowly when the trans acid is treated in the same way. It crystallizes from ether in thin needles melting at 110°.

Anal. Calcd. for $C_{18}H_{13}O_4Cl$: C, 65.6; H, 4.0. Found: C, 65.4; H, 4.1.

The Cyclic Ester XI.—The cis acid was esterified by the usual procedure with methyl alcohol and sulfuric acid and the product was separated by fractional crystallization from ether and petroleum ether into the normal ester melting at 93°—about 40%—and the cyclic ester melting at 73°—about 60%. The cyclic ester was also obtained in the calculated quantity when the cyclic acetate was

boiled with methyl alcohol. It crystallizes in colorless plates. Like the open chained esters it was readily reduced catalytically but the reduction product showed little tendency to crystallize and we were able to isolate only the saturated ketonic acid.

Anal. Calcd. for $C_{17}H_{13}O_3Cl$: C, 67.9; H, 4.4. Found: C, 67.8; H, 4.4.

Relative Stability and Isomerization.—The experiments by which the relative stability of the geometrical isomers was ascertained with sufficient accuracy for the present purpose have been described adequately in the introduction. The conditions that promote isomerization have not been studied with sufficient care for discussion at this time, but it is certain that in the case of the esters isomerization invariably leads to an equilibrium in which the cis ester preponderates. This has been found true when the isomerization was effected by increase of temperature, by exposure to sunlight, by treatment with a weak base like sodium acetate in glacial acetic acid, and by treatment with hydrochloric acid in glacial acetic acid.

Summary

This paper contains: a description and a comparison of the methods that are available for determining the configuration of unsaturated ketonic acids and their esters; a proof that each of two diastereomeric bromo esters loses hydrogen bromide in but one way and forms but one unsaturated ester; and the reason why a mixture of unsaturated esters is generally obtained, nevertheless, from each of the bromo esters.

CAMBRIDGE, MASS. RECEIVED AUGUST 8, 1934

NOTE

Note on a New Technique for the Preparation of Amino Nitriles[1]

BY G. A. MENGE

At the time, now rather remote, that this investigation was initiated, repeated attempts by the writer to duplicate the preparation of aminoacetonitrile, and other similar compounds, as described by Klages,[2] yielded results which, while not complete failures, were highly unsatisfactory, both with reference to the preliminary preparation of the cyanhydrin and to its conversion into the aminonitrile. Finally, the use of anhydrous hydrogen cyanide, freshly prepared by the method of Wade and Panting,[3] in connection with Ultee's[4] method for the preparation of the cyanhydrin gave excellent results. For the conversion of the cyanhydrin into the corresponding aminonitrile a new, and remarkably successful, technique was finally developed, involving the substitution of liquid ammonia,[5] to serve both as reagent and solvent, for the alcoholic or aqueous ammonia generally used. Application of the new technique is indicated in the following brief description of the preparation of aminoacetonitrile.

(1) Developed by the writer several years ago while a member of the Division of Pharmacology, Dr. Reid Hunt, Chief, of the then Hygienic Laboratory, U. S. P. H. S. Publication delayed in the vain hope that opportunity would develop for refining and extending the investigation.

(2) Klages, *J. prakt. Chem.*, [2] **65**, 189 (1902).

(3) Wade and Panting, *J. Chem. Soc.*, **73**, 256 (1898).

(4) Ultee, *Rec. trav. chim.*, **28**, 1, 248, 260 (1909).

(5) Grateful acknowledgment is due Dr. E. C. Franklin, for his kindly assistance and instruction in the proper and safe use of liquid ammonia.

To about 5 g. of glycolic nitrile, contained in a suitable Carius tube and cooled to the temperature of liquid ammonia, a large excess (about 20 cc.) of liquid ammonia was added. Keeping the reagents cooled, by immersion in liquid ammonia, the tube was carefully sealed and after the seal had cooled the contents were gently mixed (with the tube wrapped in a towel), forming a clear, colorless solution. After standing at room temperature for twenty-four hours a slight tinge of yellow color had developed in the clear solution. The pressure in the tube was then released by fusing the capillary seal and the ammonia allowed to evaporate spontaneously until boiling had ceased. The residue, transferred to a flask, was treated with successive portions of absolute alcohol, each portion being evaporated off under vacuum, until all free ammonia was removed, leaving a final product of very clear pale yellow liquid—presumably aminoacetonitrile. No attempt was made to distil it. The hydrogen chloride salt was prepared by dissolving the free base in dry ether and adding this solution carefully to hydrogen chloride dissolved in a 1:1 mixture of absolute alcohol and dry ether. Promptly, there resulted an abundant separation, with evolution of considerable heat, of a clean, white, crystalline solid which proved to be the pure hydrochloride salt, easily recrystallized from absolute alcohol.

Melting point: darkens gradually above 135° and melts slowly to a viscous brown mass at 165.5–166.5°; behavior identical with the pure salt obtained from the free base prepared by other methods and in close agreement with the m. p. of 165° reported by Klages.

Anal. The Pt salt was not easily prepared but was finally obtained by mixing alcoholic solutions of the free base and H_2PtCl_6 and adding dry ether to the mixture. On igniting for Pt: Calcd. for $C_4H_{10}N_4Cl_6Pt$: Pt, 37.35. Found: Pt, 37.20, 37.30.

Yield.—The entire product from the pressure-tube reaction was carefully converted into the hydrochloride salt, as described above, and the yield measured in that form. The total pure dry salt recovered weighed 7.82 g., or close