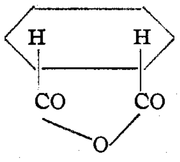
[Contribution from the Chemical Laboratories of Harvard University

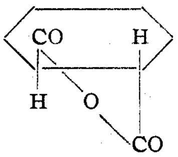
The Reactions of Certain Gamma Ketonic Acids. V. Ketonic Beta Lactones and the Walden Inversion*

By E. P. Kohler and J. E. Jansen

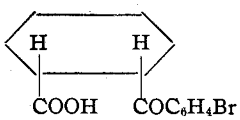
In a previous paper[1] it was shown that the rates at which two diastereomeric β-bromo acids form β-lactones are dependent on the configurations of the bromo acids. The relations described did not provide a basis for determining whether the closure and opening of the β-lactone ring does or does not involve inversion. That problem is the subject of the present paper.

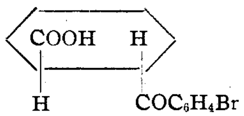
In order to secure substances of known configuration, it was necessary to resort to cyclic compounds in which the configuration is fixed by the structure and in which it can be determined by the methods that have been evolved for unsaturated ketonic acids.[2] To this end we began with two anhydrides of which the configuration is known, both from the relative ease with which they are formed and from the resolvability of the corresponding *trans* dibasic acid.


I

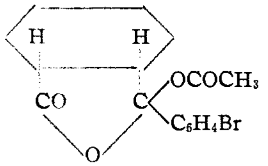

II

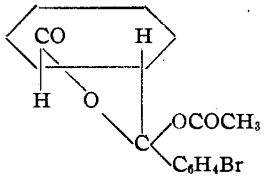
Both of these anhydrides were condensed with bromobenzene without difficulty and each gave only one γ-ketonic acid.


III


IV

The relative stability of these ketonic acids is the same as that of the corresponding dibasic acids, but, doubtless because of the greater tendency for ketones to enolize, the *cis* acid can be transformed into the *trans* by heating with bases as well as with acids. With the help of these acids of known configuration it was possible to ascertain whether a method which had been found reliable in the case of unsaturated ketonic acids can be employed for determining the configuration of their cyclic analogs. To this end each acid was dissolved in a cooled mixture composed of equal parts of acetic acid and acetic anhydride containing a trace of sulfuric acid, or each acid was dissolved in a warmed mixture of equal parts of acetic acid and acetic anhydride and, in each case, the *cis* acid was converted rapidly and completely into the compound which we assume to be the dicyclic acetate, whereas the *trans* acid was recovered unchanged. In order to convert the *trans* acid into a dicyclic acetate it was necessary to omit the acetic acid and employ only the anhydride. The configuration of these γ-keto acids can be established, therefore, by comparing the relative ease with which they form dicyclic acetates.


V

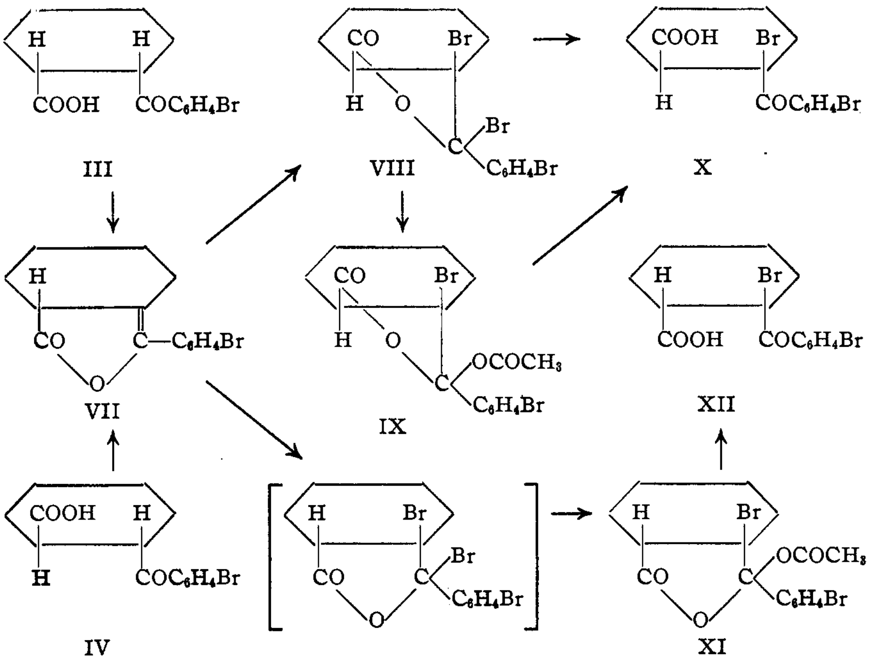

VI

The bromination of the cyclic ketonic acids proved to be unexpectedly troublesome. Neither of the acids could be brominated satisfactorily in non-polar solvents. In direct sunlight bromine reacts slowly with the *cis* acid in boiling chloroform, but the product is a mixture that is extremely difficult to separate. Under the same conditions the *trans* acid reacts still more slowly and forms only oily products. Both acids, however, can be dehydrated to an unsaturated γ-lactone which can be utilized for securing both bromo acids. This unsaturated lactone forms a dibromide which is converted into the dicyclic acetate of the *trans* bromo ketonic acid and when the unsaturated lactone is brominated in a mixture of acetic acid and acetic anhydride, it forms a mixture of the dicyclic acetates of the *cis* and *trans* bromo ketonic acids. The hydrolysis of the acetates to the corresponding bromo ketonic acids presents no difficulties. These relations are shown in the following chart.

(*) This paper was written by Professor Kohler a few months before his death. A few minor additions of experimental work, completed after the paper was written, have been included.—J. E. Jansen.

(1) Kohler, Peterson and Bickel, This Journal, **56**, 2000 (1934).

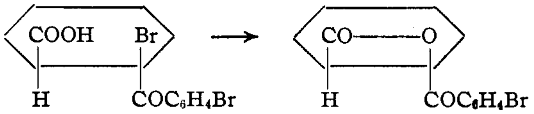
(2) Kohler and Peterson, *ibid.*, **56**, 2192 (1934).



This series of reactions, doubtless, accounts for the fact that both acids can be brominated in acetic anhydride and, also, in a mixture of acetic acid and anhydride. When they are brominated in acetic anhydride the sole product is the same dicyclic bromoacetate (IX) that is formed by the action of the anhydride on the dibromide, and when they are brominated in an acid and anhydride mixture they also form the mixture of bromoacetates that is formed by brominating the unsaturated lactone under the same conditions.

The configurations of the bromo ketonic acids were established without difficulty because they differ even more conspicuously than the unbrominated acids in the ease with which they form dicyclic acetates. The higher-melting bromo acid forms a dicyclic acetate when it is dissolved in cold acetic anhydride, in a warmed mixture of four parts of anhydride and one part acetic acid and when it is warmed with a mixture of equal parts of acetic acid and anhydride. The lower-melting bromo acid is not converted into its acetate in this manner; in order to prepare the dicyclic acetate it is necessary to employ acetic anhydride and sulfuric acid. In the higher-melting bromo acid, therefore, the carbonyl and bromobenzoyl groups are on the same side of the molecule as shown in formula XII. In these experiments two dicyclic acetates of the higher-melting bromo acid are obtained: one from the acetic anhydride solution and the other from the solutions of anhydride containing either acetic acid or sulfuric acid. The formation of two dicyclic acetates is attributable to the generation of a third center of symmetry in the molecule.

With these two bromo acids of known configuration in hand, it was possible to attack the problem of lactone formation. We found that these acids differ in their behavior toward bases precisely like the corresponding open-chained acids. The bromine derivative of the *trans* ketonic acid is extracted from an ether solution by dilute aqueous sodium bicarbonate, but its salt is converted rapidly and completely into a β-lactone. Under these conditions the bromine derivative of the *cis* ketonic acid is converted into a salt which undergoes no further change. Moreover, unlike the corresponding open chain compound, this bromo compound cannot be converted into a β-lactone by means of caustic alkalies. In this series, therefore, the β-lactone ring can be closed only when the bromine atom and the carboxyl group are on the same side of the molecule.



By analogy to cyclohexene oxide and to the cyclohexane dicarboxylic anhydrides, the β-lactone that is obtained from the bromo ketonic acid has the configuration shown in formula XIII. In view of its relative stability and the rapid cyclization, formation of a β-lactone with a *trans* configuration of the ring appears improbable and is inconsistent with the known properties of these bicyclic compounds. Also, since the isomeric bromo acid, in which the bromine and carboxyl groups are in the *trans* position, fails to form a β-lactone, it is unlikely that the reaction proceeds with inversion. If this were the case, it would be expected that this isomeric bromo acid would more readily form the β-lactone with a *cis* ring.

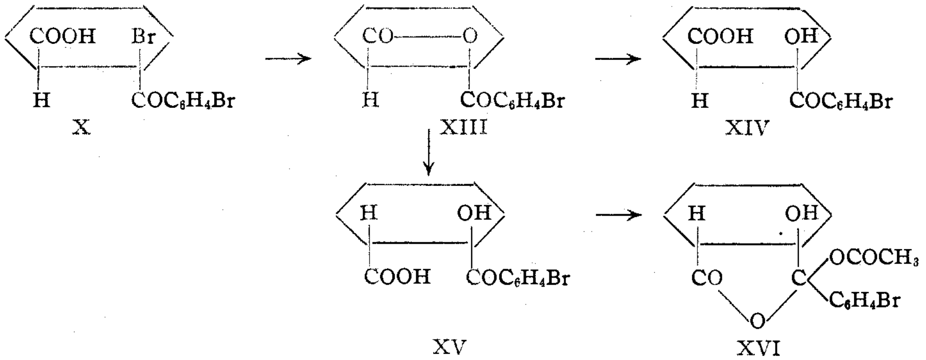
This β-lactone is exceedingly sensitive to bases. It is rapidly extracted from an ether solution by cold, dilute, aqueous potassium hydroxide, and more slowly by sodium carbonate, to yield, quantitatively, in each case, a salt of a single hydroxy acid. This hydroxy acid is not affected by dilute alkalies—it was recovered quantitatively from a solution of potassium hydroxide which had been boiled for four hours. In methyl alcohol containing a trace of sodium methylate, the β-lactone is opened quantitatively to a methyl ester of this same hydroxy acid. This methyl ester is also obtained from the hydroxy acid with methyl alcohol and sulfuric acid.

The methyl ester of a higher-melting isomeric hydroxy acid is obtained quantitatively when solutions of the β-lactone in methyl alcohol, containing sulfuric acid, are allowed to stand. This higher-melting hydroxy acid is also formed to some extent when the β-lactone is dissolved in methyl alcohol containing an excess of sodium methylate, or when it is boiled for a long time with dilute sulfuric acid. No isomerization of the lower-melting hydroxy acid, obtained from the β-lactone with bases, is observed in acid solutions. Thus, in this manner it was possible to secure the two isomeric hydroxy acids, though it was impossible to prepare more than one β-lactone.

The isomeric hydroxy acids, like all the other pairs of isomers that have been described, differed greatly in the ease with which they formed dicyclic acetates in acetic anhydride, but, unlike the bromo acids, in mixtures of acetic acid and anhydride satisfactory conversion to cyclic acetates could not be achieved. In acetic anhydride, the lower-melting hydroxy acid, which was formed by the action of bases on the β-lactone, failed to form the dicyclic compound, but the higher-melting isomer was converted into a dicyclic acetate without difficulty. On this basis, the latter acid is a derivative of the *cis* ketonic acid and the former is a derivative of the *trans* acid. However, these configurations have not been established with the certainty that was possible with the bromo acids.

The hydroxy groups in both the hydroxy acids were surprisingly resistant to attack. At the ordinary temperatures, with hydrogen bromide in acetic acid, the hydroxyl groups were not replaced with bromine and at elevated temperatures only thick oils resulted. Furthermore, it was not possible to prepare the corresponding methoxy acids by any of the ordinary methods.

With the configurations that are established, it is possible finally to decide whether the β-lactone is closed with or without inversion. Because the ring formation proceeds through closure of two groups in the *cis* position, with formation of a β-lactone of the same configuration, no inversion has occurred. The evidence obtained favors the same *cis* configuration for the hydroxy acid that is obtained from the β-lactone with bases and on this basis the ring opening with bases has also occurred without inversion. These reactions are shown in the chart.



Experimental

A part of the material employed in the investigations was prepared from dimethyl phthalate. The commercial ester was hydrogenated in the presence of Raney catalyst at a temperature of 225° and under a pressure of 2000 lbs. (133 atm.). As it was impossible to attain complete hydrogenation, the product had to be purified by fractional distillation before it was hydrolyzed to the dibasic acid from which the anhydride was made.

The rest of the material was made by adding maleic anhydride to butadiene[3] and hydrogenating the addition product. As the equipment for making butadiene[4] in quantity was available, we found it much more convenient to synthesize the anhydride by this method than to make it from the phthalate.

Tetrahydrophthalic Anhydride.—Diels and Alder operated in sealed tubes, but we found that with our much

---

[3] Diels and Alder, *Ann.*, **460**, 113 (1928).

[4] Fieser, *Org. Syntheses*, **17**, 25 (1937).

larger quantities it was quite feasible and much more convenient to operate in strong-walled flasks in the following manner. A suspension of 90 g. of maleic anhydride in 300 cc. of pure benzene was introduced into a suction flask equipped with a delivery tube that dipped under the surface of the liquid, and a Bunsen valve that was constructed out of heavy-walled tubing. The delivery tube was connected with a cooled vessel containing 70 g. of butadiene and the container was allowed to assume the temperature of the room. The gas was absorbed as fast as it was evolved, the temperature of the suspension rose rapidly and the anhydride disappeared before all of the diene had evaporated. The clear solution was allowed to remain under the pressure of butadiene until most of the addition product had separated, then cooled and filtered. The yield was 134 g. or 96%.

Hydrogenation: *cis* Cyclohexane Dicarboxylic Anhydride, I.—A suspension of 40 g. of the anhydride in 40 g. of glacial acetic acid was shaken with hydrogen in the presence of 0.1 g. of Adams catalyst. Hydrogen was absorbed rapidly, the reduction being complete in three to four hours. The catalyst was removed by filtration and the solvent by evaporation under diminished pressure. Nearly all of the residue was pure *cis* anhydride distilling at 161.7–161.9° (25 mm.) and melting at 31°. The yield was 93%.

***trans*-Cyclohexane Dicarboxylic Anhydride, II.**—The *cis* anhydride was heated for three hours at 180° with concentrated hydrochloric acid and the resulting *trans* acid was converted into its anhydride by treatment with acetyl chloride as directed by Baeyer.[5] The anhydride melted at 140–142° and the yield was 70%.

***cis*-*p*-Bromobenzoyl Cyclohexane Dicarboxylic Acid, III.**—To a solution of 50 g. of the *cis* anhydride in 250 g. of bromobenzene which was cooled to 10° was added, in a single lot, 94 g. of powdered aluminum chloride. The mixture was stirred and the temperature rose to 60–65°. After remaining at room temperature for forty-five minutes it was stirred into a mixture of ice and dilute acid and set aside to allow the acid to solidify. The solid was removed, washed with water and dissolved in sodium carbonate. After removal of the unchanged bromobenzene with ether, the carbonate solution on acidification deposited 98 g. of solid which was recrystallized from 75% acetic acid. It separated in fine needles melting at 169–171°. It is very sparingly soluble in ether, readily soluble in chloroform, benzene and acetone. The yield was 83 g. or 83%.

Anal. Calcd. for $C_{14}H_{15}O_3Br$: C, 54.0; H, 4.8. Found: C, 53.9; H, 4.9.

The methyl ester of the *cis* ketonic acid was prepared by means of diazomethane. It crystallized from ether–petroleum ether in small prisms melting at 60–61°. It also can be obtained by esterifying the acid with methyl alcohol and sulfuric acid but the yield is poor.

Anal. Calcd. for $C_{15}H_{17}O_3Br$: C, 55.4; H, 5.2. Found: C, 55.3; H, 5.2.

The Dicyclic Acetate, V.—(1) To a cooled solution of 1.0 g. of the *cis* ketonic acid in 60 cc. of acetic acid was added 20 cc. of acetic anhydride containing a trace of sulfuric acid (one drop of acid to 50 cc. of anhydride) which had been cooled to 0°. The solution was kept at 10° for half an hour, then stirred into ice water and left to itself for an hour. (2) One gram of the acid was dissolved in 40 cc. of equal parts of acetic acid and acetic anhydride and the solution kept at 60–65° for fifteen minutes. The solution was then treated as above. The resulting solid in each case was recrystallized from ether–petroleum ether. It separated in small prisms melting at 149°. The yields were 0.9 g. The mixed melting point of the two samples was not depressed.

Anal. Calcd. for $C_{16}H_{17}O_4Br$: C, 54.5; H, 4.9. Found: C, 54.5; H, 5.0.

Hydrolysis of the Acetate.—The acetate is hydrolyzed with great rapidity. In boiling moist ether it disappeared within three hours and it was removed from its ethereal solution by dilute sodium bicarbonate. In each case the *cis* ketonic acid was the only product.

***trans*-*p*-Bromobenzoyl Cyclohexane Carboxylic Acid, IV.**—By the same procedure that was employed for the preparation of the *cis* ketonic acid, the anhydride of *trans* cyclohexane dicarbonic acid was converted into the *trans* ketonic acid. The acid was recrystallized from ether–petroleum ether. It separated in irregular prisms melting at 164°. The yield was 60%.

Anal. Calcd. for $C_{14}H_{15}O_3Br$: C, 54.0; H, 4.8. Found: C, 54.2; H, 5.1.

The Methyl Ester.—The ester was prepared both with diazomethane and with methyl alcohol and sulfuric acid. It crystallized from methyl alcohol in prisms and melted at 98–99°. The yields were quantitative.

Anal. Calcd. for $C_{15}H_{17}O_3Br$: C, 55.4; H, 5.2. Found: C, 55.5; H, 5.4.

The Dicyclic Acetate, VI.—In experiments which were conducted exactly the same as that by which the *cis* ketonic acid was converted into the dicyclic compound, all of the *trans* acid was recovered. The acetic acid was omitted, therefore, and 1.0 g. of the *trans* acid was dissolved in 20 cc. of acetic anhydride containing a trace of sulfuric acid. The solution was kept at the ordinary temperature for fifteen minutes and then manipulated as described under the *cis* acetate. The result was 1.0 g. of the *trans* dicyclic acetate. It crystallized from ether–petroleum ether in small prisms and it melted at 96–97°. The *trans* acetate is more stable than the *cis* isomer in the presence of water but it is rapidly hydrolyzed by dilute acids, regenerating the *trans* acid.

Anal. Calcd. for $C_{16}H_{17}O_4Br$: C, 54.5; H, 4.9. Found: C, 54.6; H, 5.2.

Isomerization of the *cis* into the *trans* Ketonic Acid.—The *cis* ketonic acid, like the dibasic acid, can be isomerized with acids but unlike the dibasic acids it is isomerized much more rapidly with bases. Thus, after a solution of 15 g. of the acid in 400 cc. of 5% aqueous sodium carbonate had been boiled for three hours, it contained only the salt of the *trans* acid. The *trans* acid is, therefore, most easily secured by converting the *cis* anhydride into the corresponding ketonic acid and inverting this acid with sodium carbonate.

The Unsaturated γ-Lactone, VII.—A suspension of 10 g. of the *cis* ketonic acid in 50 cc. of acetic anhydride was cooled to 0°, stirred vigorously and treated with 3 drops of

---

(5) Baeyer, *Ann.*, **258**, 217 (1890).

concentrated sulfuric acid. The acid dissolved immediately and in a few moments a new solid appeared. After fifteen minutes the mixture was stirred into ice water where it was left for an hour. The solid was then collected, washed with water, dried and recrystallized from methyl alcohol. It separated in small cubes melting at 95°. The yield was 8 g. In a repetition with the same quantity of the *trans* acid, the same solid was formed in the same quantity and apparently with the same ease.

Anal. Calcd. for $C_{14}H_{13}O_2Br$: C, 57.3; H, 4.5. Found: C, 57.4; H, 4.8.

Hydrolysis.—The unsaturated lactone, like the corresponding monocyclic lactones, reverts to a ketonic acid when it is treated with bases. Thus a solution of 1 g. of the substance in 50 cc. of methyl alcohol containing a gram of potassium hydroxide was boiled for an hour, then diluted with water and acidified. The product was 0.6 g. of the *trans* ketonic acid, the only ketonic acid that is stable in the presence of bases.

Addition of Bromine: the Dibromide, VIII.—To a solution of 4 g. of the unsaturated lactone in 40 cc. of carbon disulfide, which was kept at 0°, was added 2.2 g. of bromine. The bromine disappeared as fast as it was added. After removing a part of the solvent, the residual solution was diluted with petroleum ether. It deposited 5.4 g. of a solid which, after recrystallization from ether–petroleum ether from which it separated in large tables, melted with decomposition at 119–122°.

Anal. Calcd. for $C_{14}H_{13}O_2Br_3$: C, 37.1; H, 2.9; Br, 53.0. Found: C, 37.3; H, 3.2; Br, 52.8.

Hydrolysis.—The dibromide is hydrolyzed slowly in contact with air, more rapidly when shaken with dilute acetic acid. After a suspension of 2 g. of the substance had been shaken with the dilute acid for eight hours it yielded 1.6 g. of pure *trans* bromo ketonic acid X.

Alcoholysis: the Dicyclic Bromomethyl Ether.—A solution of 0.5 g. of the dibromide in 10 cc. of methyl alcohol was kept at the ordinary temperature for three hours and then allowed to evaporate. The resulting oil was dissolved in ether. From the washed and dried ethereal solutions petroleum ether precipitated the solid ether in small hard prisms melting at 93°. The corresponding ethyl ether melts at 115°. These ethers are more stable than the bromide and the acetate but when they are digested with acetic acid and concentrated hydrochloric acid they likewise are hydrolyzed to the *trans* bromo ketonic acid.

Anal. Calcd. for $C_{15}H_{16}O_3Br_2$: C, 44.6; H, 4.0. Found: (93°) C, 44.5; H, 4.2. Calcd. for $C_{16}H_{18}O_3Br_2$: C, 46.0; H, 4.3. Found: (115°) C, 46.1; H, 4.6.

Reaction with Acetic Anhydride: the *trans* Dicyclic Bromoacetate, IX.—A solution of 0.5 g. of the dibromide in acetic anhydride almost immediately deposited 0.4 g. of the solid bromoacetate. It was crystallized from chloroform from which it separated in small, hard prisms melting with decomposition at 174–176°.

Anal. Calcd. for $C_{16}H_{16}O_4Br_2$: C, 44.5; H, 3.7. Found: C, 44.3; H, 3.8.

As this bromo compound can be obtained without difficulty by brominating either the *cis* or the *trans* ketonic acid, it was used as a source for the *trans* bromo ketonic acid. For this purpose it was prepared in the following manner: a solution of 39 g. of bromine in 50 cc. of acetic acid was added slowly to a solution of 75 g. of the *cis* ketonic acid in 200 cc. of acetic anhydride. The reaction started at once and proceeded rapidly. Hydrogen bromide was not evolved. The cyclic acetate began to precipitate before more than a third of the bromine had been added. In order to complete the precipitation the mixture was cooled for several hours in ice water before filtration. The solid was washed with dilute acetic acid, dried and recrystallized from chloroform or benzene. The yield was 94%. When the *trans* ketonic acid was brominated in the same manner the same dicyclic bromoacetate was obtained, the yield being 93%.

Hydrolysis: the *trans* Bromo Ketonic Acid, X.—The bromoacetate is not nearly so sensitive as the corresponding unsubstituted acetate, being unaffected when its ethereal solution is shaken with dilute solutions of bases. For the purpose of hydrolysis a suspension of 98 g. of the compound in 300 cc. of acetic acid and 40 cc. of concentrated hydrochloric acid was heated with constant stirring on a steam-bath for two hours. The clear solution, cooled and diluted with water, deposited a solid which, after recrystallization from ether, from which it separated in hard irregular prisms, melted at 147°. The yield was 94%.

Anal. Calcd. for $C_{14}H_{14}O_3Br_2$: C, 43.1; H, 3.6. Found: C, 43.1; H, 3.9.

The *cis* Dicyclic Bromoacetate, XI.—A solution of 2.6 g. of bromine in 20 cc. of acetic acid was added to a solution of 5.0 g. of the *cis* ketonic acid in 150 cc. of acetic acid and 75 cc. of anhydride. The reaction started slowly and required an hour for completion. When the solution was cooled it deposited 2.5 g. of the *trans* bromoacetate which was removed by filtration. The filtrate, on dilution with water, deposited 2.0 g. of solid that was separated by recrystallization from ether into 0.5 g. of *trans* and 1.5 g. of the *cis* bromoacetate. This *cis* compound crystallized from ether in flat needles melting at 149°.

Anal. Calcd. for $C_{16}H_{16}O_4Br_2$: C, 44.5; H, 3.7. Found: C, 44.3; H, 3.9.

Hydrolysis: the *cis* Bromo Ketonic Acid, XII.—The dicyclic acetate was hydrolyzed in the same manner as the *trans* compound. The product crystallized in fine needles and melted with decomposition at 185–187°.

Anal. Calcd. for $C_{14}H_{14}O_3Br_2$: C, 43.1; H, 3.6. Found: C, 42.8; H, 3.7.

The methyl ester of the *cis* bromo ketonic acid was obtained by means of diazomethane and with methyl alcohol and sulfuric acid. It crystallized from ether in small prisms and melted at 106°.

Anal. Calcd. for $C_{15}H_{16}O_3Br_2$: C, 44.6; H, 4.0. Found: C, 44.3; H, 4.4.

In the bromination of the *cis* ketonic acid the bromo derivatives of the *cis* and *trans* acids were formed in poor yields in the ratio of 30% of the former to 70% of the latter. Under the same conditions bromination of the unsaturated γ-lactone resulted in 25% of *cis* and 75% of *trans* compounds. No *cis* compounds were formed in the bromination of the *trans* ketonic acid but at least 20% of the product formed in the bromination of the methyl ester of the *trans* ketonic acid was the methyl ester of the *cis* bromo ketonic acid. Attempts to isomerize the *cis* bromo acid were unsuccessful.

Configuration of the Bromo Ketonic Acids.—Solutions of 0.5 g. of each bromo acid in 20 cc. of equal parts of acetic acid and acetic anhydride or in 20 cc. of one part acetic acid and four parts acetic anhydride were kept at 80° for forty-five minutes, then poured into ice water. The resulting solutions were stirred for an hour before filtration. The solid in each case from the bromo acid melting at 147° was unchanged bromo acid and the recovery of acid recrystallized from ether–petroleum ether was 80%. The solid from the bromo acid melting at 187° was the dicyclic acetate XI melting at 149° and the yield of pure recrystallized compound was 80%.

In another experiment in which solutions of equal quantities of the two bromo acids in acetic anhydride were kept at the temperature of the room for five hours and then manipulated as in the preceding experiment, the bromo acid melting at 147° was again recovered in an almost quantitative yield. The product from the higher melting bromo acid was a new dicyclic acetate which crystallized from ether–petroleum ether in small prisms which melted at 78°. When this acetate was hydrolyzed with acetic acid and hydrochloric acid it regenerated the bromo acid from which it had been formed.

Anal. Calcd. for $C_{16}H_{16}O_4Br_2$: C, 44.5; H, 3.7. Found: C, 44.5; H, 3.9.

These experiments show quite conclusively that the configuration of the higher-melting bromo acid is represented by XII and that of the lower-melting bromo acid by X.

The β-Lactone, XIII.—A solution of 5 g. of the lower-melting bromo acid in 250 cc. of alcohol-free ether was shaken for two hours with 250 cc. of 1% sodium bicarbonate. The ether layer was washed thoroughly with water, dried over sodium sulfate, concentrated and diluted with low boiling petroleum ether. It deposited a solid which, after recrystallization from methyl alcohol, melted at 83°. The lactone crystallizes in diamond-shaped plates and is soluble in all common solvents except petroleum ether. The yield was 97%.

Anal. Calcd. for $C_{14}H_{13}O_3Br$: C, 54.4; H, 4.3. Found: C, 54.6; H, 4.7.

The β-lactone is stable in methyl alcoholic solutions even with prolonged boiling. With hydrogen bromide in acetone solution the β-lactone was converted completely into the *trans* bromo acid from which it is formed. With ammonia in methyl alcohol only unidentified oily products were obtained.

Action of Bases; the *trans* Hydroxy Acid, XIV.—A solution of 5 g. of the lactone in ether was shaken with 300 cc. of 1% aqueous potassium hydroxide for twenty minutes. The resulting alkaline solution on acidification deposited 4.5 g. of a solid which, after recrystallization from ether–petroleum ether from which it separated in small, hard prisms, melted at 134°. The yield was 90%. As this acid is not affected by aqueous alkalies, it is also the only product that is formed when the bromo acid is shaken with dilute aqueous potassium hydroxide. Isomerization of this acid also was not detected in acid solutions.

Anal. Calcd. for $C_{14}H_{15}O_4Br$: C, 51.4; H, 4.6. Found: C, 51.3; H, 4.6.

The methyl ester, obtained by treating the *trans* hydroxy acid with diazomethane, crystallized from ether–petroleum ether in thick plates melting at 88°.

Anal. Calcd. for $C_{15}H_{17}O_4Br$: C, 52.8; H, 5.0. Found: C, 53.0; H, 5.5.

When a solution containing 2 g. of the β-lactone in 50 cc. of methyl alcohol containing 0.0007 mole of sodium methylate was allowed to stand for fifteen hours there was obtained after the usual manipulations 1.6 g. of a solid methyl ester which, after recrystallization from ether–petroleum ether, from which it separated in small prisms, melted at 142°.

Anal. Calcd. for $C_{15}H_{17}O_4Br$: C, 52.8; H, 5.0. Found: C, 52.6; H, 5.2.

This same 142° methyl ester also was obtained from the *trans* hydroxy acid with methyl alcohol and sulfuric acid in quantitative yields. When the 88° methyl ester is allowed to stand in methyl alcohol solutions containing either sulfuric acid or a trace of sodium methylate, it is converted completely into the 142° methyl ester. Both of these esters are hydrolyzed readily to the *trans* hydroxy acid with bases and less readily with acids. No evidence was obtained to show that one of them is a cyclic ether.

The *cis* Hydroxy Acid, XV.—A solution of 10 g. of the β-lactone in 600 cc. of methyl alcoholic sodium methylate containing 6 g. of sodium was left at room temperature. It deposited 5 g. of the sodium salt of the *trans* hydroxy acid. The filtrate from the salt, diluted with water and acidified, deposited 4 g. of the isomeric acid in nearly pure condition. The acid crystallized from ether in thin plates melting at 187°. The same acid was obtained in a yield of 68% when the lactone was boiled for thirty hours with 5% sulfuric acid. The methyl ester of this same hydroxy acid was also obtained in nearly quantitative yield when methyl alcoholic solutions of the β-lactone containing a few drops of sulfuric acid were allowed to stand at room temperature. This methyl ester was hydrolyzed readily with bases to the hydroxy acid.

Anal. Calcd. for $C_{14}H_{15}O_4Br$: C, 51.4; H, 4.6. Found: C, 51.2; H, 4.6.

The methyl ester obtained by treating the *cis* hydroxy acid either with diazomethane or with methyl alcohol and sulfuric acid, and from the β-lactone with methyl alcohol and sulfuric acid, crystallized from methyl alcohol in hard, irregular prisms, which melted at 54°.

Anal. Calcd. for $C_{15}H_{17}O_4Br$: C, 52.8; H, 5.0. Found: C, 53.1; H, 5.4.

Configuration of the Hydroxy Acids: the Dicyclic Hydroxy Acetate, XVI.—One gram of each of the hydroxy acids was shaken with 40 cc. of pure acetic anhydride until solution was complete—about fifteen minutes. The solutions were kept at the ordinary temperature for forty-five minutes, then poured into ice water. The resulting suspensions were stirred for an hour before the solid products were removed and purified. The solid from the lower-melting acid was unchanged hydroxy acid—the recovery of pure acid after recrystallization from ether–petroleum ether was 70%. The solid from the higher-melting hydroxy acid was a neutral compound which crystallized from ether–petroleum ether in short, stout needles melting at 95°. The yield was 77%.

Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.0; H, 4.6. Found: C, 51.7; H, 4.9.

In ether solution this neutral product was not hydrolyzed with sodium bicarbonate solution but when it was digested with a dilute solution of hydrochloric acid in acetic acid it regenerated the higher-melting hydroxy ketonic acid.

In solutions of acetic anhydride and acetic acid both hydroxy acids failed to react at the ordinary temperature. With heating in such solutions both hydroxy acids gave oils which invariably gave both the hydroxy acids on standing or when their ether solutions were extracted with dilute sodium bicarbonate. On the basis of the experiments with acetic anhydride only the higher-melting acid forms a dicyclic acetate and in this acid the carboxyl and bromobenzoyl groups are on the same side of the ring as shown in formula XV.

Summary

The configurations of two cyclic diastereomeric β-bromo γ-keto acids have been established. The bromo acid in which the bromine and carboxyl groups are in the *cis* position is the only one that will form a β-lactone. Evidence is given to show that this β-lactone formation has occurred without inversion. The β-lactone is opened with bases to give a single hydroxy acid. The evidence indicates that this hydroxy acid has the same configuration as the β-lactone and the bromo acid from which it is prepared.

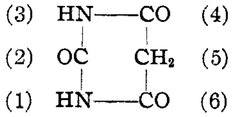
CAMBRIDGE, MASS. RECEIVED JUNE 27, 1938

[CONTRIBUTION NO. 135 FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

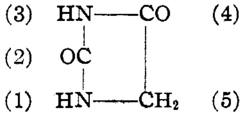
5,5-Dialkylhydantoins Containing a Dialkylamino Substituent[1,2]

BY J. WM. MAGEE WITH HENRY R. HENZE

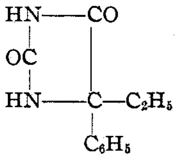
Attempts to relate chemical constitution to physiological activity have been of but moderate success and the information thus secured has been used in the development of the barbituric acid series of soporifics.[3,4] Synthesis of additional derivatives in this field has continued with the production of only a few new types. More recently interest has again been centered in the preparation of sedatives through the replacement of the hydrogen attached to the nitrogen of the barbituric acid nucleus by alkyl groups.[5,6] Here, particularly, the substitution of the methyl group for the imidic hydrogen has in certain instances produced compounds of extremely short but intense period of hypnotic activity.[7] A late publication includes evidence of success in the introduction of alkylamino groupings[8] into the alkyl commonly attached to the 5-position of the heterocycle.



I



II



III

A definite similarity exists in the structure of barbituric acid (I) and hydantoin (II), and rather close analogy is evident in the fact of the existence of compounds derived from substitution of identical groupings for the hydrogen atoms in the 5,5-, 1- and 3-positions of both the barbituric acid and hydantoin heterocycles.[4,6,9-11] Although, as yet, but one 5,5-disubstituted hydantoin[12] (III) has found clinical use, the hydantoin nucleus is innocuous and offers hope that additional compounds of value as sedatives may be derived from it by appropriate substitution. In this Laboratory attention has previously been directed to the utilization of alkoxyalkyl[13] and aryloxyalkyl[14] substituents and compounds of definite hypnotic power but unfavorable toxicity have been pro-

---

[1] From a portion of a dissertation presented by J. Wm. Magee to the Faculty of the Graduate School of The University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1938.

[2] Presented before the Division of Medicinal Chemistry at the 95th meeting of the American Chemical Society, Dallas, Texas, April 18 to 21, 1938.

[3] Shonle, *Ind. Eng. Chem.*, **23**, 1104 (1931).

[4] Shonle, Waldo, Keltch and Coles, THIS JOURNAL, **58**, 585 (1936).

[5] U. S. Patent 1,073,380 (Sept. 16, 1913); U. S. Patent 1,074,030 (Sept. 30, 1913); German Patent 537,366 (July 9, 1929); British Patent 401,693 (Nov. 17, 1933); U. S. Patent 1,947,944 (Feb. 20, 1934); German Patent 606,499 (Dec. 4, 1934).

[6] Dox and Jones, THIS JOURNAL, **51**, 316 (1929); Shonle and Doran, *ibid.*, **58**, 1358 (1936); Buck, Hjort, Ide and DeBeer, *ibid.*, **60** 461 (1938).

[7] Tabern and Volwiler, *ibid.*, **58**, 1354 (1936).

[8] Rosenberg, Kneeland and Skinner, *ibid.*, **56**, 1339 (1934).

[9] Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

[10] Bucherer and Lieb, *J. prakt. Chem.*, **141**, 5 (1934).

[11] Biltz and Slotta, *ibid.*, **113**, 245, 255 (1926).

[12] Swiss Patent 72,561 (Sept. 16, 1916).

[13] Rigler with Henze, THIS JOURNAL, **58**, 474 (1936).

[14] Whitney with Henze, *ibid.*, **60**, 1148 (1938).