[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. XI. SYNTHESIS OF β-SUBSTITUTED-$\Delta^{\alpha,\beta}$-BUTENOLIDES FROM METHYL KETONES

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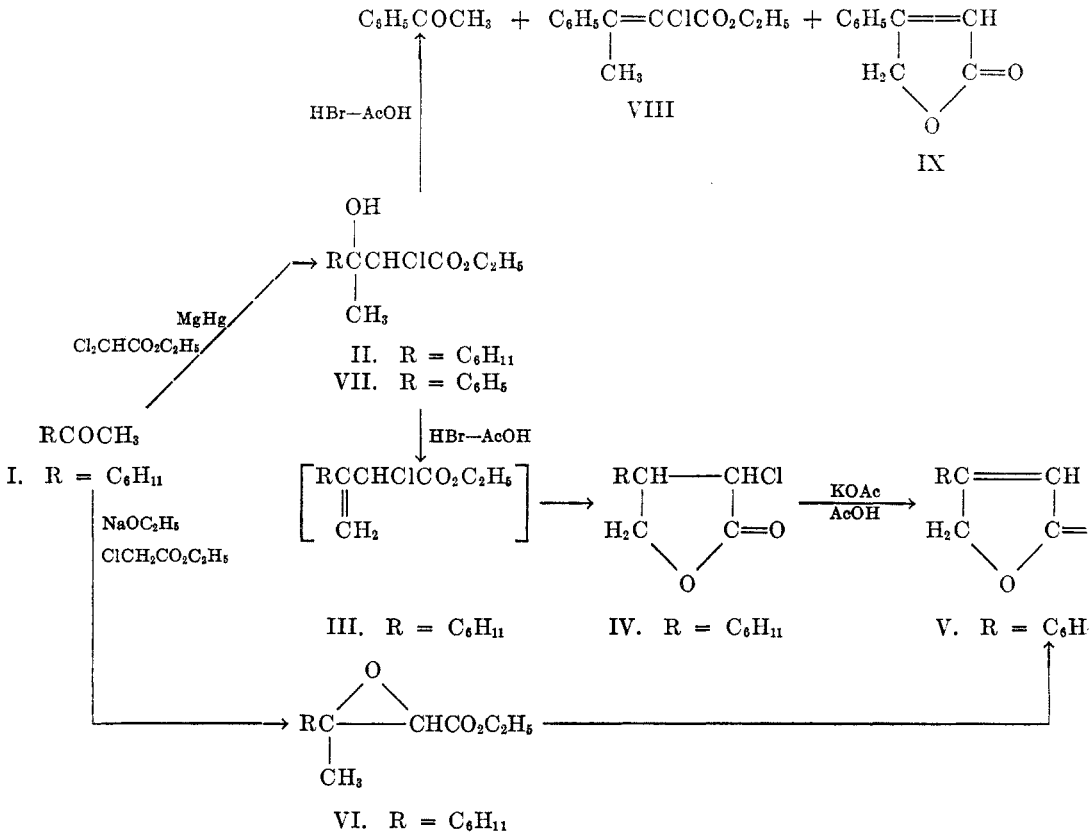
In previous communications, two general syntheses for β-substituted-$\Delta^{\alpha,\beta}$-butenolides have been described (1, 2). From the standpoint of over-all yield, accessibility of starting materials, number of steps involved, etc., these left something to be desired. In both of the earlier syntheses the double bond of the lactone was formed by removal of a β-substituent, which in turn was introduced by means of a Reformatzky reaction between ethyl bromoacetate and an alkoxy- or acyloxy-methyl ketone. In the present communication we wish to present our experience with the elimination of an α-substituent of a β-substituted butyro lactone as a means for introducing the desired double bond. The work has been confined to the preparation of simple model butenolides which are analogous to the cardiac aglycones and in which the substituent is cyclohexyl or phenyl.

Cyclohexyl methyl ketone (I) readily undergoes the Darzens (3) condensation with ethyl dichloroacetate in the presence of magnesium amalgam to yield ethyl α-chloro-β-hydroxy-β-cyclohexylbutyrate (II). When the latter is treated with a solution of hydrogen bromide in glacial acetic acid, ring closure ensues and α-chloro-β-cyclohexylbutyrolactone (IV) results in good yield. This rather novel lactone formation apparently proceeds through the intermediate unsaturated ester III, which is formed by dehydration of II, but which could not be isolated. Lactonization on the double bond then occurs in the known manner (4) after hydrolysis of the ester group. Elimination of the chlorine in the α-chloro lactone presented considerable difficulty. When the conventional method for accomplishing this by boiling the chloro lactone with quinoline was applied, extensive resinification took place. Use of the lower-boiling dimethylaniline resulted in only partial removal of hydrogen chloride and led to a mixture of unsaturated lactone and unchanged chloro lactone, together with condensation products of obscure nature. Pyridine was without action on the chloro lactone. Aqueous sodium hydroxide partially converted the chloro lactone to the corresponding hydroxy lactone. However, when the chloro lactone was heated with anhydrous potassium acetate in acetic acid, the desired removal of hydrogen chloride was accomplished yielding β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (V).

Cyclohexyl methyl ketone also condensed smoothly with ethyl monochloroacetate in the presence of sodium ethoxide when the reaction was carried out by the method of Yarnall and Wallis (5), to yield the glycidic ester, VI. This ester, on treatment with a solution of hydrogen bromide in acetic acid, gave a small yield of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide. However, the synthesis was

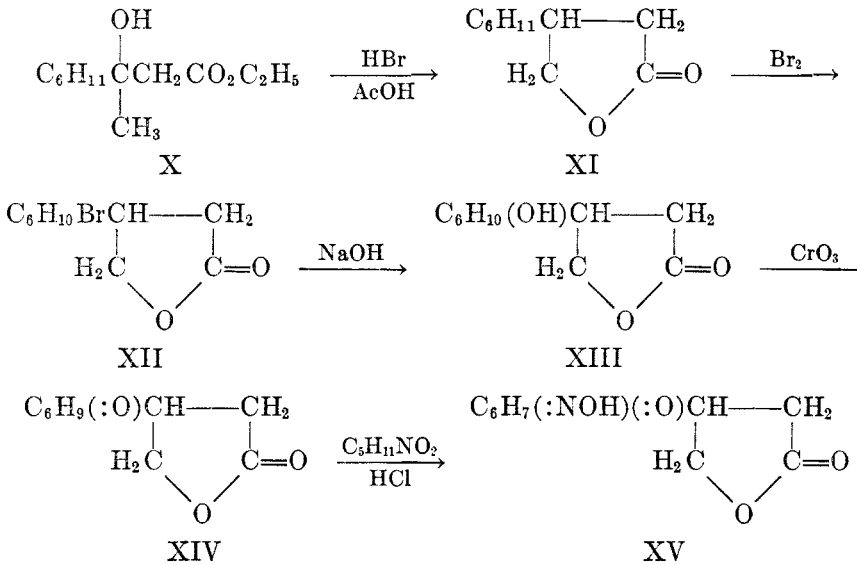


abandoned because of the poor yields and the difficulty encountered in separating the butenolide from contaminating by-products of the reaction.

In the phenyl series, acetophenone was condensed with ethyl dichloroacetate according to Darzens (3), yielding ethyl α-chloro-β-hydroxy-β-phenylbutyrate (VII) together with a small amount of acetophenone pinacol. The presence of the aromatic substituent in VII, contrasted with the cyclohexyl substituent in II, resulted in the formation of a more complex mixture of products when the ester VII was treated with hydrogen bromide in acetic acid. From the product of the reaction we have isolated acetophenone, apparently formed by a reversal of the Darzens condensation, ethyl α-chloro-β-phenylcrotonate (VIII), formed by α,β-dehydration of VI, and β-phenyl-$\Delta^{\alpha,\beta}$-butenolide (IX), formed by β,γ-dehydration of VII and subsequent lactonization and dehydrochlorination.

In view of the difficulty encountered in removing hydrogen chloride from α-chloro-β-cyclohexylbutyrolactone by the use of organic bases, it was felt that substitution of the more reactive bromine might lead to a smoother reaction. When ethyl β-hydroxy-β-cyclohexylbutyrate (X) was heated with hydrogen bromide in acetic acid, β-cyclohexylbutyrolactone (XI) was formed in excellent yield. It was then planned to brominate the saturated lactone, XI, whereby

α-bromo-β-cyclohexylbutyrolactone should be expected. However, while the lactone, XI, was readily brominated in acetic acid solution, investigation of the resulting bromo derivative disclosed that bromination had occurred on the cyclohexane ring, although the exact position taken by the bromine has not been demonstrated. The bromine atom in XII was replaced by a hydroxyl group by means of aqueous sodium hydroxide solution to yield α,β-(x-hydroxycyclohexyl)butyrolactone (XIII), the *p*-nitrobenzoate of which was not identical with the *p*-nitrobenzoate of α-hydroxy-β-cyclohexylbutyrolactone prepared from α-chloro-β-cyclohexylbtuyrolactone, IV. That the hydroxyl group in XIII is secondary was shown by oxidation to a ketone (XIV) without degradation. The possibility that bromination had occurred in the γ-position of the lactone was excluded on the basis of saponification values obtained with the keto lactone. Only one saponifiable group was found, whereas had bromination in the lactone ring



taken place, an anhydride requiring two equivalents of alkali in saponification, would have been formed by the above series of reactions. Furthermore, the keto lactone, XIV, yielded an isonitroso derivative when treated with isoamyl nitrite. The formation of such a derivative can only take place provided an unsubstituted methylene group is adjacent to the carbonyl group, a condition met only on the assumption that the ketone group in question, and hence its precursor bromine, is located on the cyclohexane ring.

EXPERIMENTAL

All melting and boiling points are corrected for stem exposure.

Ethyl α-chloro-β-hydroxy-β-cyclohexylbutyrate (II). Magnesium amalgam was prepared by heating 12.5 g. (0.5 mole) of magnesium turnings with 625 g. of dry mercury in a one-liter round-bottom flask. It was found to be unnecessary to carry out the amalgamation under an atmosphere of hydrogen as suggested by Darzens (3). To the well cooled amal-

gam was added a mixture of 400 cc. of anhydrous ether, 63 g. (0.5 mole) of cyclohexyl methyl ketone, and 90 g. (0.58 mole) of ethyl dichloroacetate all at one time. The stoppered flask was then shaken by hand until the amalgam had completely dissolved, the temperature being controlled so that it did not rise above 30°. Mechanical shaking for one hour completed the reaction. The solution was then poured into an excess of ice and concentrated hydrochloric acid and the resulting mixture was extracted with ether. After washing the ether extract free from acid, first with sodium carbonate solution and then with water, and drying over anhydrous magnesium sulfate, the residue, after evaporation of the ether, was distilled under reduced pressure. The yield of ethyl α-chloro-β-hydroxy-β-cyclohexylbutyrate boiling at 110–135° at 1.8 mm. was 84.5 g., or 68%. n_D^{25} 1.4776.

Anal. Calc'd for $C_{12}H_{21}ClO_3$: C, 57.9; H, 8.5; Cl, 14.3.
Found: C, 57.9; H, 8.5; Cl,14.5

α-Chloro-β-cyclohexylbutyrolactone (IV). A solution of 90 g. of ethyl α-chloro-β-hydroxy-β-cyclohexylbutyrate in 120 cc. of glacial acetic acid which had been previously saturated with dry hydrogen bromide at 0°, and 350 cc. of glacial acetic acid, was refluxed. After about half an hour a low-boiling liquid began to condense, and the reflux condenser was replaced by one set downward for distillation. Forty-eight grams of distillate, boiling up to 62°, was collected. Alternate refluxing and distilling were then continued for 24 hours, during which, at the end of 16 hours, 25 cc. more of glacial acetic acid, saturated with hydrogen bromide, was added. The residual mixture was then poured into a large amount of ice and water and extracted with ether. After washing the ether extract free from acid and drying, the residue, after removal of the solvent, was distilled under reduced pressure yielding 39 g., or 48% of α-chloro-β-cyclohexylbutyrolactone. The chloro lactone is a heavy, mobile, yellow oil which boiled at 131–135° at 0.9 mm. On standing, the chloro lactone crystallized as stout white prisms which were very soluble in the usual organic solvents. After crystallization from isopentane, the substance melted at 131–131.5°.

Anal. Calc'd for $C_{10}H_{15}ClO_2$: C, 59.2; H, 7.5.
Found: C, 59.2; H, 7.6.

α-Hydroxy-β-cyclohexylbutyrolactone. Five and six-tenths grams of α-chloro-β-cyclohexylbutyrolactone was refluxed for 4 hours with 100 cc. of 4% sodium hydroxide solution. The alkaline solution was extracted with ether to remove a slight amount of insoluble material and then acidified with hydrochloric acid. The acidified solution was warmed on a steam-bath for 4 hours, during which the lactone separated as a heavy yellow oil as relactonization proceeded. After concentrating to about 25 cc. the solution was extracted several times with chloroform. After washing and drying the extract and removing the solvent, 2.7 g. of material which boiled at 122–127° at 0.4 mm., was obtained. This distillate crystallized on scratching, and was found to consist, for the most part, of α-chloro-β-cyclohexylbutyrolactone. About 200 mg. of α-hydroxy-β-cyclohexylbutyrolactone was separated by fractional crystallization of the distillate from petroleum ether (Skellysolve B), in which the chloro lactone is much more soluble than the hydroxy lactone. The hydroxy lactone formed white monoclinic needles which melted at 144°.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7.
Found: C, 65.0; H, 8.8.

The p-*nitrobenzoate* of the above lactone crystallized as clusters of light yellow needles from 50% alcohol and melted at 154–154.5°.

Anal. Calc'd for $C_{17}H_{19}NO_6$: C, 61.2; H, 5.8.
Found: C, 61.0; H, 6.1.

β-Cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (V). A mixture of 6 g. of α-chloro-β-cyclohexylbutyrolactone, 12 g. of anhydrous potassium acetate, and 15 cc. of glacial acetic acid was heated to boiling under reflux. A copious precipitate of potassium chloride separated almost immediately and heating was continued for 12 hours. The mixture was then poured into ice and water and extracted with ether. After washing and drying the extract, the solvent was removed and the residue was distilled under reduced pressure, yielding 2.4 g. or 49% of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide which boiled at 115–117° at 0.1 mm. The lactone gave no

Beilstein test for halogen and gave the characteristic red nitroprusside reaction; n_D^{25} 1.5002; d_4^{25} 1.044; M_D^{25} obs. 46.32; M_D^{25} calc'd 45.17.

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.2; H, 8.5.
Found: C, 72.2; H, 8.7.

Inasmuch as these values do not agree any too well with the previously reported ones of n_D^{25} 1.5059 and d_4^{25} 1.0985 (1), the compound was further identified by conversion to the semicarbazone of methyl β-cyclohexyl-β-formylpropionate by treating it with an alcoholic solution of potassium hydroxide, followed by methylation with diazomethane and treatment of the resulting product with semicarbazide. The semicarbazone thus obtained melted at 118–119° and gave no depression with a sample prepared from the lactone according to Paist, Blout, Uhle, and Elderfield (6).

Ethyl α,β-oxido-β-cyclohexylbutyrate (VI). Dry, freshly prepared sodium ethoxide, prepared from 12.7 g. (0.55 mole) of clean sodium and 350 cc. of freshly distilled absolute alcohol according to Yarnall and Wallis (5), was added in three portions to a mixture of 67.4 g. (0.55 mole) of ethyl monochloroacetate and 63.1 g. (0.50 mole) of cyclohexyl methyl ketone at −80°. A tan-brown mush was obtained which, after standing at −80° for 10 min., was brought to room temperature and left overnight. The next day the paste was heated on the steam-bath for 2.5 hrs. and poured into a mixture of ice and ether. After the alkaline solution had been extracted, it was acidified with hydrochloric acid and further extracted with ether. The combined ether extracts were then washed until neutral, dried over anhydrous magnesium sulfate, and the ether removed. Distillation yielded 23.4 g. or 22% of the theoretical yield of ethyl α,β-oxido-β-cyclohexylbutyrate boiling at 86–90° at 0.3 mm.; n_D^{25} 1.4588.

Anal. Calc'd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.6.
Found: C, 67.5; H, 9.3.

Lactonization of the glycidic ester. A mixture of 10 g. of ethyl α,β-oxido-β-cyclohexylbutyrate, 25 cc. of glacial acetic acid previously saturated with dry hydrogen bromide at 0°, and 25 cc. of glacial acetic acid was alternately refluxed and distilled for 2 hrs. A small amount of low-boiling distillate was collected. After removal of the acetic acid under reduced pressure, the residue was taken up in ether, washed free of acid with sodium bicarbonate solution, dried, and the solvent removed. Distillation yielded 4 g. of material boiling at 134–140° at 0.5 mm.; n_D^{25} 1.4888. This material had an odor similar to β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide and gave a red nitroprusside reaction, but was evidently contaminated with other substances of approximately the same boiling point. It was not investigated further.

Ethyl α-chloro-β-hydroxy-β-phenylbutyrate (VII) was prepared essentially according to Darzens (3) except that the amalgam was not made under hydrogen. Yields of from 45 to 60% were obtained. The ester boiled at 124–126° at 1.5 mm.

In addition to the ester, we have isolated from 5 to 10% of a by-product which boiled at 140–144° at 1.5 mm. and melted at 122°. This substance gave analytical figures and a melting point corresponding to those for acetophenone pinacol. Cimiacian and Silber (7) report the melting point of this pinacol to be 122°.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5.
Found: C, 79.6; H, 7.6.

Action of hydrobromic-acetic acid on ethyl α-chloro-β-hydroxy-β-phenylbutyrate. A solution of 20 g. of the above chloro ester was heated with a mixture of hydrobromic and acetic acids in a manner similar to that used with the analogous cyclohexyl compound. The crude product was isolated as in the previous case and fractional distillation at reduced pressure yielded three fractions.

Fraction I weighed 3 g. and boiled at 53–56° at 0.3 mm. and was identified as acetophenone through its 2,4-dinitrophenylhydrazone, which melted at 233–233.5° and gave the following analytical figures:

Anal. Calc'd for $C_{14}H_{12}N_4O_4$: N, 18.7. Found: N, 18.8.

Fraction II amounted to 4 g. and boiled at 103° at 0.5 mm. The analytical figures ob-

tained corresponded to ethyl α-chloro-β-phenylcrotonate (VIII), which obviously resulted from α,β-dehydration of the hydroxy ester.

Anal. Calc'd for $C_{12}H_{13}ClO_2$: C, 64.1; H, 5.8.
Found: C, 64.4; H, 5.9.

Fraction III amounted to 3.8 g. and boiled at 126–136° at 0.5 mm. On trituration with petroleum ether the oil set, for the most part, to a white crystalline substance. After recrystallization from ether-isopentane the substance formed stout prisms which melted at 93°. It was identified as β-phenyl-$\Delta^{\alpha,\beta}$-butenolide by mixed melting point with a known sample prepared by the method of Linville and Elderfield (2).

Anal. Calc'd for $C_{10}H_8O_2$: C, 75.0; H, 5.1.
Found: C, 75.1; H, 5.1.

β-Cyclohexylbutyrolactone (XI). A mixture of 100 g. of ethyl β-hydroxy-β-cyclohexylbutyrate, prepared by the usual Reformatzky reaction from cyclohexyl methyl ketone and ethyl bromoacetate, as described by Rubin (8), 100 cc. of glacial acetic acid previously saturated with dry hydrogen bromide at 0°, and 300 cc. of glacial acetic acid was heated to boiling under reflux. At the end of half an hour a low-boiling fraction was removed by distillation and the residue was refluxed for a total of 4 hrs. After pouring into ice and water the mixture was extracted with ether. The ether extract, after washing free from acid, drying and removal of the solvent, left a residue which on distillation under reduced pressure gave 62 g., or 79% of β-cyclohexylbutyrolactone. The lactone boiled at 124–126° at 1.2 mm. and corresponded in all respects with that prepared by catalytic reduction of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (6); n_D^{25} 1.4794.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6.
Found: C, 71.5; H, 9.6.

The butyro lactone was also obtained in 78% yield by refluxing a mixture of 20 g. of ethyl β-hydroxy-β-cyclohexylbutyrate with a mixture of 20 cc. of conc'd sulfuric acid, 35 cc. of glacial acetic acid, and 50 cc. of water. After 5 hrs. the original two phases had merged into one and the mixture was worked up in a manner similar to that used above.

Bromination of β-cyclohexylbutyrolactone (XII). A solution of 40 g. (0.25 mole) of dry bromine in 350 cc. of glacial acetic acid was added slowly, and with stirring, to a solution of 33.7 g. (0.2 mole) of β-cyclohexylbutyrolactone in 150 cc. of glacial acetic acid. The reaction was started by the addition of 2 drops of acetic acid saturated with hydrogen bromide, and the mixture was kept at steam-bath temperature during the course of the reaction. The bromine was absorbed promptly and the reaction was complete in about an hour. After pouring onto ice, the mixture was extracted with chloroform and the chloroform extracts were washed free from acid and dried with anhydrous sodium sulfate. Distillation of the residue, after removal of the solvent, yielded 38.3 g., or 77.5% of the bromo-β-cyclohexylbutyrolactone, which boiled at 130–135° at 1 mm. The bromo lactone crystallized on standing and formed fine white needles which melted at 63–63.5° after recrystallization from isopentane. We propose that this substance be designated as β-(*x*-bromocyclohexyl)butyrolactone. Such nomenclature indicates that the bromine is on the cyclohexane ring, although its exact position remains to be determined.

Anal. Calc'd for $C_{10}H_{15}BrO_2$: C, 48.6; H, 6.1; Br, 32.3.
Found: C, 48.9; H, 6.2; Br, 32.2.

β-(x-Hydroxycyclohexyl)butyrolactone (XIII). A mixture of 10 g. of the above bromo lactone, 30 cc. of alcohol, and 100 cc. of 2 *N* sodium hydroxide solution was shaken for 15 hrs. at room temperature, at the end of which time a homogeneous solution was formed. The solution was acidified with hydrochloric acid and warmed for 3 hrs. on the steam-bath in order to complete relactonization. The alcohol was removed by concentration to 75 cc. and the resulting aqueous suspension of a heavy yellow oil was extracted with ether. The residue, after removal of the ether, yielded 5.5 g., or 74% of β-(*x*-hydroxycyclohexyl)-butyrolactone, which boiled at 140–152° at 0.7 mm.; n_D^{25} 1.4946.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7.
Found: C, 65.1; H, 8.7.

The p-*nitrobenzoate* of the above hydroxy lactone crystallized from alcohol in small, light yellow needles which melted at 163–164.5°.

Anal. Calc'd for $C_{17}H_{19}NO_6$: C, 61.2; H, 5.8; N, 4.2.
Found: C, 61.3; H, 6.0; N, 4.5.

When this p-*nitrobenzoate* was mixed with p-*nitrobenzoate* of α-hydroxy-β-cyclohexylbutyrolactone described above, the melting point of the mixture was depressed. It softened at 131° and melted at 148°.

β-(x-Ketocyclohexyl)butyrolactone (XIV). A solution of 2.3 g. of chromic acid in 25 cc. of 90% acetic acid was slowly added to a solution of 8.5 g. of the above hydroxy lactone in 75 cc. of 90% acetic acid, the temperature being kept below 30°. After standing for 20 min. at room temperature, the excess chromic acid was decomposed by the addition of 3 cc. of alcohol. After concentrating the mixture under reduced pressure to 15 cc., 500 cc. of water was added and the solution was extracted with 5 portions of ether. Removal of the ether from the washed and dried extracts and distillation of the residue yielded 3.5 g. of a heavy oil which boiled at 118–125° at 0.1 mm.; n_D^{25} 1.4960. Concentration of the aqueous solution from the ether extract to a small volume and extraction of this with chloroform yielded 2.5 g. of crystalline material which formed clusters of white needles after recrystallization from 50% methanol, and melted at 82–83.5°. When the oil obtained above was seeded with the crystals, about one-half of it crystallized. This failure to crystallize may be accounted for by the presence of two racemic mixtures, one of which crystallizes readily and the other does not. The total yield of keto lactone was 6 g., or 73%.

Anal. Calc'd for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7.
Found: For the oily substance, C, 65.9; H, 8.0.
For the crystalline substance, C, 65.9; H, 8.0.

The p-*nitrophenylhydrazone* prepared from the oily material formed yellow monoclinic prisms from alcohol, which softened at 184° and melted at 187–188° with decomposition.

Anal. Calc'd for $C_{16}H_{19}N_3O_4$: C, 60.6; H, 6.1; N, 13.2.
Found: C, 60.5; H, 6.2; N, 13.5.

That the ketone group formed in the above oxidation, and hence its precursor hydroxyl group, is located on the cyclohexane ring, was further indicated by the behavior of the keto lactone on saponification. When 29.1 mg. of the keto lactone was saponified in 5 cc. of neutral alcohol with 6 cc. of 0.1 *N* sodium hydroxide, and the excess alkali then titrated back, the neutralization equivalent found was 188. Calc'd for one lactone, 182. If by an unlikely possibility the ketone and hydroxyl groups were in the γ-position of the lactone ring, the keto lactone would be a cyclohexylsuccinic anhydride and its neutralization equivalent would be 91.

Isonitroso derivative of β-(x-ketocyclohexyl)butyrolactone (XV). Freshly prepared isoamyl nitrite (0.92 cc.) was added dropwise with shaking to a solution of 920 mg. of crystalline keto lactone in 3 cc. of absolute alcohol, 3 cc. of ether, and 0.1 cc. of conc'd hydrochloric acid (9). After standing at room temperature for 24 hrs., the acid solution was neutralized with dilute sodium bicarbonate solution and evaporated almost to dryness. After addition of 15 cc. of 25% alcohol the solution was extracted with ether. The ether extract, on drying and concentration, yielded a sticky yellow gum which crystallized on trituration with ethyl acetate. Recrystallization from ethyl acetate and petroleum ether yielded clusters of very pale yellow prisms which melted at 160–161° with decomposition.

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.9; H, 6.2.
Found: C, 57.1; H, 6.3.

Action of potassium acetate on β-(x-bromocyclohexyl)butyrolactone. A mixture of 10 g. of the bromo lactone, 15 g. of anhydrous potassium acetate, and 30 cc. of glacial acetic acid was heated under reflux for 8 hrs. During this time a copious precipitate of potassium bromide was formed. An additional 5 g. of potassium acetate was then added and refluxing was continued for another 12 hrs. The reaction mixture was poured into water and the product was extracted with ether. Distillation of the product gave 5.5 g. of a substance

which boiled at 110–114° at 0.2 mm. The analytical figures obtained with this corresponded to a mixture of acetoxycyclohexylbutyrolactone and cyclohexenylbutyrolactone, the latter obviously having been formed by removal of hydrogen bromide. The mixture, however, gave no color reaction with sodium nitroprusside, again substantiating the view that the bromine had been introduced on the cyclohexane ring.

Anal. Calc'd for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0.
Calc'd for $C_{10}H_{14}O_2$: C, 72.2; H, 8.5.
Found: C, 68.8; H, 8.1.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. β-Substituted butyro lactones have been prepared from β-substituted, β-hydroxybutyrates.

2. A new synthesis for β-substituted-$\Delta^{\alpha,\beta}$-butenolides from methyl ketones, has been described.

3. Bromination of β-cyclohexylbutyrolactone takes place on the cyclohexane ring.

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