SYNTHESES OF β-ANISOYLOPROPYLSUCCINIC ACID AND HOMOLOGUES BY MEANS OF REFORMATSKY AND OTHER REACTIONS.

BY

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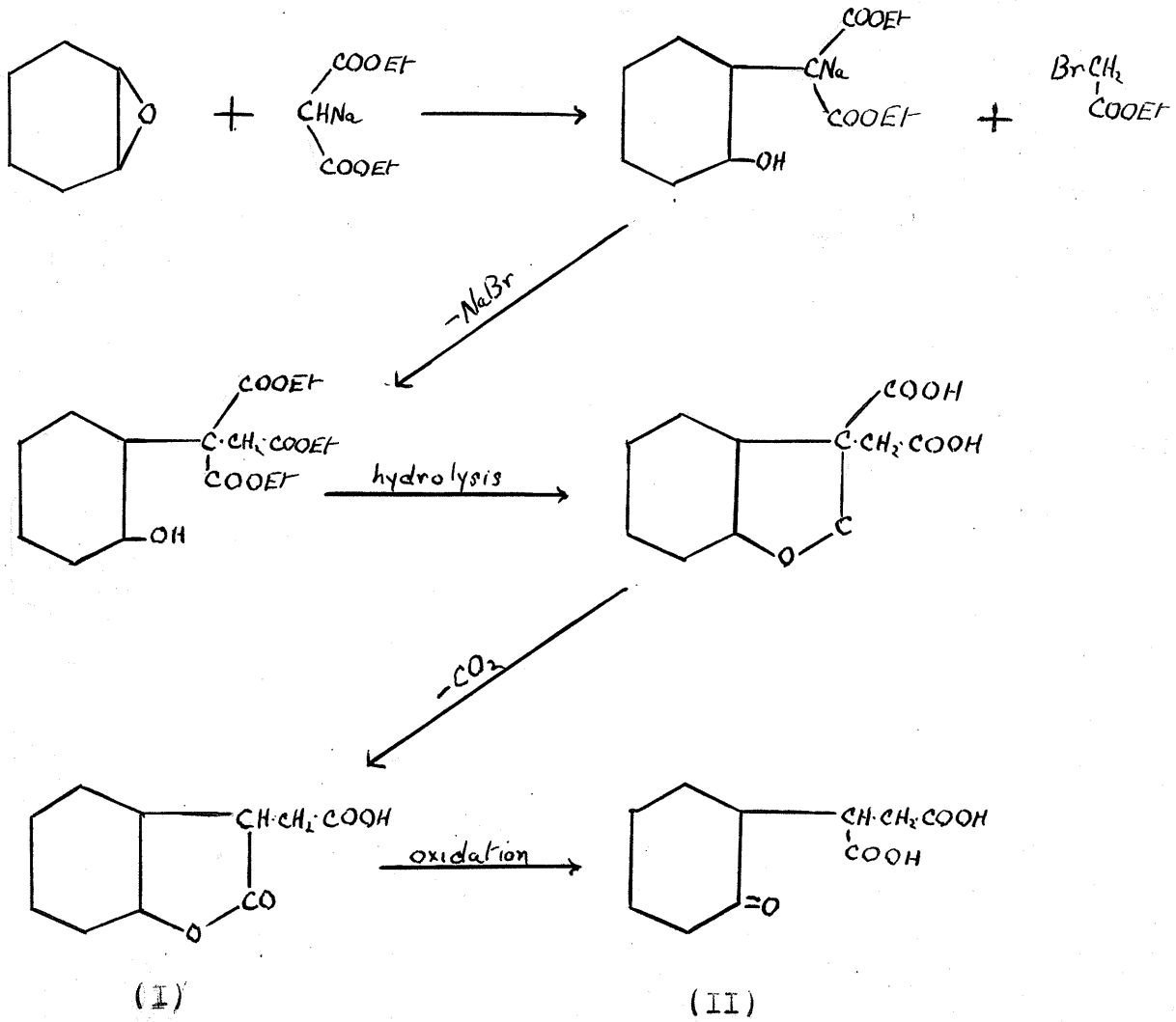
SYNTHESIS OF β-KETOCYCLOHEXYLSUCCINIC ACID AND HOMOLOGUES BY MEANS OF REFORMATSKY AND OTHER REACTIONS.

PRELIMINARY DISCUSSION.

D. G. Alexander (1) has prepared several β-ketocyclohexylcarboxylic acids by the oxidation of the γ-lactones of the cyclohexanol carboxylic acids. These γ-lactones were prepared by the condensation of the sodio derivative of ethyl malonate with cyclohexene oxide and α or β-brominated carboxylic esters, followed by hydrolysis and decarboxylation. For example, the γ-lactone (I) yields on oxidation β-ketocyclohexylsuccinic acid (II).



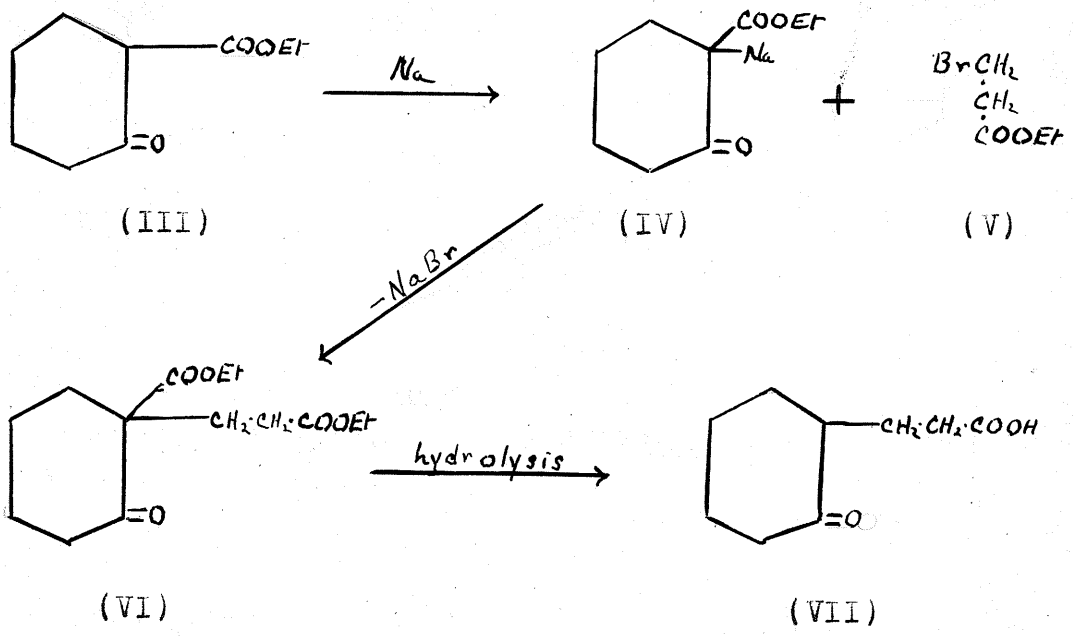
(I) (II)

This general method has also been used by Coffey (9), Kendall (17), and Charlesworth (6).

It was thought that other, entirely different methods of synthesis should be attempted with a view to a simpler means of preparation, and also to confirm the structure of the keto acids. With this in mind, three methods suggested themselves as possible means of preparation. These methods may be described as follows:

1. The elimination of sodium bromide between the sodio derivative of ethyl cyclohexanone-2-carboxylate and brominated esters, followed by hydrolysis.

e.g. The preparation of 2-ketocyclohexyl-β-propionic acid.

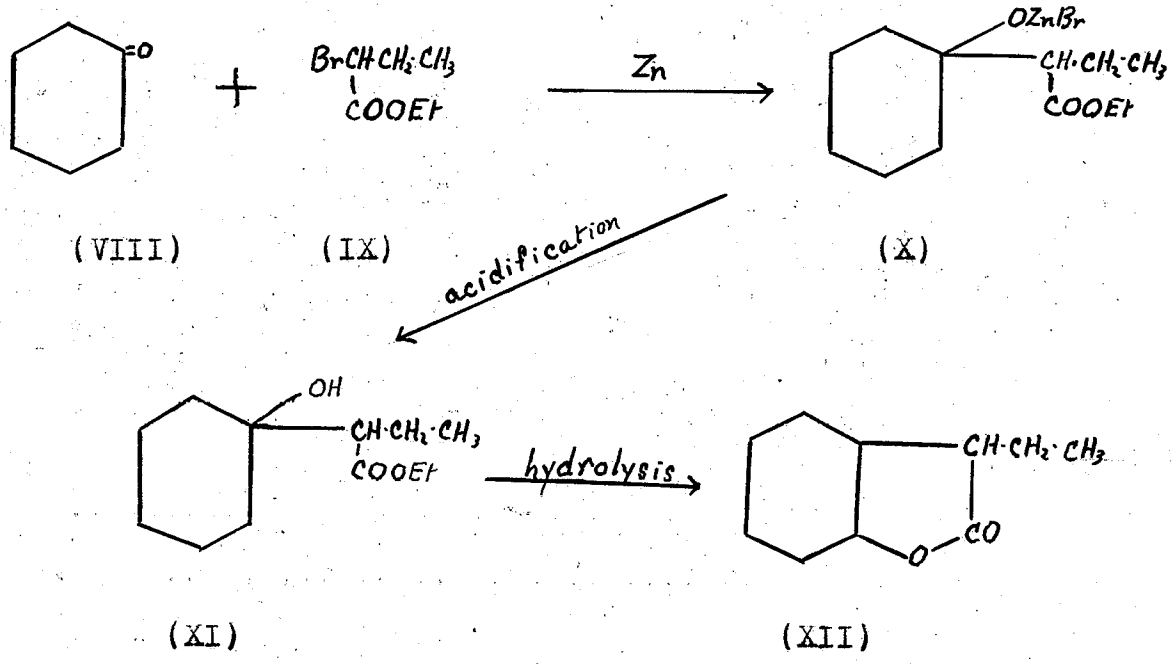


Note: In this thesis hexagons will represent saturated benzene rings.

Ethyl cyclohexanone-2-carboxylate (III), on treatment with sodium gives the sodio derivative (IV) which condenses with ethyl β-bromopropionate (V), splitting off sodium bromide to give ethyl cyclohexanone-2-carboxylate-2-β-propionate (VI); this on hydrolysis yields 2-ketocyclohexyl-β-propionic acid (VII).

5. The oxidation of the γ-lactones of cyclohexanol carboxylic acids, which are prepared by Reformatsky reactions between cyclohexanone and brominated carboxylic esters followed by hydrolysis.

e.g. The preparation of the γ-lactone of cyclohexanol-α-butyric acid.



(VIII) (IX) (X)

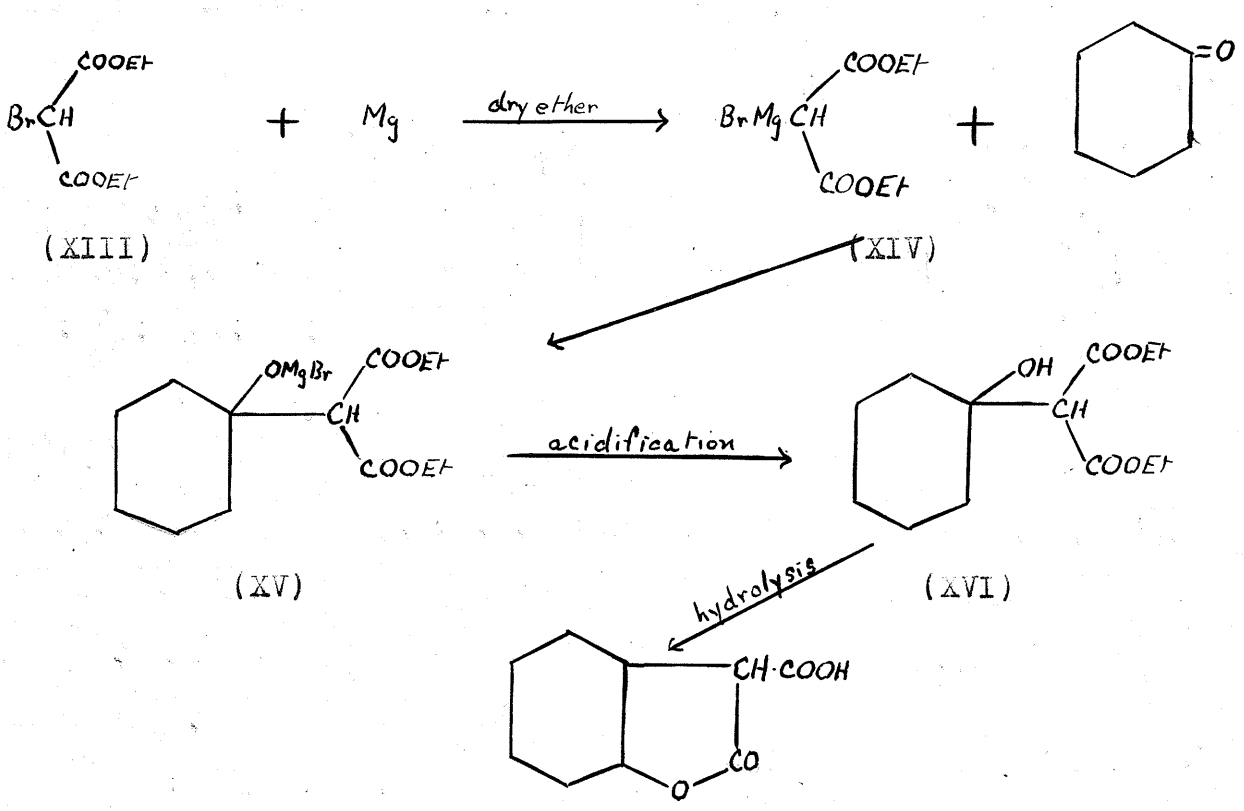
(XI) (XII)

Cyclohexanone (VIII), reacts with ethyl α-bromobutyrate (IX), in the presence of zinc to give the compound (X) which on acidification yields ethyl α-(1-cyclohexanol) butyrate (XI); this on

hydrolysis give the γ-lactone of cyclohexanol α-butyric acid (XII).

5. The oxidation of the γ-lactones of cyclohexanol carboxylic acids, formed by Grignard reactions between cyclohexanone and brominated carboxylic esters followed by hydrolysis.

e.g. The preparation of the γ-lactone of cyclohexanol malonic acid would take place according to the following scheme:



Ethyl bromomalonate (XIII) with magnesium in dry ether would give the Grignard reagent (XIV), which with cyclohexanone would yield the compound (XV); this on acidification would give ethyl 1-cyclohexanol malonate (XVI), which on hydrolysis would result in the γ-lactone (XVII) of cyclohexanol malonic acid.

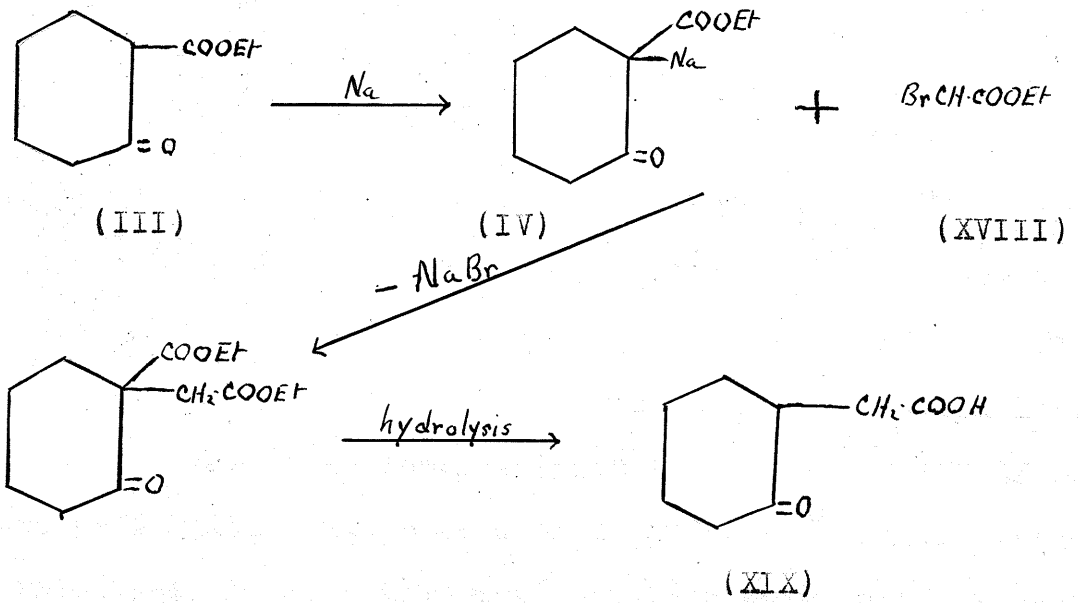
DISCUSSION OF EXPERIMENTAL RESULTS.

SYNTHESIS INVOLVING ETHYL CYCLOHEXANONE-2-CARBOXYLATE.

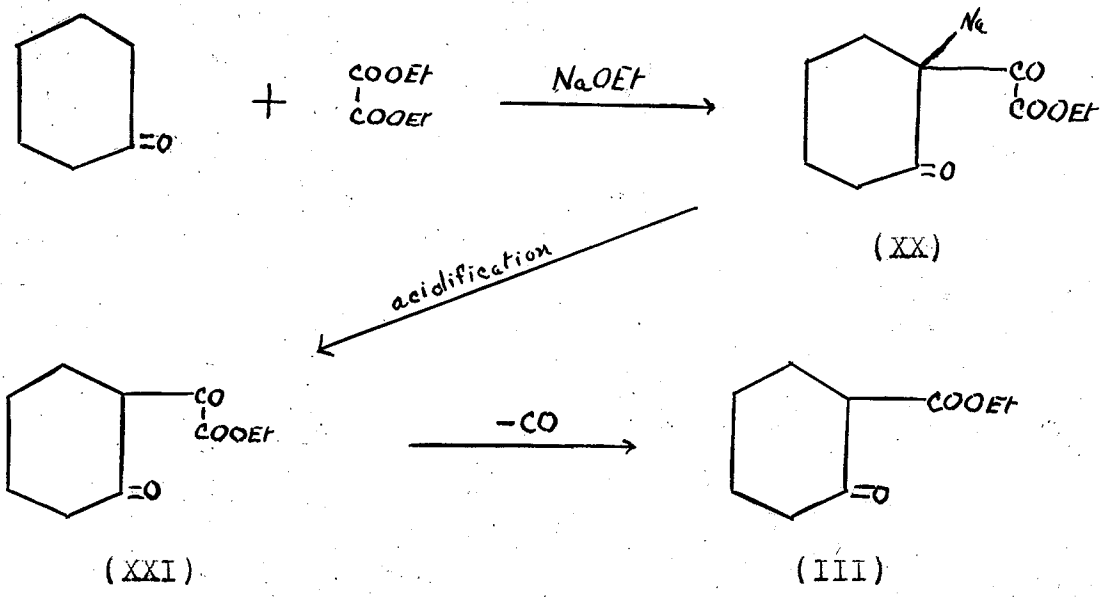
SYNTHESIS OF 2-KETOCYCLOHEXYLACETIC ACID (XIX).

Chang-Kong Chuang and Chi-Ming Ma (6), Kripendrath Chatterjee (7), and Nemajit Ghosh (10) have synthesised 2-ketocyclohexylacetic acid (XIX) by the elimination of sodium chloride between the sodio derivative of ethyl cyclohexanone-2-carboxylate and ethyl chloracetate.

A method similar to this has been followed in this work. Sodium bromide was eliminated between ethyl bromoacetate (XVIII) and the sodio derivative (IV) of ethyl cyclohexanone-2-carboxylate, this sodio derivative being prepared by the action of metallic sodium on ethyl cyclohexanone-2-carboxylate (III) in benzene solution:



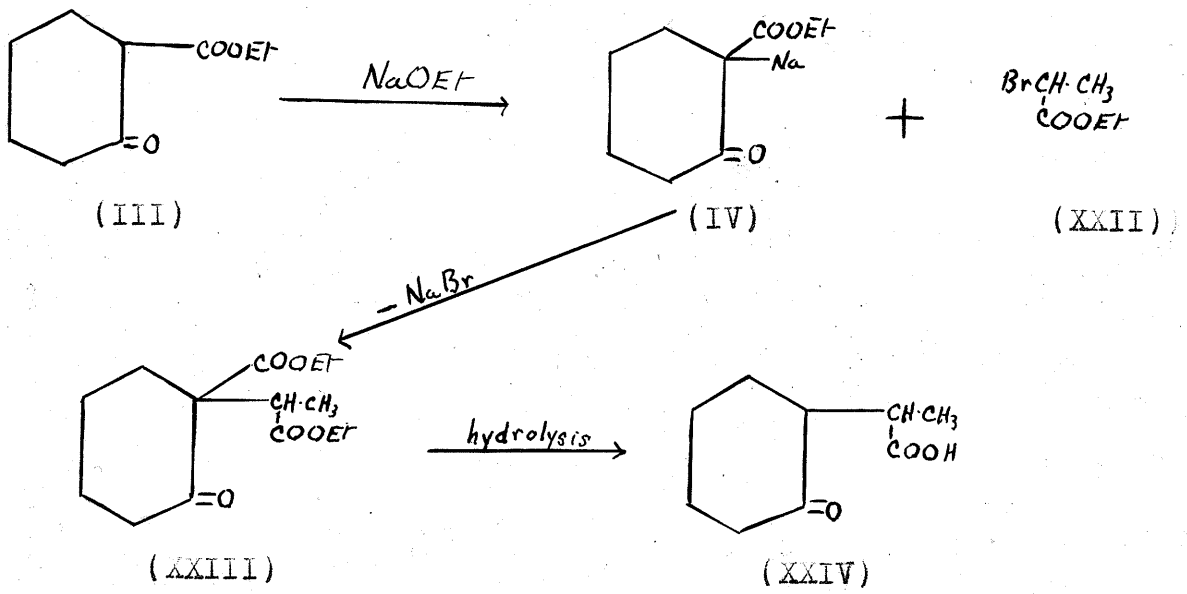
The ethyl cyclohexanone-2-carboxylate (III) was prepared by the method of Kotz and Michels (19). Cyclohexanone and ethyl oxalate condense in the presence of sodium ethylate to form the sodium compound (XX), this on acidification gives cyclohexanone oxalyl ethyl ester (XXI) which loses carbon monoxide to give ethyl cyclohexanone-2-carboxylate (III).



The Chinese workers give a melting point of 39°-41° for 2-keto-cyclohexylacetic acid, while the Indians give only the boiling point. Alexander (1) found that the acid melted at 75°-76° after careful recrystallisation. We have found that the acid melted at 75°-78° although unable to recrystallise it from any solvent. Although the acid melted over such a wide range, on analysis it gave results which were in good agreement with the calculated figures.

SYNTHESIS OF 2-KETOCYCLOHEXYL-α-PROPIONIC ACID (XXIV).

2-Ketocyclohexyl-β-propionic acid (VII) has been prepared by Openshaw and Robinson (22), F. Lions (21), and Haworth and Mavin (16). The first two, used sodium ethylate as condensing agent; and, as some difficulty had been experienced in preparing the sodio derivative of ethyl cyclohexanone-2-carboxylate by the action of metallic sodium in benzene, it was decided to use sodium ethylate in the preparation of 2-ketocyclohexyl-α-propionic acid.

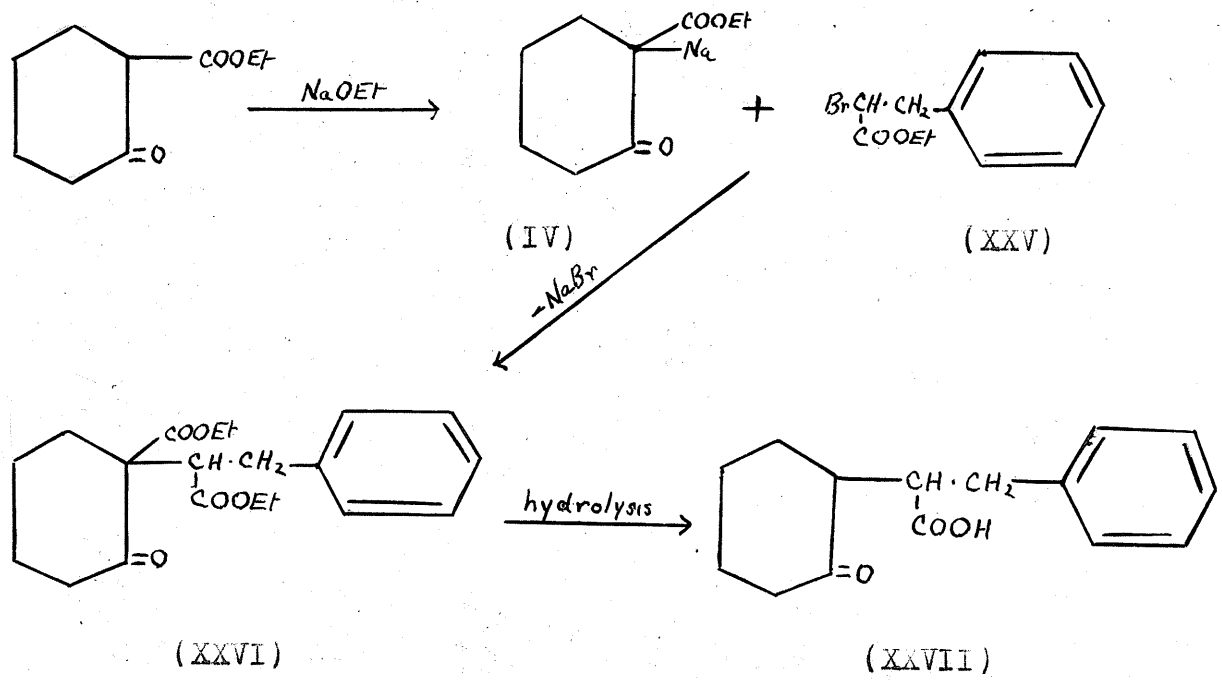


Ethyl cyclohexanone-2-carboxylate (III), in the presence of sodium ethylate yields the sodio derivative (IV), which reacts with ethyl α-bromopropionate (XXII) with the elimination of sodium bromide to give ethyl cyclohexanone-2-carboxylate-2-α-propionate (XXIII) this, on hydrolysis results in 2-ketocyclohexyl-α-propionic acid (XXIV).

Considerable difficulty was experienced in getting the acid to solidify and also in recrystallising it. Finally the acid was purified and was found to melt at 104°-105°.

ATTEMPTED SYNTHESIS OF δ-KETOCYCLOHEXYL-α-HYDROCINNAMIC ACID (XXVII).

Alexander (1) prepared this acid by the method he had already used in the preparation of the other keto acids. He never obtained the pure acid although he did succeed in isolating the lactone of the corresponding hydroxy acid. Furthermore his preparation required a considerable length of time. In view of this the preparation of the acid was attempted following the same procedure as that used in the preparation of δ-ketocyclohexyl- -propionic acid.

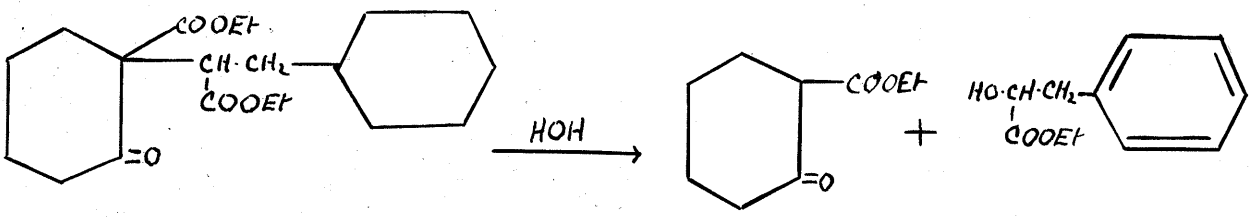


The sodio derivative (IV) is condensed with ethyl α-bromohydrocinnamate (XXV) to yield ethyl cyclohexanone-2-carboxylate-2-α-hydrocinnamate (XXVI), which on hydrolysis should give δ-keto-

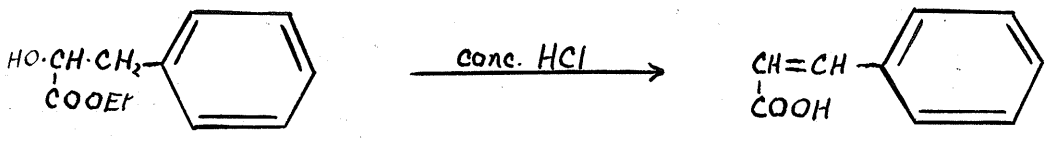
cyclohexyl-α-hydrocinnamic acid (XXVII).

However following through the above procedure, cinnamic acid was isolated. The oil resulting from the sodio condensation had a composition in quite close agreement with that of the compound XXVI. This composition also agrees with that of ethyl α-hydroxy hydrocinnamate (XXVIII), the boiling points agree, and the molecular weight determined ebullioscopically in benzene was found to be 156, which would indicate that the substance was the latter. Thus the cinnamic acid (XXIX) isolated, was formed by the elimination of water in the above-mentioned ester.

The only possible explanation of the formation of ethyl α-hydroxy hydrocinnamate is that the sodio condensation proceeded as expected; but, that on pouring the ethyl cyclohexanone-2-carboxylate-3-α-hydrocinnamate (XXVI) into water, it broke down as shown in the following scheme:



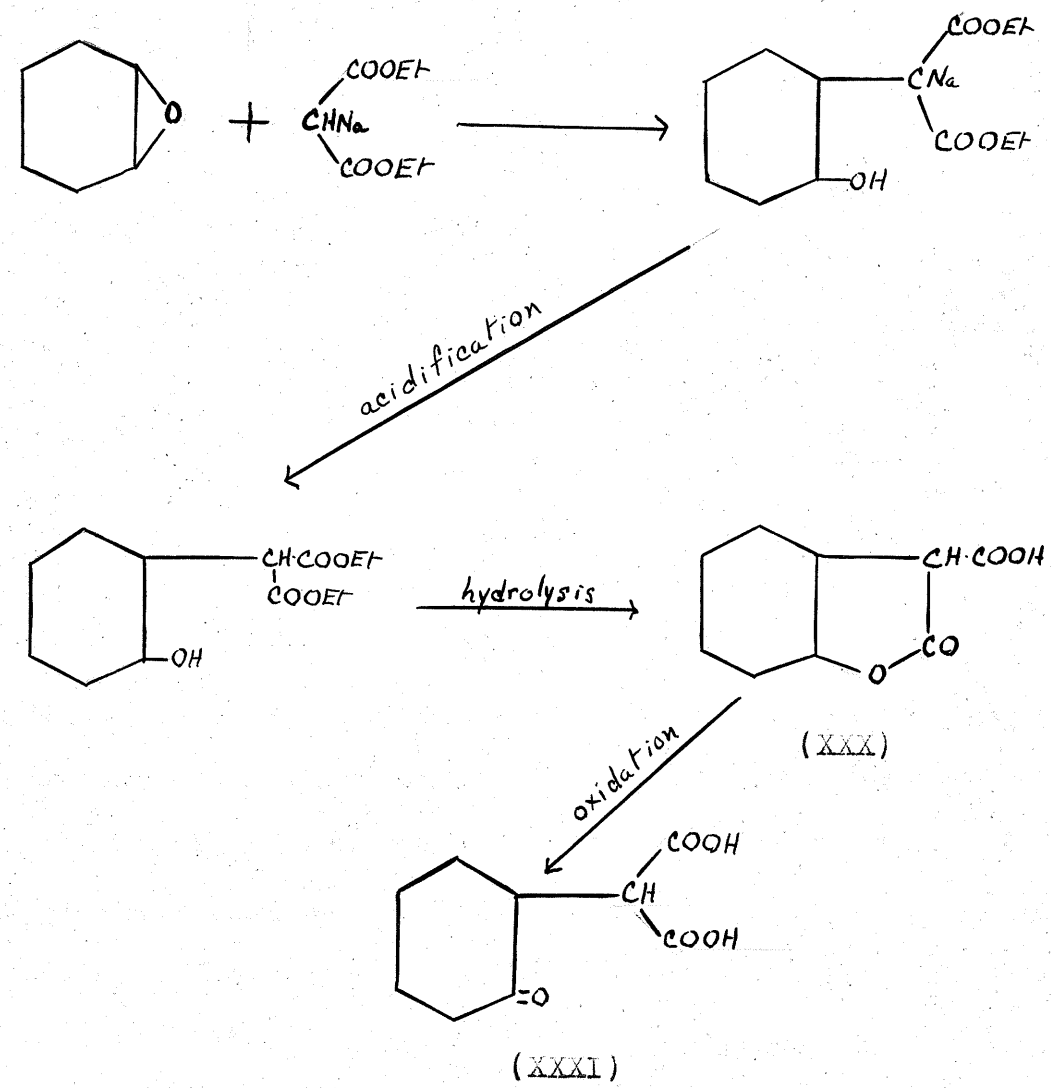
(XXVI) (XXVIII)



(XXVIII) (XXIX)

ATTEMPTED SYNTHESIS OF 2-KETOCYCLOHEXYLMALONIC ACID (XXXI).

This acid has been synthesised by Alexander (1) who prepared it by the oxidation of the γ-lactone (XXX) of cyclohexanol malonic acid in the following way:

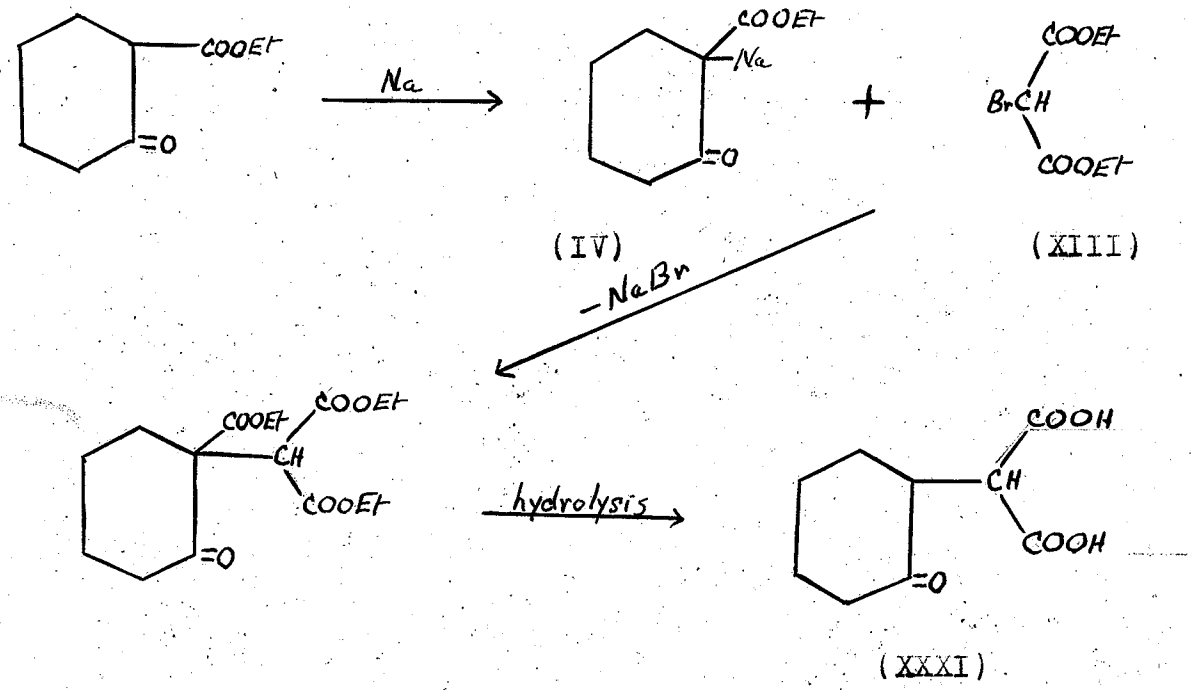


(XXX)

(XXXI)

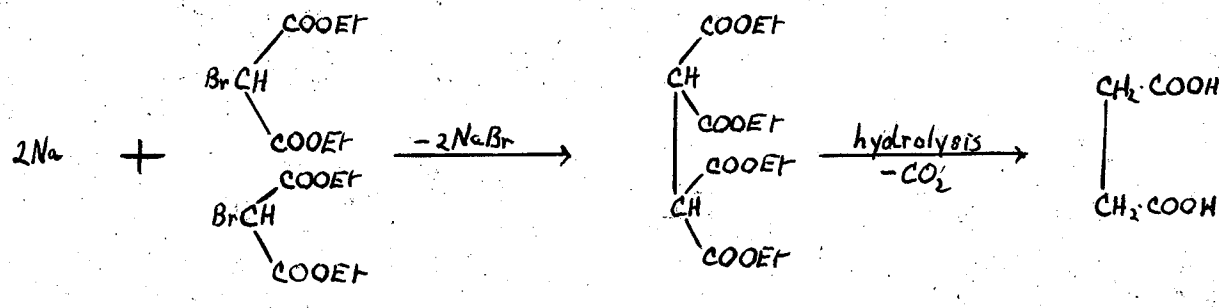
Attempts were made to prepare the acid by the methods already used in the preparation of 2-ketocyclohexylacetic and -4-propionic acids; that is, by the elimination of sodium bromide between the

sodio derivative (IV) of ethyl cyclohexanone-2-carboxylate and ethyl bromomalonate (XIII).



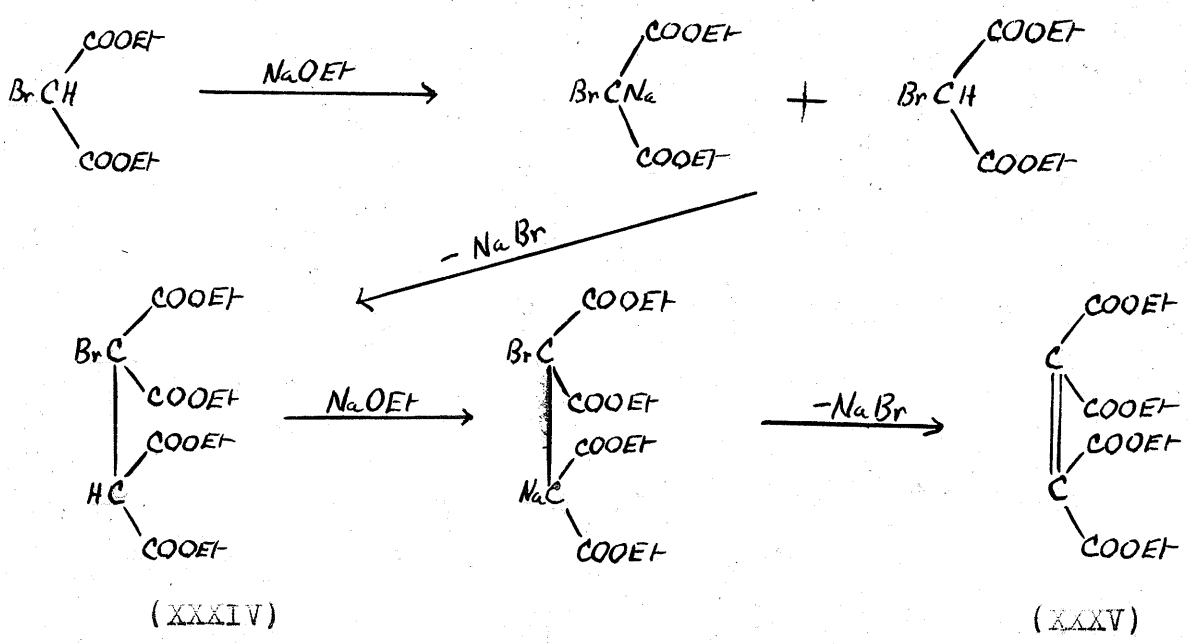
(XXXI)

When the reaction was attempted in benzene solution using metallic sodium, succinic acid was isolated after the final step. Due to the difficulty of preparing the sodio derivative by this method, the succinic acid (XXXIII) was probably formed by the hydrolysis and decarboxylation of ethane tetracarboxylic ethyl ester (XXXII), this latter resulting from the elimination of sodium bromide between two moles of ethyl bromomalonate and some undissolved sodium.



(XXXII) (XXXIII)

Due to this formation of succinic acid, the preparation was attempted using sodium ethylate as condensing agent. In this case, after the condensation two substances were isolated: monobromethane tetracarboxylic ethyl ester (XXXIV), and ethylene tetracarboxylic ethyl ester (XXXV). The former was probably formed by the substitution of sodium in one molecule of ethyl bromomalonate, followed by the elimination of sodium bromide between this and another molecule of ethyl bromomalonate; the latter would then result from the substitution of sodium in the monobromethane tetracarboxylic ester followed by intramolecular elimination of sodium bromide.



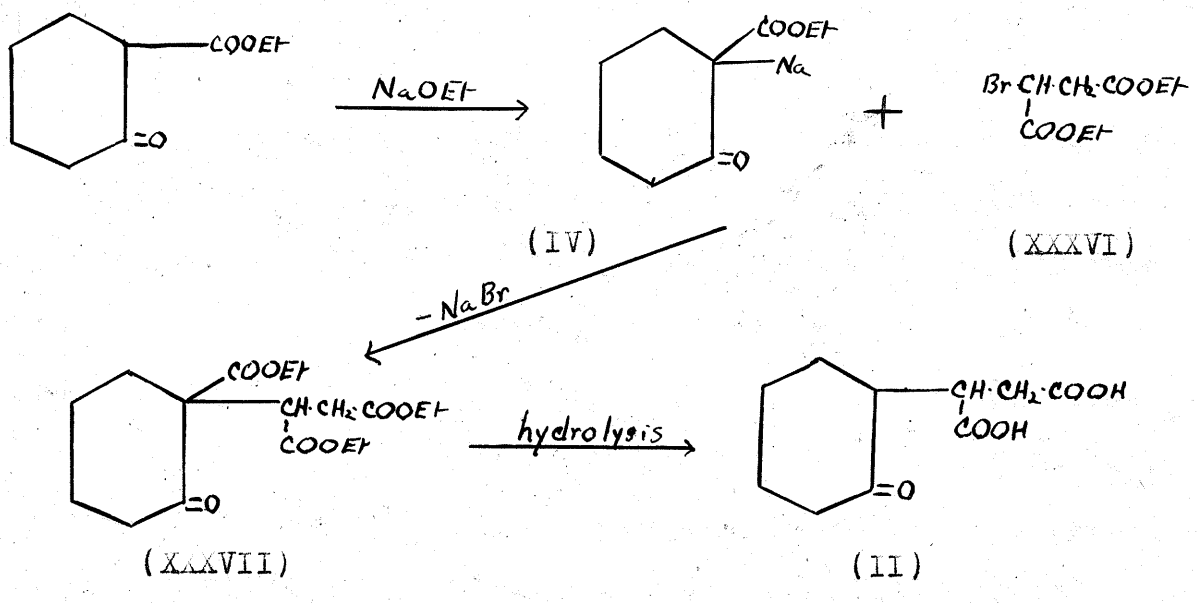
(XXXIV) (XXXV)

It would seem that it is impossible to prepare 2-ketocyclohexylmalonic acid by this method, as it appears that the methylene group in ethyl bromomalonate is more reactive than that in ethyl cyclohexanone-2-carboxylate, the sodium substituting in the former

rather than in the latter.

Attempted synthesis of 2-ketocyclohexylsuccinic acid (II).

This acid has also been prepared by Alexander (1) by the method described on page one. In this work the synthesis has been attempted using the method already described; that is, by the elimination of sodium bromide between the sodio derivative (IV) and ethyl bromosuccinate (XXXVI), followed by hydrolysis of the ethyl cyclohexanone-2-carboxylate-2-succinate (XXXVII) formed.

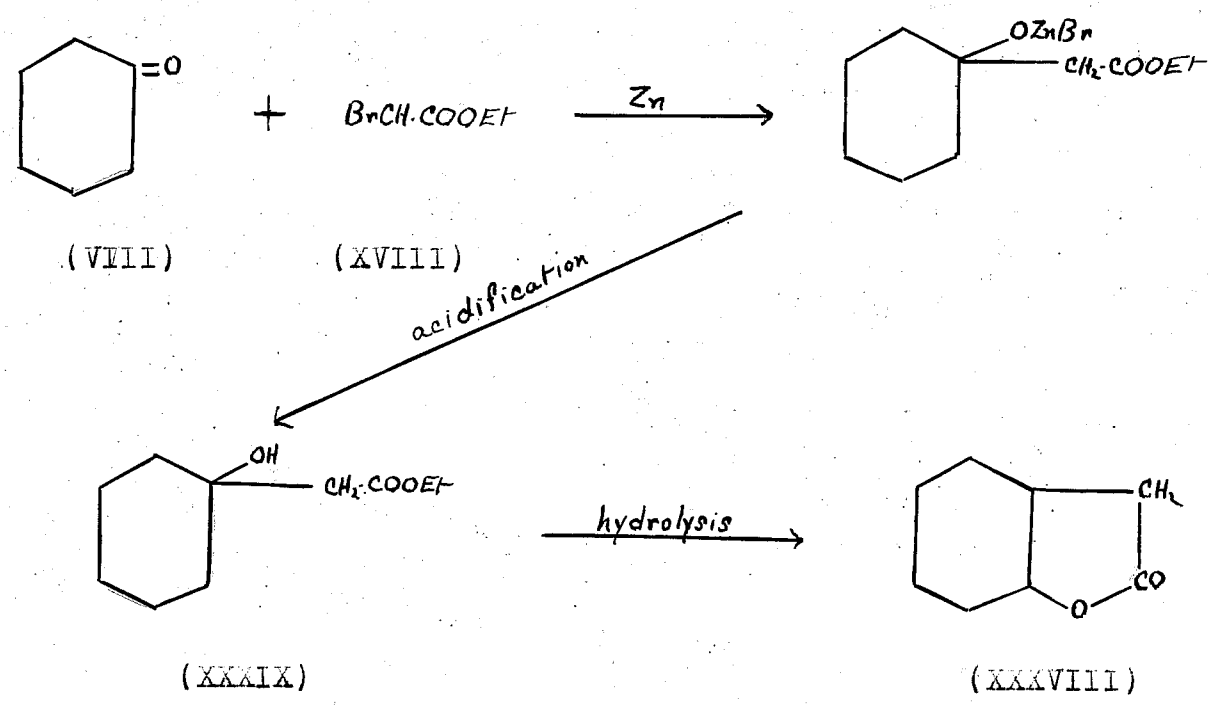


A very small quantity of a solid was isolated; although it has not been identified, it is definitely not 2-ketocyclohexylsuccinic acid.

SYNTHESES INVOLVING REFORMATSKY REACTIONS.

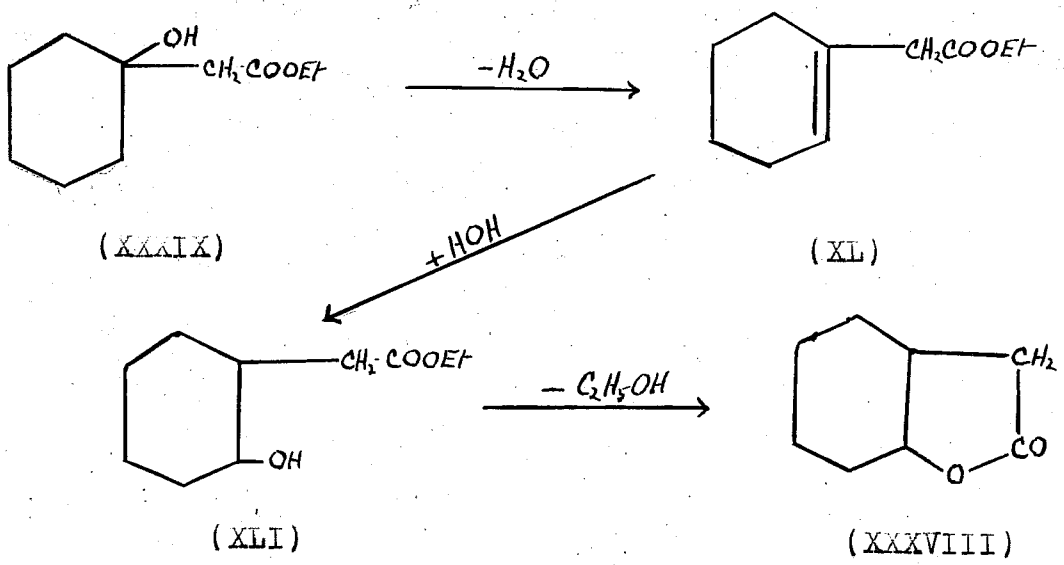
The classical Reformatsky reaction for the synthesis of β-hydroxy esters, consists in the condensation of the α-bromo ester of a monocarboxylic acid with a ketone in the presence of zinc. Studies with various ketones and oxides and α-chloro, α-bromo, or α-iodo esters of monocarboxylic acids are reported in the literature (3, 8, 11, 15, 16, 20, 22, 24). There are only two reports of attempted Reformatsky reactions using α-halogenated esters of dicarboxylic acids. In both these cases esters of bromomalonic acid were used. Kohler, Heritage and Hatsod (10) report that using unsaturated ketones and methyl bromomalonate 1,4 addition takes place. Iyer (15) attempted Reformatsky reactions using acetone and ethyl bromomalonate; he states that water is eliminated between two molecules of acetone yielding mesityl oxide, and then 1,4 addition takes place as previously suggested.

Reformatsky reactions have been utilized in the preparation of the α-(1-cyclohexanol) fatty acid esters by Ballauh (27, 28) and Amore and Ellinger (3). C. H. Boehringer (4) has prepared the β-lactones of cyclohexanol fatty acids by boiling these α-(1-cyclohexanol) fatty acid esters with mineral acids. For instance the β-lactone (XXXVIII) of cyclohexanol acetic acid results from the interaction of cyclohexenone (VIII) and ethyl bromacetate (XVIII) with the intermediate formation of ethyl 1-cyclohexanol acetate (XXXII).



(VIII) (XVIII) (XXXIX) (XXXVIII)

The formation of the lactone ring probably takes place through the removal of water from the hydroxy ester (XXXIX) forming 1-cyclohexone acetic acid (XL), re-introduction of the hydroxyl group in the adjacent position to give ethyl 2-cyclohexanol acetate (XLI), ethyl alcohol is then removed to give the lactone (XXXVIII).



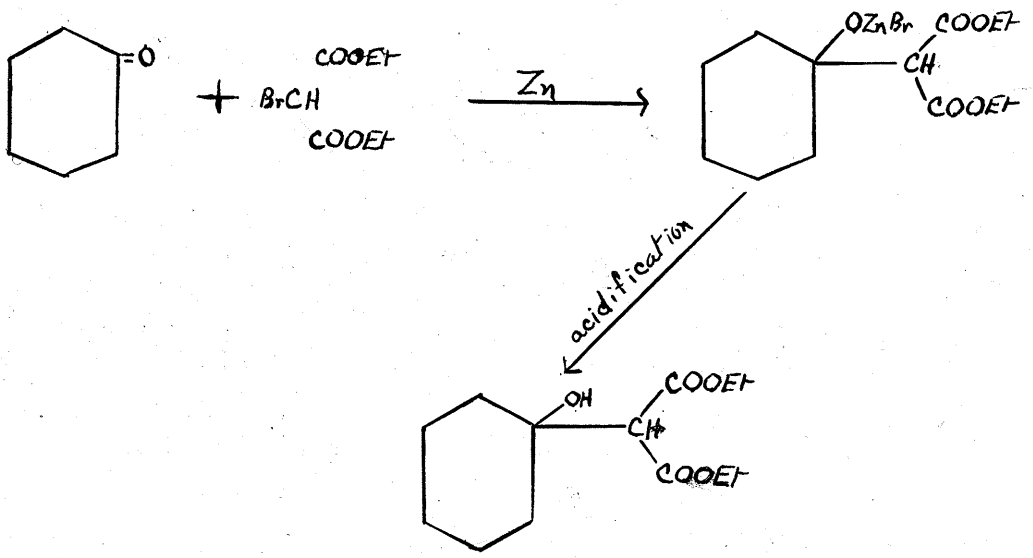
(XXXIX) (XL) (XLI) (XXXVIII)

SYNTHESIS OF THE γ-LACTONE OF CYCLOHEXANOL ACETIC ACID (XXXVIII).

The γ-lactone of 1-cyclohexanol acetic acid was prepared with little difficulty by a Reformatsky reaction between cyclohexanone and ethyl bromacetate. Boiling with concentrated hydrochloric acid yielded the γ-lactone (XXXVIII) boiling at 152°-156°/26 mm.

ATTEMPTED SYNTHESIS OF ETHYL 1-CYCLOHEXANOL MALONATE (XLII) AND ETHYL 1-CYCLOHEXANOL SUCCINATE (XLIII).

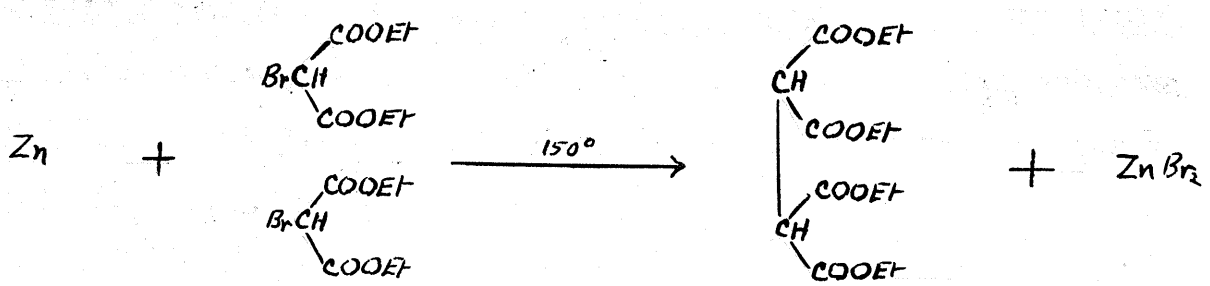
Reformatsky reactions have been attempted several times, under different experimental conditions using cyclohexanone and ethyl bromomalonate with the object of preparing ethyl 1-cyclohexanol malonate (XLII).



(XLII)

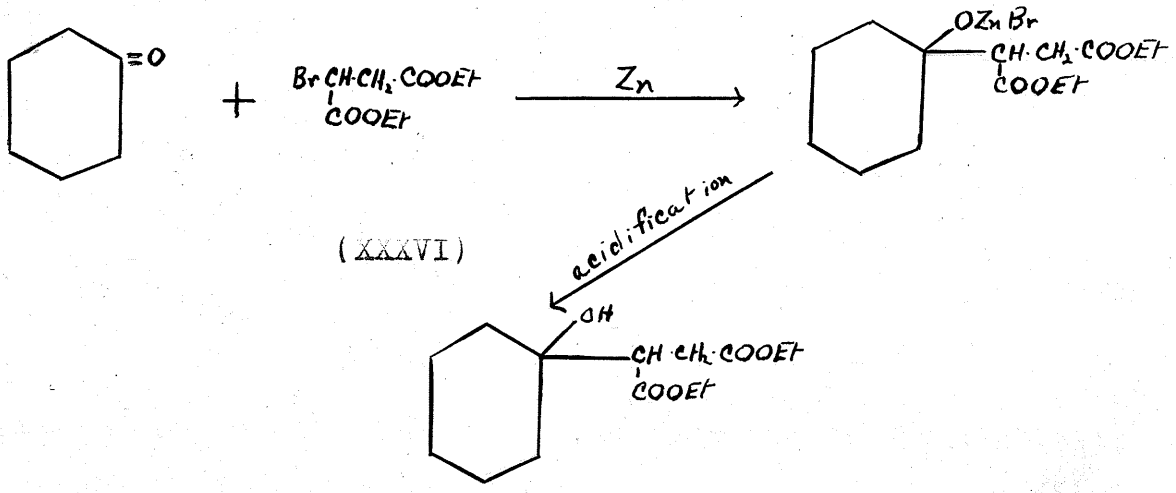
The amounts of both substances, the amount of zinc and the temperature at which the reaction was carried out have all been varied. In only one case, at the usual temperature (the boiling

point of benzene), was anything besides cyclohexanone and ethyl malonate isolated; and in this case, in which an excess of zinc was used, the resulting substance did not have the required composition for ethyl 1-cyclohexanol malonate. Under conditions of temperature near the boiling point of cyclohexanone, it was found that zinc was reactive enough to remove bromine from two molecules of ethyl bromomalonate forming ethane tetracarboxylic ethyl ester (XXXII).



(XXXII)

Similarly, when ethyl bromosuccinate (XXXVI) was used, in the hope of obtaining ethyl 1-cyclohexanol succinate (XLIII) a large quantity of ethyl succinate and a small quantity of a higher boiling liquid were obtained.



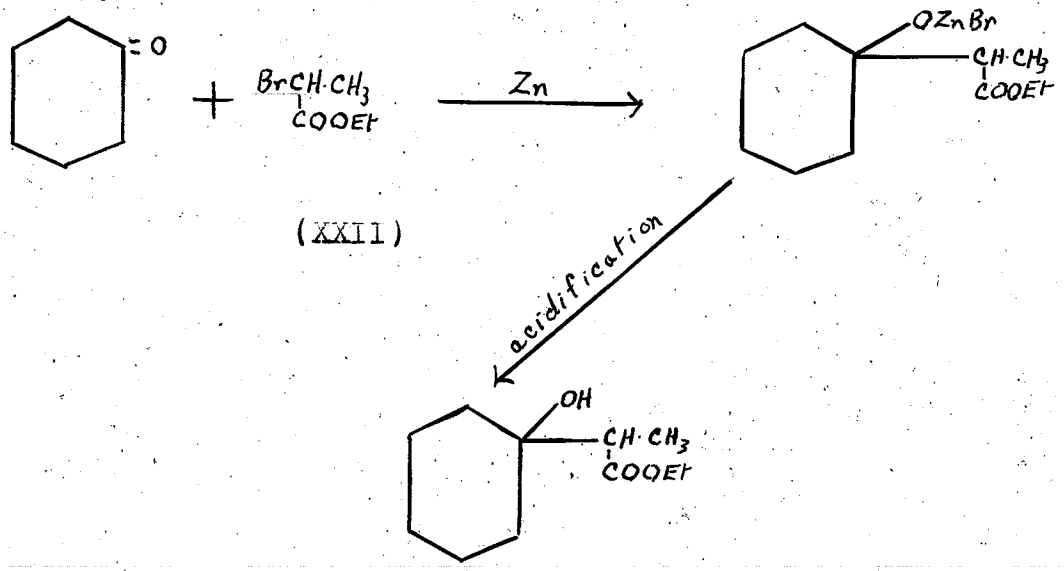
(XXXVI)

(XLIII)

Assuming that a Reformatsky reaction takes place somewhat as does a Grignard reaction; that is, by the formation of a complex, such as $BrZnCH(COOEt)_2$ in the case of ethyl bromomalonate, and that under the conditions of the experiment this complex does not react with the ketone present; then, on acidification a carboxylic ester, in this case ethyl malonate, would result. Thus the formation of ethyl malonate and succinate could be explained.*

Synthesis of the γ-Lactone of Cyclohexanol-α-Propionic Acid (XLV).

Ethyl α-(1-cyclohexanol) propionate (XLIV) readily resulted from the interaction of cyclohexanone and ethyl α-bromopropionate (XXII) in the presence of zinc.

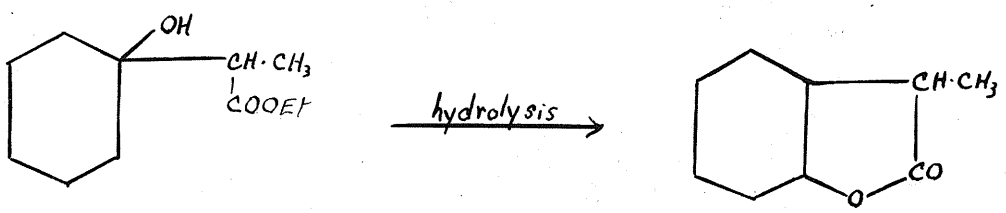


(XXII)

(XLIV)

This hydroxy ester on boiling with concentrated hydrochloric acid yielded the γ-lactone of cyclohexanol α-propionic acid (XLV) boiling at 160°/21 mm.

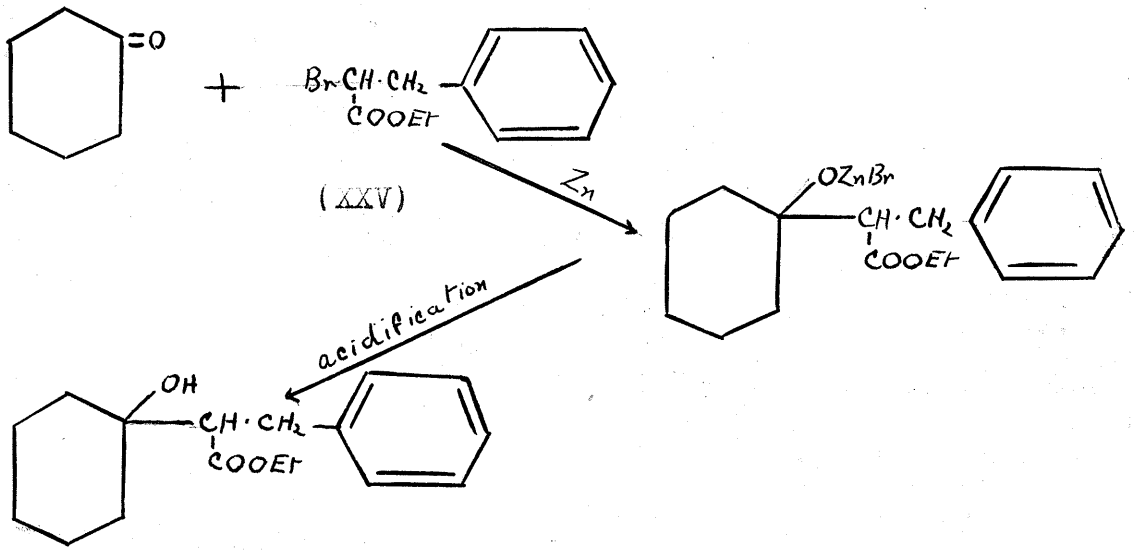
*See p. 37.



(XLIV) (XLV)

Synthesis of Ethyl α-(1-Cyclohexanol) Hydrocinnamate (XLVI).

A Reformatsky reaction between cyclohexanone and ethyl α-bromo-hydrocinnamate (XXV) gave a small yield of ethyl (1-cyclohexanol) hydrocinnamate (XLVI), contaminated with a small amount of ethyl α-bromohydrocinnamate.



(XLVI)

It was found necessary to raise the temperature slightly, in comparison with the other Reformatsky reactions, in order to have the reaction proceed with a reasonable velocity.

ATTEMPTED CONDENSERS INVOLVING GRIGNARD REACTIONS.

On finding that Reformatsky reactions did not take place between cyclohexanone and ethyl bromomalonate it was decided to see if perhaps ethyl 1-cyclohexanol malonate could be prepared by means of a Grignard reaction between ethyl bromomalonate and cyclohexanone. All attempts failed however, and in every case ethane tetracarboxylic ethyl ester (XXIII) was isolated, probably being formed by the formation of magnesium bromide between the magnesium and two molecules of ethyl bromomalonate.

The results obtained in this work seem to indicate a great difference in activity between α-brominated simple monocarboxylic esters and dicarboxylic esters. There is no doubt that both of the main methods used would proceed successfully in the case of all α-brominated fatty acid esters. It is possible, that ethyl bromomalonate because of its active methylene group, constitutes a special case, although the results of the attempted ethyl bromo-succinate condensations seem to oppose this view. The failure of the zodic condensation using ethyl α-bromohydrocinnamate is possibly due to the influence of the benzene nucleus on the molecule.

EXPERIMENTAL DETAIL.

PREPARATION OF ETHYL BROMACETATE (XVII).

Ethyl bromacetate was prepared by the method of Cohen (10).

Bromacetyl bromide was found to boil at 70°-75°/25 mm. rather than at 80°-82°/30-40 mm. as stated by Cohen.

The pure bromacetyl bromide was cautiously treated with two to three times the required amount of absolute alcohol. The resulting ethyl bromacetate was purified by distillation (B.P. 150°-160°).

PREPARATION OF ETHYL BROMOMALONATE (XIII).

Ethyl bromomalonate was prepared by the method of Palmer and Hatherton (26). Yields up to 75% of the theoretical were obtained.

PREPARATION OF ETHYL BROMOSUCCINATE (XXVI).

The preparation was first attempted as with ethyl bromomalonate but the yields were too low to warrant the method being used further.

The preparation was then carried out as follows:

Succinic acid (118 gr.) was mixed with red phosphorous (20 gr.), in a 1 litre three-necked flask fitted with a reflux condenser, mercury-sealed stirrer and dropping funnel. The stirrer was started and bromine (480 gr.) was slowly dropped in. At this point it was found necessary to add about 75 cc. carbon tetrachloride to moderate the reaction. After the addition of the bromine, the mixture was heated on a water bath until the color of bromine had disappeared. Twice the calculated amount of absolute alcohol was then slowly dropped in, and the whole was heated another ½ hour on the water bath. The ethyl bromosuccinate was distilled under reduced pressure, boiling at 120°-128°/24 mm.

PREPARATION OF ETHYL α-BROMOPROPIONATE (XXII).

This was prepared in a similar manner to the ethyl bromo-succinate, the ethyl α-bromopropionate boiling at 158°-161°.

PREPARATION OF ETHYL α-BROMOHYDROCINNAMATE (XXV).

The α-bromohydrocinnamic acid was prepared by the method of C. S. Marvel (22). The crude acid was esterified by refluxing 4 hours with twice the required amount of absolute alcohol and 4 cc. concentrated sulphuric acid. The ester boils at 150°-152°/10 mm.

PREPARATION OF ETHYL CYCLOHEXANONE-2-CARBOXYLATE (XXI).

This was prepared by the method of Kotz and Nichols (19).

Cyclohexanone (50 gr.) and ethyl oxalate (75 gr.) were slowly added to the sodium compound from sodium (11.7 gr.) in absolute alcohol (150 cc.), the whole being cooled in a freezing mixture. The mixture was allowed to stand overnight in a cool place when the mass solidified. It was acidified with dilute sulphuric acid, extracted with ether and the ether solution dried over sodium sulphate.

After distilling off the ether, the alcohol and unreacted cyclohexanone and oxalic ester were distilled off under reduced pressure up to 100°. At this point the carbon monoxide began to come off, shown by a rapid falling of the manometer. The heating was continued until all the carbon monoxide had come off and the distillate was then redistilled, the ethyl cyclohexanone-2-carboxylate being collected at 130°-140°/10 mm.

PREPARATION OF 2-KETOCYCLOHEXYLACETIC ACID (XLV).

Ethyl cyclohexanone-2-carboxylate (40 gr.) and finely divided sodium (2.3 gr.) were refluxed with dry benzene (100 cc.) until the hydrogen ceased coming off (about 4 hours). Ethyl bromacetate (38 gr.) was then slowly added and the whole was refluxed 5 hours on a water bath. On cooling, the mixture was treated with dilute sulphuric acid, washed with water and dilute sodium bicarbonate solution and dried over calcium chloride. The benzene was distilled off and the ethyl cyclohexanone-2-carboxylate-2-acetate was distilled under reduced pressure, boiling at 195°-210°/45 mm.

Ethyl cyclohexanone-2-carboxylate-2-acetate (19 gr.) was refluxed 8 hours with twice its volume of concentrated hydrochloric acid. The mineral acid was distilled off under reduced pressure and the 2-ketocyclohexylacetic acid was purified by distillation, boiling at 190°-195°/20 mm.

This oil after prolonged cooling partially solidified. Most of the remaining oil was removed by filtration, and the solid was left between filter papers which absorbed the rest of the oil. The solid which would not recrystallise from any solvent used melted at 75°-76°.

2-ketocyclohexylacetic acid, $C_8H_{12}O_3$, requires: C 61.54%, H 7.69%; equivalent weight 156.

Found: C 60.3%, H 8.06%; equivalent weight 158.6.

Phenylhydrazone M.P. 162°-163°.

PREPARATION OF 2-KETOCYCLOHEXYL-α-PROPIONIC ACID (XLIV).

Sodium (2.3 gr.) was dissolved in absolute alcohol (60 cc.); to this was slowly added with shaking, a mixture of ethyl cyclo-

hexanone-2-carboxylate (18 gr.) and ethyl α-bromopropionate (26.7 gr.). The whole was heated 4 hours on a water bath and was then poured into cold water (400 cc.). A brown oil separated, this was taken up with ether and the ether solution dried over sodium sulphate. After distilling off the ether, the residue was distilled under reduced pressure, the ethyl cyclohexanone-2-carboxylate-2-α-propionate (17 gr.) boiling at 100°-130°/17 mm.

Ethyl cyclohexanone-2-carboxylate-2-α-propionate, $C_{14}H_{22}O_5$. requires: C 62.2%, H 8.16%.

Found: C 61.20%, H 7.94%.

To ethyl cyclohexanone-2-carboxylate-2-α-propionate (16 gr.) was added concentrated hydrochloric acid (60 cc.). This was allowed to stand overnight and was then refluxed 1 hour. The greater part of the mineral acid was distilled off under reduced pressure, and a saturated solution of ammonium sulphate was added. The oil separating, was taken up with ether; the ether solution was shaken with dilute sodium hydroxide solution which in turn was acidified. The acid solution was extracted with ether, and the extract was dried over sodium sulphate. The ether was evaporated off and the brown oil remaining partially solidified after prolonged cooling. Most of the remaining oil was removed by filtration and the solid was boiled with light petroleum ether. About 0.5 grams pale yellow solid, M.P. 103°-105°, was obtained.

2-ketocyclohexyl-α-propionic acid, $C_9H_{14}O_3$, requires: C 63.53%, H 8.23%; equivalent weight 170.

Found: C 63.7%, H 8.3%; equivalent weight 177.

ALTERNATIVE PREPARATION OF β-KETOCYCLOHEXYL-α-HYDROCINNAMIC ACID (XXVII).

To the sodium compound from sodium (4.0 gr.) in absolute alcohol (80 cc.) was added a mixture of ethyl α-bromohydrocinnamate (60 gr.) and ethyl cyclohexanone-2-carboxylate (52 gr.). The mixture was refluxed 10 hours and was then poured into cold water (300 cc.). The yellow oil separating was taken up with ether dried over sodium sulphate, and the ether distilled off. The residue was distilled under reduced pressure, yielding a pale yellow oil (14 gr.) boiling at 140°-150°/15 mm.

Ethyl cyclohexanone-2-carboxylate-2-α-hydrocinnamate (XXVI). $C_{20}H_{26}O_5$. requires: C 69.36%, H 7.51%.

Ethyl α-hydroxy hydrocinnamate (XXVII). $C_{11}H_{14}O_3$. requires: C 68.07%, H 7.22%.

Found: C 68.5%, H 8.1%.

The boiling point of (XXVII) is 156°/20 mm.

The oil could be either (XXVI) or (XXVII).

This oil (10 gr.) and concentrated hydrochloric acid were allowed to stand two days, after which time a solid began to separate. The solution was refluxed 6 hours and the solid which separated on cooling was filtered off and recrystallised from water. The solid melted at 158°-159°.

β-ketocyclohexyl-α-hydrocinnamic acid. $C_{15}H_{18}O_3$. requires: C 73.2%, H 7.32%; equivalent weight 246.

Found: C 73.1%, H 8.04%; equivalent weight 140.9.

The solid gave the oder of benzaldehyde on warming with alkaline permanganate. It was thought that it might be cinnamic acid M.P. 133° which requires: C 72.97%, H 6.08%; equivalent weight 148.

A mixed melting point was taken, and the mixture melted at the same temperature as pure cinnamic acid.

These tests conclusively demonstrate that the substance is cinnamic acid; and therefore, it is safe to assume that the oil from which it was prepared is ethyl α-hydroxy hydrocinnamate (XXVII).

ATTEMPTED PREPARATION OF 2-KETOCYCLOHEXYLMALONIC ACID (XXXI).

A. Ethyl cyclohexanone-2-carboxylate (40 gr.) and metallic sodium (5.5 gr.) were refluxed with dry benzene (200 cc.) for 6 hours. Ethyl bromomalonate (67 gr.) was then added and the mixture was refluxed a further 8 hours. On cooling the mixture was shaken with dilute sulphuric acid, washed with water and dilute sodium carbonate solution, and dried over sodium sulphate. After distilling off the benzene, the residue was distilled under reduced pressure, yielding a yellowish oil (18 gr.) boiling at 200°-210°/21 mm. unchanged ethyl cyclohexanone-2-carboxylate (8 gr.) and ethyl bromomalonate (16 gr.).

The yellow oil was refluxed 6 hours with three times its volume of concentrated hydrochloric acid. The mineral acid was distilled off under reduced pressure; and the residue was recrystallised from glacial acetic acid, giving a white solid which melted at 187°-188°.

2-ketocyclohexylmalonic acid, $C_9H_{12}O_5$, requires: C 54.0%, H 6.0%; equivalent weight 100.

Found: C 40.0%, H 6.00%; equivalent weight 89.91.

It was thought that the substance might be succinic acid, M.P. 188°, which requires: C 40.68%, H 5.08%; equivalent weight 59. Finally a mixed melting point showed that the substance was succinic acid.

3. Sodium (1.5 gr.) was dissolved in absolute alcohol (30.0 cc.) and to this was added ethyl cyclohexanone-2-carboxylate (11 gr.). This mixture was warmed for 15 minutes and ethyl bromomalonate (24.0 gr.) was added. The whole was refluxed 6 hours on a water bath, and was then poured into cold water (300 cc.). The yellow oil which separated was taken up with ether and the ether solution was dried over sodium sulphate. After distilling off the ether, the residue was distilled under reduced pressure. A reddish oil (10 gr.), boiling at 190°-220°/16 mm., was obtained. On standing crystals separated out; these were separated from the oil by filtration, and on recrystallization from ligroin, white crystals (M.P. 54°-55°) were obtained. This substance decolorised bromine water very slowly.

Ethyl cyclohexanone-2-carboxylate-2-malonate, $C_{16}H_{24}O_7$, requires: C 58.53%, H 7.32%.

Found: C 58.95%, H 7.04%.

The substance is believed to be ethylene tetracarboxylic ethyl ester (XXXV). $C_{14}H_{20}O_8$. (M.P. 56°) which requires C 53.16%, H 6.33%.

The oil remaining after separation of the crystals contained bromine. It was redistilled boiling at 210°/14 mm., and analysed for bromine.

Found: Br 20.39%; molecular weight (ebullioscopic in benzene) 309.

This liquid is believed to be monobromethane tetracarboxylic ethyl ester (XXXIV): Br 21.61%; molecular weight 337.

ALTERNATIVE PREPARATION OF 2-KETOCYCLOHEXANEGLUTARIC ACID (II).

Sodium (2.3 gr.) was dissolved in absolute alcohol (60 cc.); to this was added a solution of ethyl cyclohexanone-2-carboxylate (25 gr.) and ethyl bromosuccinate (37 gr.). This mixture was heated 5 hours on a water bath, and was then poured in cold water (300 cc.), extracted

with ether, and the ether solution dried over sodium sulphate. After removal of the ether, the residue was distilled under reduced pressure yielding a colorless oil (9 gr.), boiling at 227°/10 mm.

Ethyl cyclohexanone-1-carboxylate-1-succinate (XXXVII). $C_{17}H_{26}O_7$, requires: C 60.34%, H 7.69%.

Found: C 60.61%, H 8.67%.

This oil (9 gr.) was boiled 6 hours with concentrated hydrochloric acid (75 cc.). After distilling off the mineral acid under reduced pressure, the residue was treated as in the preparation of 2-ketocyclohexyl-α-propionic acid. About 0.1 gram of solid resulted, which on recrystallization from glacial acetic acid yielded a few crystals, M.P. 102°-103°, equivalent weight 85.29. This is definitely not 2-ketocyclohexylsuccinic acid.

PREPARATION OF THE γ-LACTONE OF CYCLOHEXANOL ACETIC ACID (XXXVIII).

Cyclohexanone (25 gr.), ethyl bromacetate (45 gr.), and zinc (16 gr.) were refluxed in dry benzene (125 cc.) on a water bath until almost all the zinc had dissolved (2 hours). After cooling, the mixture was acidified with dilute sulphuric acid, washed with water and dilute sodium carbonate solution, and dried over sodium sulphate. The benzene was distilled off, and the ethyl 1-cyclohexanol acetate distilled under reduced pressure (20 gr.), boiling at 140°-146°/37 mm.

Ethyl 1-cyclohexanol acetate (20 gr.) was heated 9 hours with twice its volume of concentrated hydrochloric acid. The solution was extracted with ether; the extract was shaken with dilute sodium carbonate solution, washed with water and dried over sodium sulphate.

After distilling off the ether the lactone was distilled under reduced pressure, boiling at 152°-156°/20 mm.

The γ-lactone of cyclohexanol acetic acid, $C_8H_{12}O_2$, requires: C 68.57%, H 8.57%.

Found: C 67.9%, H 8.96%.

ATTEMPTED PREPARATION OF ETHYL 1-CYCLOHEXANOL MALONATE (XLII).

A. Ethyl bromomalonate (100 gr.), cyclohexanone (41 gr.), and zinc (45 gr.) were refluxed in dry benzene (200 cc.). After about ½ hour a violent reaction occurred; and, when this reaction abated, the mixture was heated 1 hour further on the water bath. It was then acidified with dilute sulphuric acid, extracted with ether, the ether extract washed with dilute sodium bicarbonate solution and water, and dried over sodium sulphate.

After distilling off the ether two fractions were finally obtained:

1. 40 gr. colorless oil, B.P. 105°-108°/35 mm.

2. 4 gr. dark red oil, B.P. 150°-160°/35 mm.

Ethyl 1-cyclohexanol malonate, $C_{13}H_{22}O_5$, requires: C 60.46%, H 8.53%.

Found: 1. C 58.7%, H 7.87%;

2. C 70.20%, H 8.88%.

The first substance was thought to be ethyl malonate, $C_7H_{12}O_4$, requiring C 52.5%, H 7.5%. It was treated with strong ammonia, yielding a white solid M.P. 170°, malonamide melts at 170°.

The second substance has not been identified.

B. Cyclohexanone (25 gr.) ethyl bromomalonate (50 gr.), and zinc (16 gr.) were refluxed in dry benzene (100 cc.) for 10 hours. After the usual treatment there was obtained cyclohexanone, considerable ethyl malonate, and some ethyl bromomalonate.

C. Cyclohexanone (29.4 gr.) and zinc (6.5 gr.) were heated to 155° on an oil bath, ethyl bromomalonate (23.9 gr.) was then slowly added. A violent reaction occurred and the solution turned dark red. It was refluxed 1½ hours, and then given the usual treatment. A yellow oil, boiling at 240°-250°/15 mm. was obtained; this soon solidified, and on recrystallization from hexane yielded a white solid, M.P. 75°-76°. This was thought to be ethane tetracarboxylic ethyl ester $C_{16}H_{22}O_8$ (M.P. 75°).

$C_{16}H_{22}O_8$ requires: C 55.0%, H 6.3%.

Found: C 55.3%, H 7.56%.

D. Ethyl bromomalonate (46 gr.) was refluxed with magnesium (4.9 gr.) in dry ether (35 cc.) until most of the magnesium had dissolved. Cyclohexanone (19.2 gr.) in an equal volume of dry ether was added and the whole was refluxed for 1½ hours on a water bath. On cooling, it was acidified with dilute sulphuric acid, washed with water and dilute sodium carbonate solution, and dried over sodium sulphate. After distilling off the ether the residue was distilled under reduced pressure yielding a yellow oil boiling at 245°-250°/25 mm.

This solidified and was found to be ethane tetracarboxylic ethyl ester.

ATTEMPTED REDUCTION OF ETHYL 1-CYCLOHEXANOL SUCCINATE (XLIII).

Cyclohexanone (50.5 gr.), ethyl bromosuccinate (100 gr.) and zinc (50 gr.) were refluxed with a small crystal of iodine in dry benzene (250 cc.) for 9 hours. On cooling there was obtained, after the usual treatment, the following:

1. 40 gr. colorless oil, B.P. 155°-157°/22 mm.

2. 20 gr. reddish oil, B.P. 160°-170°/25 mm.

Ethyl 1-cyclohexanol succinate, $C_{12}H_{20}O_5$, requires: C 61.76%, H 8.63%.

Found: C 64.78%, H 8.61%, for first substance.

The first substance was thought to be ethyl succinate, $C_8H_{14}O_4$, which requires C 60.17%, H 8.04%. The amide was prepared and found to melt at 240°, succinamide melts at 242°.

It was not possible to get the second liquid to boil over a narrower range, so it was thought that analysis would not help in identifying it, as it was obviously not pure.

PREPARATION OF THE γ-LACTONE OF CYCLOHEXANOL α-PROPIONIC ACID (XLV).

Cyclohexanone (85 gr.), ethyl α-bromopropionate (46 gr.), and zinc (16 gr.) were refluxed in dry benzene (150 cc.) until almost all the zinc had dissolved. The mixture, after treatment in the usual manner, yielded a colorless oil (80 gr.) boiling at 140°-146°/20 mm.

Ethyl α-(1-cyclohexanol) propionate, $C_{11}H_{20}O_3$, requires: C 66%, H 10%.

Found: C 66.72%, H 10.10%.

Ethyl α-(1-cyclohexanol) propionate (20 gr.) was boiled 9 hours with twice its volume of concentrated hydrochloric acid. The solution was extracted with ether; the ether extract was washed with water and dilute sodium carbonate solution and dried over sodium sulphate. After distilling off the ether, there was obtained a colorless, sweet-smelling oil boiling at 150°/21 mm.

The γ-lactone of cyclohexanol α-propionic acid, $C_9H_{14}O_2$, requires: C 70.13%, H 9.09%.

Found: C 69.84%, H 9.04%.

PREPARATION OF ETHYL α-(1-CYCLOHEXANOL) HYDROCINNAMATE (XLVI).

Cyclohexanone (9.8 gr.), ethyl α-bromohydrocinnamate (25.7 gr.), and zinc (6.5 gr.) were refluxed 6 hours in dry benzene (80 cc.) and then treated in the usual manner. There was obtained a brownish oil containing halogen boiling at 215°-220°/15 mm.

Ethyl α-(1-cyclohexanol) hydrocinnamate, $C_{17}H_{24}O_3$, requires: C 74.27%, H 8.65%.

Found: C 70.0%, H 8.79%, Br 2.22%.

This would indicate that there is present a small percentage of ethyl α-bromohydrocinnamate, particularly because on redistillation the carbon and hydrogen percentages had been raised a little. It was found impossible to get the distillate entirely free from this impurity.

SUMMARY.

1. 2-ketocyclohexylacetic acid and the lactone of the corresponding hydroxy acid have been synthesized.

2. 2-ketocyclohexyl-α-propionic acid and the lactone of its hydroxy acid have also been synthesized. The preparation of this lactone is at present being attempted, using the method used by Alexander (1) in the preparation of the γ-lactone of cyclohexanol hydrocinnamic acid.

3. Ethyl α-(1-cyclohexanol) hydrocinnamate has been synthesized.

4. Attempts to synthesize 2-ketocyclohexylmalonic, -succinic, and -α-hydrocinnamic acids have failed, the reactions taking an unexpected course, particularly in the first and last cases.

5. Attempts to synthesize ethyl 1-cyclohexanol malonate and succinate have also failed.

In conclusion, the author wishes to acknowledge his indebtedness to Dr. H. H. Charlesworth for his invaluable advice and willing supervision. This work has been carried out under the tenure of a National Research Council Bursary, for which the author wishes to express his thanks; also, the author is grateful to the Research Committee of the University of Manitoba for the grant used in the purchase of chemicals used during the research.

In addition to the work described, the author has been engaged on a war project for the Department of National Defence, details of which cannot be given here.

The period of tenure of the scholarship expires at the middle of May, by which time the still unfinished portions of the work are expected to be completed.

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ADDENDUM.

Further evidence that the ethyl malonate results from the breakdown of a complex between zinc and ethyl bromomalonate, is given by the fact that zinc dissolves in ethyl bromomalonate on boiling in benzene solution. A viscous red liquid is formed; this liquid on acidification yields ethyl malonate. Also, on burning this liquid, an inorganic residue remains, showing the presence of zinc in the substance.