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Studies on Cyclopropanepolycarboxylic Acids

by

Jacques Kagan

A THESIS
SUBMITTED TO THE FACULTY
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
Doctor of Philosophy

Houston, Texas
May, 1960
To my Mother
ACKNOWLEDGMENT

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I am also indebted to Dr. E. S. Lewis for many helpful discussions and to the faculty and the graduate students of the Chemistry Department for their assistance in breaking the language barrier.

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I also thank Dr. R. L. Sass and Mr. J. P. Church who took interest in some of my crystalline products and studied them by X-ray diffraction.

Words cannot express my gratitude to Dr. R. K. Daily for her consideration and friendship during my stay in Houston.
INTRODUCTION

This thesis is concerned with some cyclopropanecarboxylic acids and especially with problems arising from the chemistry of Feist's acid, 3-methylenecyclopropane-trans-1,2-dicarboxylic acid. The acid was originally prepared by Feist in 1893, but the correct structure was not upheld until 1952, in a communication from these laboratories, and remained controversial for another five years.

Dr. Flynt Kennedy, in a dissertation accepted here in 1956, had investigated many new and interesting aspects of the chemistry of Feist's acid. The present thesis embodies a continuation of the work.
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CHAPTER 2
THE REACTION OF ETHYL BROMOISODEHYDROACETATE
WITHALKALI

In 1893, Feist (1) reported that the reaction of ethyl bromoisodehydroacetate (3-bromo-5-carboethoxy-4,6-dimethyl-2-pyrone, I) with alkali yielded a diacid C₆H₆O₄, possessing a three-membered ring, to which he assigned the structure II.

Thirty years later, Goss, Ingold and Thorpe (2) revised the structure and preferred III. This latter structure was in agreement with the finding by Feist that the optical resolution of the diacid was possible (3) and therefore any formula possessing a plane of symmetry was eliminated. For twenty years, structure III was accepted until Ettlinger (4) proved in 1952 that Feist's acid was actually 3-methylene cyclopropane-trans-1,2-dicarboxylic acid (IV).

Ettlinger's formulation has been supported by chemical and
spectroscopic evidence as well as by X-ray diffraction (5) and is not questioned any more.

Ethyl bromoisodehydroacetate is obtained in two steps from ethyl acetoacetate and a possible mechanism for the formation of Feist's acid may be formulated as follows:
The carbanion undergoing cyclization is actually a hybrid of four contributing structures:

![Chemical structures](image)

Although C-alkylation of \( \beta \)-ketoesters usually occurs in preference to O-alkylation, the strain introduced in the formation of the three-membered ring can allow participation of an alternate mechanism as Perkin already noticed in the reaction of ethyl\( \text{acetooacetate} \) with 1,2-dibromoethane, which yielded a mixture of cyclopropane and dihydrofuran derivatives (6).

![Chemical structures](image)

The intermediate V formed by O-alkylation could aromatize to the furan ring system, either through decarboxylation or through double bond migration.

![Chemical structures](image)
When \( R = C_2H_5 \) the electronic density of the enolate is high on the carbon atom adjacent to three unsaturated groups, and Feist's acid is predominantly formed in the reaction.

When \( R = H \), however, the acid group being present as a carboxylate ion diminishes the localization of a negative charge on the \( \alpha \)-carbon, and \( \alpha \)-alkylation might therefore be expected as the main reaction path.

In fact, Feist observed that bromoisodehydroacetic acid yielded 2,4-dimethyl-furan-3,5-dicarboxylic acid (VI) on treatment with alkali (1).

\[
\begin{array}{c}
\text{HOOC}
\
\text{CH}_3
\
\text{Br}
\end{array}
\rightarrow
\begin{array}{c}
\text{HOOC}
\
\text{CH}_3
\
\text{Br}
\end{array}
\rightarrow
\begin{array}{c}
\text{VI}
\end{array}
\]

Isodehydroacetic acid itself was found to give 2,4-dimethyl-3-furoic acid (VII) when brominated in water (1). Although this reaction was performed under acidic conditions, in contrast to the previous ones, a very similar mechanism can be postulated, involving the same intermediate.

\[
\begin{array}{c}
\text{HOOC}
\
\text{CH}_3
\
\text{H}
\end{array}
\rightarrow
\begin{array}{c}
\text{HOOC}
\
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{HOOC}
\
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{H}
\end{array}
\]

Investigating the products of the reaction of ethyl bromoisodehydroacetate in alkali, we were surprised to find an acid, isomeric with the 2,4-dimethyl-3-furoic acid expected, which was identified as 2,5-dimethyl-3-furoic acid (VIII).

The experimental conditions giving the best yield of this dimethylfuroic acid are not known. It was found, however, that the course of the reaction was remarkably dependent on the concentration of alkali. When a 20% potassium hydroxide solution was used, esterification of the reaction products, followed by distillation, yielded almost exclusively the diethyl ester of Feist's acid and very little forerun (about 3% by weight relative to Feist's ester). By lowering the concentration of alkali to 16%, the amount of forerun was increased to 50% of the Feist's ester obtained. Although the forerun could be distilled at constant temperature, it was not a pure compound. It decolorized potassium
permanganate and absorbed in the ultraviolet with a maximum at 254 mµ, 

E_{1%}^{1%} = 578 \text{ (ethanol).}

Upon saponification, a crystalline acid was obtained with a neutral equivalent of 140. It had an ultraviolet absorption maximum at 250 mµ (ε 4050 in ethanol, 4000 in 0.01 N ethanolic hydrochloric acid). In alkaline solution the maximum vanished, but an inflexion was still present around 240 mµ, ε 4000 (0.01 N ethanolic sodium hydroxide).

These absorption data ruled out the presence of an enol since in this case a shift to longer wave length would be expected on treatment with base. Dimedone (IX) for example absorbs with a maximum at 259 mµ (ε 15200) at pH 2 and 282 mµ (ε 24300) in sodium hydroxide (7). The acid obtained must then have been a carboxylic acid containing at least two carbon-carbon double bonds. Crotonic acid (X), with only one carbon-carbon double bond has a maximum absorption at 203 mµ, ε 16000 (ethanol) (8). Sorbic acid (XI), with two double bonds conjugated with

![Chemical structures]

the carboxyl group, absorbs with a maximum at 254 mµ, ε 26000 (95% ethanol). This maximum is shifted to 249 mµ, ε 23500 in 0.2 N sodium hydroxide in 76% ethanol and to 258.5 mµ in 0.2 N sulfuric acid in 76% ethanol (8).
With this knowledge, a search through the literature led to 2,5-dimethyl-3-furoic acid, despite the lower melting point previously reported. It was prepared by an independent synthesis and was found to be indeed identical with our material. From comparison of the extinction coefficients for the absorption of the forerun previously mentioned and for the authentic ester, the content of ethyl 2,5-dimethyl-3-furoate in the forerun was only about 22%.

As the products of the reaction of ethyl bromoisodehydroacetate with alkali were acidified, extracted, and esterified in ethanol and sulfuric acid before they were separated, it is not clear in which step the furan derivative was formed. However, since the course of the reaction was so dependent on the concentration of alkali, it is probable that the furoic acid or a precursor was formed by an independent path at this stage.

A possible mechanism can be written using the intermediate XII already postulated in the formation of Feist's acid.
The substance XIII is an intermediate in the standard synthesis of 2,5-dimethyl-3-furoic acid (VIII) (11).
EXPERIMENTAL

The preparation of ethyl bromoisodehydroacetate gives the best yield when carried out as described by Kennedy (9). However, for large scale preparation, the yields were slightly sacrificed for the sake of convenience and the following conditions were used.

Ethyl isodehydroacetate. Practical ethyl acetoacetate (3 liters), cooled externally with ice water from the line (9\(^\circ\)), was treated with a stream of hydrogen chloride through fritted glass for 8 hours and stored in the dark for 3 days in a closed container. The product was cooled again and treated with hydrogen chloride under similar conditions for 8 more hours. The cooling was applied for 24 hours while the flask was open to allow the excess gas to be evolved. The reaction mixture was then allowed to stand 36 hours at room temperature, washed free of acid and distilled to furnish 1217 g. (54\%) of ethyl isodehydroacetate, b.p. 144\(^\circ\)/1.8 mm.

Ethyl bromoisodehydroacetate. Ethyl isodehydroacetate (201 g.) was dissolved in chloroform (500 ml.) and cooled as above. Bromine (60 ml.) was added with stirring during a 35 minute period. The mixture was stirred for one more hour and was allowed to stand overnight at room temperature. Stirring for one hour, followed by heating at 80\(^\circ\) for one hour, removed most of the hydrogen bromide formed in the reaction. The solution was washed free of acid and concentrated to a small volume. Crystallization occurred upon addition of petroleum ether and yielded 219 g. (78\%) of ethyl bromoisodehydroacetate, m.p. 83-84\(^\circ\).

Treatment of ethyl bromoisodehydroacetate with alkali. The reaction in 20\% potassium hydroxide was carried out as described by Kennedy
on 100-g. portions of ethyl bromoisodehydroacetate in 770 ml. of 20% potassium hydroxide (133 g. of 35% potassium hydroxide pellets in 735 ml. of water). The reaction mixtures from four portions were combined, acidified and extracted with ethyl acetate. The extracts were esterified with ethanol and sulfuric acid and distilled to yield 3 g. of forerun and 116 g. (40.4%) of Feist's ester, b.p. 90-110°/0.3 mm. With all other conditions identical, a reaction in 16% potassium hydroxide (155 g. of potassium hydroxide pellets in 770 ml. of water) yielded 9.25 g. of forerun and 17 g. (25.2%) of Feist's ester from 94 g. of ethyl bromoisodehydroacetate. The forerun was redistilled at 70° and 1.9 mm. It possessed an irritating odor and decolorized aqueous 2% potassium permanganate. The refractive index at 28° was 1.4296 and the maximum of absorption in the ultraviolet was at 254 mμ, ε1% 578. 2,5-dimethyl-3-furoic acid. Hydrolysis of the forerun in acid did not lead to any crystalline product, whereas with sodium hydroxide a material was obtained after acidification and extraction, which upon recrystallization from aqueous ethanol melted at 135.9-136.4°. Several recrystallizations raised the melting point to 138.3-139.1° (lit. 135.4° (11)). The acid had a neutral equivalent of 140 (calcd. 140). Harrow's characteristic color test of the acid (10) was repeated. A few crystals were strongly heated over a burner in a test tube with 0.5 ml. of concentrated hydrochloric acid. To the hot solution 0.5 ml. of concentrated sulfuric acid was added and heating was resumed. A color, first yellow then red, was produced.

The method of Hurd and Wilkinson (11) was used for the synthesis of authentic 2,5-dimethyl-3-furoic acid, substituting bromoacetone for chloroacetone. The sodium salt obtained from 30.4 g. of ethyl acetol-
acetate was alkylated with 21.3 g. of bromoacetone. Distillation of
the product yielded 7.25 g., b.p. 58-63°/2 mm., and 10.9 g., b.p.
110°/2 mm., \( \lambda_{\text{max.}} \) 225 m\( \mu \), \( \epsilon \) 795 (ethanol). The second fraction was
cyclized in cold concentrated sulfuric acid and the product was hydro-
lyzed in 5% sodium hydroxide to yield 5.05 g. (61%) of 2,5-dimethyl-3-
furoic acid, m.p. 136.8-138°. Similar treatment of the first fraction
yielded the same product, but it was yellow and difficult to purify.
The acid chloride, prepared by treating the acid with thionyl chloride
at reflux, reacted with ethanol to yield ethyl 2,5-dimethyl-3-furoate,
\( n_D^{26.5} \) 1.4690; \( \lambda_{\text{max.}} \) 252.5 m\( \mu \), \( \epsilon \) 4540 (ethanol).
1. F. Feist, Ber., 26, 747 (1923).
   D. R. Petersen, ibid., 904 (1956).
CHAPTER II
THE PREPARATION OF
*cis*-Cyclopropane-1,2,3-Tricarboxylic Acid

Cyclopropane-1,2,3-tricarboxylic acid is among the oldest known cyclopropane derivatives, having first been prepared in 1865 by Baeyer (1). Its structure was not recognized then and it was named aceconitic acid.

The substance can exist as two stereoisomers, *cis* and *trans*.

All the methods so far devised to prepare this triacid give the more stable *trans*-isomer, and, as might have been predicted, all attempts to convert the *trans*-triacid to its *cis*-isomer through anhydride formation have failed (2).

*cis*-Cyclopropane-1,2,3-tricarboxylic acid remained then one of the simplest and most attractive cyclopropane derivatives to be obtained, since it might have been predicted that its high degree of symmetry would be reflected by unusual properties.
General methods of synthesis of cyclopropane-1,2,3-tricarboxylic acid

1. Treatment of ethyl bromoacetate with sodium.
This was the first synthesis used by Baeyer (1) who obtained "aceconitic acid", later proved to be trans-cyclopropane-1,2,3-tricarboxylic acid.

Hexaethyl cyclopropane-1,1,2,2,3,3-hexacarboxylate on mild hydrolysis in barium hydroxide solution (3) and cyclopropane-1,1,2,3-tetra-carboxylic acid on heating at the melting point lead to the trans-1,2,3-triacid. One report of the cis-isomer (4) assumed the cis-tetraester I to be the starting material, but I is still unknown at the present time and the report was later corrected (2).

\[ \text{COOC}_2\text{H}_5 \]
\[ \text{COOC}_2\text{H}_5 \]
\[ \text{COOC}_2\text{H}_5 \]
\[ \text{COOC}_2\text{H}_5 \]
\[ \text{COOC}_2\text{H}_5 \]
\[ \text{COOC}_2\text{H}_5 \]

The trans-tetraester II could only lead to the trans-triacid and the presumed cis-triacid was actually a mixture of trans-triacid and tricarballylic acid.

3. Base condensation of ethyl chloroacetate with diethyl maleate or fumarate (5).
Whereas this method applied to other unsaturated esters gives rise to mixtures of cis and trans isomers, no cis-triester was produced here, thus suggesting that if any was formed, it isomerized readily under
the influence of the medium.

4. Reactions of ethyl diazoacetate.

The reactions of fumaric or maleic esters with diazoacetic ester lead to a common intermediate, the $\Delta^2$-pyrazoline III. Buchner studied these reactions with the methyl esters (6) and found that only the trans-cyclopropane triester was obtained upon elimination of nitrogen from III.

![Chemical structure of III]

The reaction of ethyl diazoacetate with a suitable unsaturated compound, followed by oxidation of the adduct is another means to obtain the cyclopropane-1,2,3-tricarboxylic acid, which is very stable to oxidation.

In the case of benzene the reaction is indicated:

![Chemical reaction diagram]

Two stereoisomeric structures of adducts with cyclopropane rings are possible, widely different in steric strain, **cis** (IV) and **trans** (V).
However, these two configurations can be readily interconverted through the planar system of ethyl 2,4,6-cycloheptatriene-carboxylate (VI), and it can be predicted that the proportion of molecules in the structural configuration IV will be small.

On oxidation, only the triacid derived from V, the trans-triacid, was obtained (7).

The adduct (VII) of ethyl diazoacetate and naphthalene must be stereochemically more stable because the formation of the cycloheptatriene structure VIII involves the loss of aromaticity in the benzene ring and is therefore endothermic.

To explain an unusual rearrangement of the azide derived from VII, Doering (8) postulated the presence of a cis intermediate, analogous to IV, despite the report that oxidation of VII (R = H) leads to trans-cyclopropane-1,2,3-tricarboxylic acid (9).
In light of our own work, the conditions used to oxidize VII (R = H) (potassium permanganate in aqueous alkali) should not allow epimerization, and therefore the trans-triacid should come from a precursor with a trans structure (IX).

A cis intermediate could only come from a later stage of the reaction sequence, namely the Curtius rearrangement of the azide, which however is considered to be stereospecific.

All the methods mentioned involve either trans intermediates or conditions which lead to the more stable trans isomer of the cyclopropane-1,2,3-tricarboxylic acid (or any of its derivatives).

The only exception would be ethyl cyclopropanehexacarboxylate (X) which has the required cis structure on each side of the ring. The mechanism of the decarboxylation of the corresponding acid is unknown, but may reasonably proceed to the trans-1,1,2,3-tetracarboxylic acid and thence to the observed product.

Any successful method to prepare the cis-1,2,3-triacid must therefore involve cis intermediates and a medium unable to isomerize them. These conditions were met in our successful approach to the problem.
Synthesis of cis-cyclopropane-1,2,3-tricarboxylic acid

Feist's acid XI is known to react with bromine water to give a dibromo diacid XII and a bromolactone acid (XIII). The latter can be reduced by sodium amalgam (11) to a lactone acid (XIV) which on oxidation by potassium permanganate in sodium bicarbonate yields trans-cyclopropane-1,2,3-tricarboxylic acid (12).

This path does not alter the steric configuration of the two acid groups and has the net effect to change the methylene group into a carboxyl, necessarily cis to one of the initial carboxyl groups.

If the starting material instead of having a trans configuration already possesses two cis-carboxyls, one can hope to obtain the desired cis-cyclopropane-1,2,3-tricarboxylic acid, providing that the experimental conditions do not isomerize any intermediate.

It may be noted that free acids should be resistant to isomerization in base, the polar effect of the carboxylate ion greatly retarding ionization on the α-carbon.

The known (13) cis isomer of Feist's acid (XV) was hence sub-
jected to the sequence of reactions indicated above.

Bromination in water of XV gave only a cis-bromolactone acid (XVI), and no dibromo diacid. This can be explained by assuming the bromine to attack the molecule on its least hindered side, bringing the methylene group cis to the two carboxyls.

If the carbonium ion picks up a bromide ion, the product formed will have three large groups on the same side of the ring. A very strong steric interaction will result, which can be partly overcome by joining two of the substituents in a five-membered lactone ring.

The bromolactone acid XVI was different from XIII and could be reversibly hydrolyzed, without any isomerization taking place during the treatment in base.
Since reduction of XVI with zinc in acetic acid was unsuccessful, a basic medium was tried. Zinc in 5% sodium hydroxide solution gave in poor yield a saturated product in which the lactone ring was not present any more and which must therefore be trans-3-hydroxymethylcyclopropane-cis-1,2-dicarboxylic acid (XVII).

\[ \begin{align*}
&\text{XVII} \\
&\text{XVIII} \\
&\text{XIX}
\end{align*} \]

Reduction by 2.5% sodium amalgam was finally successful. To prevent an eventual isomerization, the aqueous medium was kept neutral by a stream of carbon dioxide. The lactone ring presumably remained intact during the reduction, preventing a change of configuration at C-3. Under these conditions a lactone acid (XVIII) was obtained, different from the corresponding one (XIV) derived from the trans-acid.

Oxidation of XVIII with potassium permanganate in bicarbonate solution was unsuccessful, presumably because the lactone ring required much more basic conditions for opening. By adjusting the alkalinity during oxidation with sodium hydroxide, the desired cis-cyclopropane-1,2,3-tricarboxylic acid (XIX) was obtained in good yield.

This triacid was a white crystalline material, melting slightly lower than the trans-isomer (196° instead of 220°). It was stable in aqueous alkali, in contrast to 3-methylenecyclopropane-cis-1,2-dicarboxylic acid (XV) (13). As might have been expected from its structure, it was a strong acid by its first dissociation (pK\(_1\) 1.93),
as strong as maleic acid (pK 1.92) (14). The other constants were given by pK₂ 4.49, pK₃ 10.00. The last constant was expected to be small because of the inductive effect of the carboxylate groups (see discussion in Chapter 4).

The steric effect of cis carboxyls can be appreciated by comparing the acidity constants with those of the open-chain tricarballylic acid (XX) (pK₁ 3.49, pK₂ 4.58, pK₃ 5.83) (15).

\[
\text{HOOC-C}_2\text{H}_4\text{COOH} \\
\text{XX}
\]

On treatment with diazomethane, XIX yielded a crystalline trimethyl ester. X-ray study of these crystals (16) showed that they belong to the space group C\text{\textsubscript{3}v} - R3c which has a threefold symmetry axis. The cell constants are a = 13.46 ± 0.02 Å, c = 10.70 ± 0.01 Å.

There are six molecules per unit cell and the high symmetry in the crystal is responsible for its high melting point (157.6-157.9°).

The presence of the threefold symmetry axis confirms nicely the cis structure of the trimethyl ester (and therefore of its precursors), which was demonstrated also by isomerization of the ester with sodium methoxide to the known trimethyl trans-cyclopropane-1,2,3-tricarboxylate, m.p. 54°.
EXPERIMENTAL

3-Methylenecyclopropane-cis-1,2-dicarboxylic acid. Twenty grams (0.141 mole) of Feist's acid was dissolved in 400 ml. of acetic anhydride in a 2-liter flask. The solution was refluxed for 15 minutes with 0.4 g. of potassium acetate and was neutralized with 0.3 g. of p-toluene-sulfonic acid monohydrate. The solvent was removed under vacuum on the steam bath and the dark residue distilled under reduced pressure. During the distillation, a capillary stream of nitrogen was passed through to prevent the decomposition of the high boiling residue, which had been found to be sometimes violent. The yield of slightly yellow anhydride was 12.46 g. (72%), b.p. 84°/0.7 mm.

On reflux in water, the anhydride yielded 3-methylenecyclopropane-cis-1,2-dicarboxylic acid, m.p. 118-119.1°.

3-Bromo-cis-3-hydroxymethylcyclopropane-cis-1,2-dicarboxylic acid lactone.

A solution of 4.675 g. (0.033 mole) of 3-methylenecyclopropane-cis-1,2-dicarboxylic acid in 200 ml. of water was treated with 1.8 ml. (0.035 mole) of bromine. The mixture was stirred for about 2 hours at room temperature until a colorless solution was obtained, concentrated under vacuum to a small volume and extracted several times with ether. The extracted material was crystallized from ether-petroleum ether and gave 5.005 g. (68%) of cis-bromolactone acid, m.p. 146-150°. By concentration of the mother liquor, 0.180 g. more was obtained. Several recrystallizations from ethyl acetate-petroleum ether raised the melting point to 162.6°. A mixture with the trans isomer (m.p. 172°) melted at 135-142°.

Anal. Calcd. for C₆H₅O₄Br: C, 32.58; H, 2.26; Br, 36.20.

Found: C, 32.65; H, 2.22; Br, 36.50.
Neut. equiv. Calcd., 221; Found, 218.

with excess base Calcd., 110.5; Found, 104.

The neutral solution was acidified and concentrated under vacuum. Extraction of the residue with ethyl acetate yielded 0.023 g., m.p. 156-160°. A mixture with the starting material melted at 155-158°.

Reduction of cis-bromolactone acid in alkali. The bromolactone acid (0.389 g.) was treated with 0.817 g. of zinc dust in 20 ml. of 5% sodium hydroxide. After heating for 2 hours on the steam bath, the zinc was filtered and the solution was treated with 1.1 g. of sodium bicarbonate and centrifuged. The precipitate was washed with 20 ml. of hot water and the solution and washing were acidified with 5 ml. of 6 N hydrochloric acid. After concentration under vacuum, the residue was extracted with ethyl acetate. The solvent was concentrated and the product, 0.036 g. of trans-3-hydroxymethylcyclopropane-cis-1,2-dicarboxylic acid, crystallized from ethyl acetate-petroleum ether. After 3 recrystallizations it melted at 191.5-192°.

Anal. Calcd. for C₆H₇O₅: C, 45.00; H, 5.00.

Found: C, 45.10; H, 5.18.

Neut. equiv. Calcd., 80; Found, 83.3.

No change occurred when the neutral solution was heated over the steam bath for 10 minutes.

cis-3-hydroxymethylcyclopropane-cis-1,2-dicarboxylic acid lactone. A stream of carbon dioxide was bubbled through a solution of 3.136 g. of bromolactone acid in 30 ml. of water and 42 g. of 2.5% sodium amalgam was added in small portions. After completion of the addition, the flask was heated over a steam bath for two hours while the stream of carbon dioxide was continued. The solution was decanted, acidified
to pH 2 by 6 N hydrochloric acid and concentrated under vacuum until salt began to precipitate. Several extractions with ethyl acetate followed by crystallization of the extracted material from ethyl acetate-ether yielded 0.945 g. (47%), m.p. 168-170°, of cis-lactone acid and 0.040 g., m.p. 188-191°, presumably trans-3-hydroxymethyl-cyclopropane-cis-1,2-dicarboxylic acid. Several recrystallizations of the main fraction from ethyl acetate, alone or mixed with ether or petroleum ether, yielded pure material, m.p. 172°.

**Anal.**

Calcd. for C₆H₆O₆: C, 50.70; H, 4.22.

Found: C, 50.75; H, 4.20.

**Neut. equiv.**

Calcd., 142; Found, 143.

with excess base Calcd., 71; Found, 71.5.

**cis-Cyclopropane-1,2,3-tricarboxylic acid.** The cis-lactone acid (0.266 g.) was added to a solution of 0.292 g. of sodium hydroxide pellets in 5 ml. of water. The flask was heated for 30 minutes to insure opening of the lactone ring and cooled to room temperature. A solution of 0.373 g. of potassium permanganate in 10 ml. of water was added and the reaction mixture was allowed to stand overnight at room temperature. The excess of permanganate was destroyed by addition of sodium bisulfite and 6 N hydrochloric acid until a colorless solution was obtained, which was concentrated under vacuum to a small volume and extracted with ethyl acetate. The organic solution was washed, dried and concentrated to furnish 0.161 g. (50%) of white crystals, m.p. 192°. The product recrystallized several times from ethyl acetate, melted at 195.6-195.8°. Because of the low value of the last ionization constant of this acid, phenolphthalein was not a suitable indicator for titration.
The infrared spectrum of the acid in a potassium bromide disk showed
bonds at 3.35 (s, broad), 3.85 (infl.), 5.71 (s), 5.85 (s), 5.98 (s),
6.94 (s), 7.04 (s), 7.45, 7.74, 8.02 (s), 8.42 (s), 8.58 (s), 9.54,
10.18, 10.6 (infl.), 11 (broad), 11.75, 12 (broad), 12.2 (infl.), 12.55
(w), 13.06 (v). (The wavelengths are expressed in μ and the ab-
breviations for intensity are s-strong, w-weak).

**Anal.**

Calcd. for C₈H₆O₆:

<table>
<thead>
<tr>
<th></th>
<th>C,</th>
<th>H,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcd.</td>
<td>41.38</td>
<td>3.44</td>
</tr>
<tr>
<td>Found</td>
<td>41.37</td>
<td>3.53</td>
</tr>
</tbody>
</table>

**Stability in base.** In a total of 32 ml. of solution, 0.037 g. (0.00021
mole) of cis-cyclopropane-1,2,3-tricarboxylic acid was refluxed for 3½
hours in presence of 0.00125 mole excess of alkali. After acidifica-
tion to Congo Red and extraction with ethyl acetate, two recrystalliza-
tions yielded 0.020 g., m.p. 187-189° of product having the same infra-
red spectrum as the starting material and showing no depression of
melting point when mixed with it.

**Trimethyl cis-cyclopropane-1,2,3-tricarboxylate.** An excess of diazo-
methane in ether was added to 0.061 g. of cis-cyclopropane-1,2,3-
tricarboxylic acid dissolved in ether. After reaction, the solvent
was evaporated and after washing with petroleum ether there was
obtained 0.061 g. (30.6%) of triester, m.p. 155°. An analytical sample
was recrystallized from ethyl acetate-petroleum ether, twice from
acetone-petroleum ether and sublimed. The melting point of the product
was 157.5-157.9° with a transition at 145°.

**Anal.**

Calcd. for C₉H₁₂O₆:

<table>
<thead>
<tr>
<th></th>
<th>C,</th>
<th>H,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcd.</td>
<td>50.00</td>
<td>5.55</td>
</tr>
<tr>
<td>Found</td>
<td>49.34</td>
<td>5.40</td>
</tr>
</tbody>
</table>
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CHAPTER III
ISOMERIZATION OF CYCLOPROPANECARBOXYLIC ESTERS IN BASE

This section deals with the isomerization in base of substituted cyclopropanecarboxylic esters I. The mechanism of such a reaction presumably involves the reversible formation of a planar enolate ion II which leads to the more stable configuration.

\[
\begin{array}{c}
\text{I} \quad \text{H} \quad \text{COOR} \\
\leftrightarrow \\
\text{II} \quad \text{H}^+ \quad \text{C} \quad \text{O}^- \quad \text{OR} \\
\leftrightarrow \\
\text{II} \quad \text{H} \quad \text{COOR}
\end{array}
\]

According to Brown (1) the formation of the planar system II is accompanied by an increase in the strain of the ring (I-strain) due to a larger distortion of the bond angles. This deformation of the bond angles is 49.5° (109.5° to 60°) in I and is increased to 60° (120° to 60°) in II. Although the ion would then have a higher energy, it can still exist. Systems involving the same type of strain, methylene-cyclopropane and particularly substituted methylene-cyclopropanes like Feist's acid, are known to be stable. The ion II is stabilized by resonance.

\[
\begin{array}{c}
\text{II} \quad \text{H} \quad \text{C} \quad \text{O}^- \quad \text{OR} \\
\leftrightarrow \\
\text{II} \quad \text{H} \quad \text{C} \quad \text{O}^- \quad \text{OR}
\end{array}
\]

The acidity of \(\alpha\)-hydrogens on a cyclopropane ring is extremely reduced as compared to larger cycloalkyl and alkyl groups. For instance,
whereas aliphatic nitro compounds are acidic and can easily be alkylated in the $\alpha$-position, nitrocyclopropane shows no tendency to form an anion III.

\[
\begin{array}{c}
\text{III} \\
\text{N} \\
\text{O}^- \\
\end{array}
\]

Nitrocyclopropane is insoluble in strong aqueous base and does not form salts in homogeneous alkaline media at $25^\circ$ (2). Again, cyclopropyl methyl ketone is alkylated exclusively on the methyl group after treatment with sodamide or triphenylmethy1sodium whereas larger cycloalkyl methyl ketones react at the $\alpha$-carbon of the ring (3). The possibility of removing a ring hydrogen is demonstrated by treating cyclopropyl phenyl ketone with the same condition; the sodium derivative can be alkylated on the three-membered ring by benzyl chloride (4). Another example is furnished by cyclopropane itself, which can be carbonated to cyclopropanecarboxylic acid after treatment with amylsodium (5).

Organometallic compounds $R\text{Me}$ may be subject to the equilibrium $R\text{-Me} \rightleftharpoons R^- + \text{Me}^+$. Depending on the solvent and the structure of $R$, the position of the equilibrium may vary. Optically active alkylmetal compounds have been found to racemize at low temperature; only two examples have been reported where some optical activity is retained by the acid formed by carbonation of an alkyllithium derivative. Whereas only 20% of optical activity was retained at $-70^\circ$ in the carbonation of 2-octyllithium in a petroleum ether-ether solution (6),
56% was retained at -10° during the carbonation of sec-butyllithium in pentane (7). This solvent dependence suggests that the racemization of alkyllithium reagents proceeds by an ionization mechanism:

\[
RLi \rightleftharpoons R^- + Li^+
\]

The carbanion formed would be unable to retain its steric configuration at the temperatures considered.

Alkyl carbanions are isoelectronic with amines which are known to equilibrate too rapidly to allow their separation into optical isomers. The resolution of amines is possible only when the nitrogen is held in a rigid system (8).

Vinyllithium compounds have been found to exist as geometrical isomers stable in ether at low temperature (9). The carbanion produced in the equilibrium proposed may therefore be able to retain its geometric configuration.

\[
\begin{align*}
\text{C} & \equiv \text{C} \quad \text{C} & \equiv \text{C} \\
R_1 & \quad R_2 \quad R_3 & \quad R_1 \quad R_2 \quad R_3 \\
\end{align*}
\]
A similar situation is found in the corresponding nitrogen derivatives.

\[ \begin{align*}
R_1C & = \text{N}^* \nonumber \\
R_2 & \nonumber \\
R_3 & \nonumber
\end{align*} \]

It is well known that oximes (R_3 = OH) can exist with two separable steric conformations, **syn** and **anti**. Stereoisomeric imines (R_3 = alkyl or aryl) have also been isolated (10). These examples show that a pair of electrons placed on a trigonal atom can keep its steric configuration.

Much evidence supports the concept that a cyclopropane ring possesses some double bond character (11). It could therefore be possible for a cyclopropyl carbanion to behave similarly to a vinyl carbanion. Asymmetric cyclopropyllithium derivatives have been prepared and have retained their optical activity in subsequent reactions. 1-Bromo-1-methyl-2,2-diphenyl-cyclopropane has been treated with n-butyllithium at 60°C and the cyclopropyllithium decomposed with methanol to yield 1-methyl-2,2-diphenyl-cyclopropane with 60% retention of optical activity (12). In unpublished work (13), another cyclopropyllithium has been carbonated with at least 95% retention of configuration.

N-Substituted ethylenimines are isoelectronic with cyclopropyl carbanions and Roberts (14) showed that the mean lifetime of one configuration is 0.017 sec. at 108°C and is much larger at lower temperature.
Although the amount of carbanion coming from the cyclopropyl-lithiums is unknown, it is therefore conceivable that some was present. The Haller-Bauer reaction of unenolizable ketones is believed to proceed via a carbanion (15).

\[ \text{RCOR}^+ + \text{Na}_2\text{NH}_2 \rightarrow R^- - C - R' \rightarrow R^- + R'\text{CONH}_2 \]

On treatment with these conditions, 1-methyl-2,2-diphenyl-cyclopropyl phenyl ketone gave the corresponding hydrocarbon with retention of optical activity (16). This reaction would indicate that the carbanion formed did not lose its steric configuration.

Except for the examples mentioned, the cyclopropyl carbanions IV studied in the literature possess a group R (nitrile, ketone, carboxylic acid or ester) able to delocalize the electron pair of the carbanion.

The resonance energy of the planar configuration, added to an eventual relief of steric interactions, will probably outweigh the strain of the exocyclic double bond.
Substituted cyclopropyl cyanides isomerize easily from a cis to a trans-configuration or lose their optical activity in basic solution (17 to 20). cis-Cyclopropyl ketones likewise invert easily to the more stable trans-form. For instance, the very strained ketone V isomerizes to the form having the keto group trans, showing as expected that the keto enolate is easier to form than that involving the atom bearing the carboxylate group (21).

\[ \text{V} \]

Mild basic conditions can cause such a steric change. Ammonia has been reported to isomerize the ketones VI and VII (22).

\[ \text{VI} \]
\[ \text{VII} \]

A demonstration that these inversions involve a carbanion-enolate ion was given by Kohler (23) who showed that the ketone VIII was isomerized to the trans-form both by base and by acid. The acid treatment clearly involves the production of an intermediate enol.

\[ \text{VIII} \]
For cyclopropanecarboxylic esters the situation is not as clear as for the nitriles and ketones.

In some cases the acidity of the α-hydrogen is too low to permit extensive formation of the cyclopropyl carbanion. Ethyl cyclopropanecarboxylate yielded an imide (IX) and a ketone (X) when treated with sodamide and triphenylmethylsodium respectively (4).

\[
\text{IX} \quad \text{X}
\]

Optically active methyl 2,2-diphenylcyclopropanecarboxylate was reported not to racemize during a 15-hour reflux in a concentrated solution of sodium methoxide in methanol (10).

However, strained cyclopropanecarboxylic esters have been found to isomerize in base. The relief of steric interactions in the molecule must assist the removal of the α-hydrogen and the formation of the planar enolate ion. The first example recorded was the isomerization of dimethyl 1-methyl-cyclopropane-cis-1,2-dicarboxylate (XI) in sodium methoxide (24).

\[
\text{XI}
\]
This method was later used by Kennedy (23) to prove the structure of the two 3-methylcyclopropane-cis-1,2-dicarboxylic acids and 3-methyl-cyclopropane-1,1,2-tricarboxylic acids. In recent work it was also shown that a mixture of stereoisomeric ethyl 2-p-chlorophenylcyclopropanecarboxylates was converted to the trans-configuration by treatment with sodium methoxide in methanol (11) and that methyl cis-2-phenoxy-cyclopropanecarboxylate and methyl cis-chrysanthemate were isomerized to trans by treatment with various bases (25).

It may be noted that in some cases the cyclopropyl carbanion-enolate ion can undergo further changes. Ring opening may occur if in the process the negative charge is better stabilized. The ketone VIII is an example. Isomerization to the trans-form has been recorded but ring opening also occurred on treatment with sodium methoxide, leaving the negative charge stabilized by the malonic ester group (23).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH} & \text{OC}_6\text{H}_5 \quad \text{C}_6\text{H}_5\text{CH} \equiv \text{C} - \text{COC}_6\text{H}_5 \\
\text{C}_6\text{H}_5\text{CH} \quad \text{C}_6\text{H}_5\text{CH} & \equiv \text{C} - \text{COC}_6\text{H}_5
\end{align*}
\]

VIII

Cyclopropyl carbanions can also undergo elimination of a negatively charged substituent from a \(\beta\)-carbon atom, leaving a cyclopropene derivative as first found by Kohler (26).
In this research, the isomerization in base of several cis-cyclopropanepolycarboxylic esters has been studied and the trans products have been isolated prior to hydrolysis.

In the literature, except for studies by Kennedy, all the examples cited involved hydrolysis of the reaction products and identification of the trans-acids. A slight doubt therefore remained as to the step responsible for the isomerization.

In order to avoid transesterification, the alkoxide corresponding to the ester groups has always been used and no investigation has been made on the effect of the basicity on the ease of isomerization.

Cyclopropane triesters

In this research, cyclopropane-cis-1,2,3-tricarboxylic acid was prepared for the first time. In order to demonstrate its structure, its conversion to the known trans-compound was sought. Reflux of the cis-triacid in excess dilute alkali did not alter its configuration, although the carboxyl group of the all-cis acid XII was known to invert on treatment with concentrated base (20).
The cis-trimethyl ester XIII was then treated with a solution of sodium methoxide in methanol and the isomerization was found to be very easy.

```
               COOCH₃
               CH₃OC\longrightarrow COOCH₃
               COOCH₃
```

XIII

It occurred at room temperature in 0.2 N methoxide, but was always accompanied by partial saponification, no matter how carefully the solvent was dried. This phenomenon may have been caused by the climatic conditions of our work or may have been related to the finding that methyl benzoate was saponified almost quantitatively by sodium methoxide in methanol at 100° under rigorously anhydrous conditions (27).

After treatment of the cis-trimethyl ester with methoxide, chromatography yielded a neutral fraction identified as the trans-trimethyl ester, and an acidic portion which was converted to the trans-triester by diazomethane. The relative ease of this isomerization, compared with the drastic conditions (reflux in concentrated methoxide) which were reported not to racemize methyl 2,2-diphenylcyclopropanecarboxylate, may be credited to the important strain of the cis-1,2,3-trisubstituted cyclopropane, which is accompanied by an easy access to the α-hydrogen by the base, and perhaps to the inductive effect of the two ester groups not directly involved. The energy liberated upon relief of the steric strain constitutes the driving force for the reaction.
A similar isomerization has been carried out on triethyl 3-methyl-
cyclopropane-1,1,2-tricarboxylate.

Two stereoisomers can exist, cis (XIV) and trans (XV).

As a means to establish the structure of the cis-ester, it was treated
with a solution of sodium ethoxide in ethanol. One could predict that
the isomerization would not be as easy as in the previous case, since
it involves the passage from one 1,2,3-cis interaction to two 1,2-cis
interactions. It was found, however, that a four-hour reflux in 0.45
N ethoxide sufficed to obtain practically pure trans-isomer from a
mixture containing at least 82% of the cis-triester.

Monoesters of cyclopropane-1,2-diacids

Compared to a ketone or an ester group, a carboxylate ion greatly
lowers the acidity of the α-hydrogen, because the formal negative
charge distributed between the oxygen atoms diminishes further ac-
ceptance of a negative charge in the enolate.

Half esters of 1,2-diacids are therefore expected to undergo
inversion of the ester group in base much faster than of the carboxylic
acid group. This argument was used by Kennedy (28) to provide a proof
of structure for the two 3-methylcyclopropane-cis-1,2-dicarboxylic
acids, **trans,cis** (XVI) and **cis,cis** (XVII).

Isomerization of the dimethyl esters should lead to the same trans-diesters, whereas two different products should be obtained from the monomethyl esters.

Kennedy found that the two different trans-monomethyl esters could apparently be obtained by the inversions, but such an extensive saponification had taken place that we found it necessary to reexamine this work.

The **cis,cis** monoester XVIII, being a cis-1,2,3-trisubstituted cyclopropane, was expected to isomerize with ease in order to relieve the strain in the molecule. Isomerization of the **trans,cis** monoester XIX, however, changes one type of cis-1,2 interaction (carboxylate-carbomethoxy) to another (methyl-carbomethoxy) and because of the smaller size of the methyl, the latter interaction may be expected to be more favorable. Hence inversion should occur, but more slowly than
with the \textit{cis,cis} compound. It was found indeed that whereas 30 minutes of heating of the \textit{cis,cis}-monoester in 4 N sodium methoxide sufficed to isomerize it completely, a treatment eight times longer in similar conditions left about 15\% of the \textit{trans,cis}-monoester unchanged.

The amount of saponification increased with the reaction time and must be responsible for the 54\% of starting material not recovered as monoesters in the latter experiment.

The product from the \textit{trans,cis}-monoester was found identical to the monomethyl ester XX obtained by partial hydrolysis of dimethyl 3-methylcyclopropane-\textit{trans}-1,2-dicarboxylate with strongly acidic ion-exchange resin as catalyst. Since the molecule must be adsorbed on the surface of the catalyst, the less hindered group is expected to hydrolyze first.

\begin{center}
\begin{tikzpicture}
\draw (0,0) -- (1,1) -- (1,-1) -- cycle;
\node at (0.3,0.3) {$\text{CH}_3$};
\node at (0.7,-0.7) {$\text{COOCH}_3$};
\node at (-0.7,-0.7) {$\text{COOH}$};
\node at (0,-0.7) {XX};
\end{tikzpicture}
\end{center}

Conversely, the less hindered carboxyl group of the 3-methylcyclopropane-\textit{trans}-1,2-dicarboxylic acid must esterify the faster. Partial esterification of the diacid gave a monoacid XXI identical to that obtained from the \textit{cis,cis}-monomethyl ester.
The monomethyl ester XXII of cyclopropane-cis-1,2-dicarboxylic acid is expected to isomerize to trans (XXIII) with greater ease than XIX since the inverted product does not suffer any cis-interaction. The experimental conditions were different in both cases. The milder treatment used for XXII did not carry out the reaction to completion. However this method was found more satisfactory for the preparation of XXIII than the partial hydrolysis of the corresponding diester.

![Structural formulas XXII and XXIII]

It may be noted that the isomerization of XXII does not give any indication as to which group is involved. Because of the previous results it is very likely that it is the ester group which in fact isomerizes.

**Methylenecyclopropane derivatives**

An exocyclic carbon-carbon double bond lowers the energy of the resonating carbanion-enolate ion obtained from a cyclopropane ester by giving one more contributing structure.
Although it might have been difficult to predict a priori, the contribution of the extra structure, which involves a cyclopropene ring, appears to be quite important. Thus, the salt of the cis-isomer of Feist's acid (XXIV, R = O\) was half isomerized to trans by boiling 15 minutes in 0.025 N alkali (29), under conditions that would not affect a saturated salt.

![Chemical Structure X](image)

**XXIV**

When all contributing structures are more nearly equivalent as for XXIV (R = C\(_2\)H\(_5\)), one may expect still easier inversion. Although the experiment was performed in different conditions and therefore a comparison with the salt cannot be made, it was found that the dimethyl ester of the cis-isomer of Feist's acid was quantitatively isomerized after a reflux of 5 minutes in 0.09 N methoxide. This isomerization precedes the addition of methoxide which is known to give dimethyl 3-methoxy-3-methylcyclopropane-1,2-dicarboxylate (XXV)(30).

![Chemical Structures](image)

**XXV**
The inversion of the monomethyl ester of the cis-isomer of Feist's acid was used as a convenient method to prepare the monoester of the trans-isomer.

Although no rate determination was made, the reaction was found to be essentially complete after 15 minutes of heating on the steam bath in 0.2 N methanolic methoxide. The ease of these isomerizations confirms that the ion involved in base is the highly resonating hybrid XXVI.
Experimental

Trimethyl cyclopropane-trans-1,2,3-tricarboxylate. A 0.21 N methoxide solution was prepared by dissolving 0.11 g. of sodium in 22.5 ml. of dry methanol. In 5 ml. of this solution, 0.0357 g. of trimethyl cyclopropane-cis-1,2,3-tricarboxylate was allowed to stand 13 hours at room temperature. After addition of 5 ml. of glacial acetic acid, the mixture was concentrated under vacuum. Ether (20 ml.) was added to the residue and an homogeneous solution was obtained from which sodium acetate precipitated after about 10 minutes. The precipitate was filtered, dissolved in 3 ml. of water and extracted several times with ether. The ether solutions were dried over magnesium sulfate and evaporated to provide 0.0355 g. of residue having a slight odor of acetic acid. Chromatography of this material over 2 g. of silicic acid gave two fractions. The first fraction, 0.0147 g. (41.3%), was eluted with 1:1 chloroform-carbon tetrachloride. This product was dissolved in petroleum ether and the solvent was allowed to evaporate at room temperature. Crystals were obtained, m.p. 51-53°; m.p. 53° when mixed with authentic trimethyl cyclopropane-trans-1,2,3-tricarboxylate of m.p. 54°. The second fraction was eluted with a 10% solution of ether in chloroform and consisted of 0.0146 g. of product which could not be crystallized. It was treated with excess diazomethane in ether and yielded 0.0124 g. (34.8%) of material which crystallized from petroleum ether; m.p. 51-53°, unchanged when mixed with authentic trans-triester.

Triethyl 3-methylcyclopropane-trans-1,1,2-tricarboxylate. A 0.45 N ethoxide solution was prepared by dissolving 0.508 g. of sodium in 50 ml. of dry ethanol. Triethyl 3-methylcyclopropane-cis-1,1,2-tricar-
boxylate (6.632 g.), \( n_D^{25} 1.4461 \), containing at least 32% of the cis isomer by vapor phase chromatography, was refluxed in the ethoxide solution for 4 hours. After cooling, the solution was acidified with acetic acid diluted with ether and washed with water, saturated sodium bicarbonate and brine. After drying over magnesium sulfate, distillation yielded 4.297 g. (64.8%), b.p. 114°/0.3 mm., saturated to permanganate, \( n_D^{23} 1.4418 \). Vapor phase chromatography showed essentially one peak having the same retention time as the trans-isomer.

**trans-2-Carbomethoxy-cis-3-methylcyclopropanecarboxylic acid.**

A. The technique described by Kennedy (28) was followed: from 5 g. of trans-diacid treated for 5: 3/4 hours with 50 ml. of methanol and 25 drops of concentrated sulfuric acid, there was obtained only 0.696 g. of the desired monomethyl ester, m.p. 74-76.1°. A by-product was 3 g. of dimethyl ester, identified by infrared spectrum.

B. The cis-isomer of Feist's acid was reduced according to Kennedy (28) to yield cis-3-methylcyclopropane-cis-1,2-dicarboxylic acid. This cis,cis diacid (3.397 g.) was refluxed for 3½ hours in acetyl chloride. The mixture was evaporated under vacuum and the residue was treated directly with dry methanol. After 1½ hour of reflux and standing overnight at room temperature, the excess solvent was removed under vacuum and the residue was crystallized from chloroform-petroleum ether to furnish 2.880 g. (67%), m.p. 94-95° and 0.307 g. (7%), m.p. 93-94°, of cis-2-carbomethoxy-cis-3-methylcyclopropanecarboxylic acid. This monomethyl ester (0.1345 g.) was treated for 30 minutes on the steam bath with 2 ml. of 4 N methanolic sodium methoxide. A white scum was formed. Neutralization with 2 ml. of glacial acetic acid followed by concentration under vacuum at room temperature left a
residue which was taken up in 3 ml. of water and strongly acidified to Congo Red with concentrated hydrochloric acid. The solution was extracted five times with a total of 100 ml. of chloroform. The extracts were dried over magnesium sulfate and concentrated, and the residue was chromatographed on 5 g. of silicic acid. Only one component was present in the different fractions eluted with 1:1 chloroform-carbon tetrachloride or pure chloroform. After recrystallization from petroleum ether, the fractions melted sharply between 76.9° and 78.3°. The infrared spectra were identical with the spectrum of the trans-2-carbomethoxy-cis-3-methylcyclopropanecarboxylic acid obtained in procedure A. A total of 0.1272 g. (68.3%) of crystals was obtained and no trace of the starting material was found.

**trans-2-Carbomethoxy-trans-3-methylcyclopropanecarboxylic acid.**

A. Amberlite IR-120 ion exchange resin (15 g.) was allowed to swell in 1 N hydrochloric acid and was washed with deionized water until the washings were neutral. Dimethyl 3-methylcyclopropane-trans-1,2-dicarboxylate (1.258 g.) was dissolved in 60 ml. of 50% aqueous dioxane and the solution was refluxed with stirring in presence of the resin for 3 hours and 45 minutes. The resin was filtered and washed with aqueous acetone and the liquids were concentrated under vacuum to about 20 ml. The solution was extracted with three 30-ml. portions of chloroform followed by three 30-ml. portions of ether. The extracts were dried and concentrated, and the residue was chromatographed on silicic acid. Elution with 10% ether in chloroform gave 0.419 g. of the trans-2-carbomethoxy-trans-3-methylcyclopropanecarboxylic acid, m.p. 54.5-54.7°, having an infrared spectrum identical to that of the known material taken by Kennedy. Elution with ether yielded 0.497 g. of the trans-
diacid, m.p. 123°. No trace of the isomeric monoester was found.

B. Diethyl 4-methyl-2-pyrazoline-3,5-dicarboxylate (31) was decomposed at 200-230° over platinum (28) to give diethyl trans-3-methyl-
cyclopropane-cis-1,2-dicarboxylate in 37% yield. Hydrolysis of 13.4 g.
of this diester in 200 ml. of 6 N hydrochloric acid yielded 4.59 g.
(47.4%) of trans-3-methylcyclopropane-cis-1,2-dicarboxylic acid, m.p.
100-110°. The mother liquor furnished 1.05 g. of material having a
lower melting point. The diacid was transformed to its anhydride,
m.p. 74°, by reflux in acetyl chloride and the anhydride was treated
with methanol as described by Kennedy (23) to give cis-2-carbomethoxy-
trans-3-methylcyclopropanecarboxylic acid, m.p. 43-49.5°, in 90% yield.
A solution of 0.1343 g. of this monomethyl ester in 2 ml. of 4 N
methoxide was heated for 20 minutes on the steam bath and then for 3
hours and 40 minutes on a metal bath at 110°. The reaction mixture
was cooled and the white precipitate formed was dissolved by addition
of 3.5 ml. of glacial acetic acid. The solvent was removed under
vacuum, 3 ml. of water was added and the solution was acidified to
Congo Red with concentrated hydrochloric acid. The solution was ex-
tracted eight times with a total of 120 ml. of chloroform, which was
dried over magnesium sulfate and concentrated under vacuum. The residue
was chromatographed twice on 5 g. of silicic acid. One fraction,
0.0416 g., eluted with 1:1 chloroform-carbon tetrachloride, crystallized
and melted at 53.5°. Recrystallization from petroleum ether raised the
melting point to 54-54.5°. A mixture with authentic trans-2-carbo-
methoxy-trans-3-methylcyclopropanecarboxylic acid (m.p. 55°) melted
at 54.5-55°. A second fraction of 0.0073 g., eluted with 5% ether
in chloroform, had an infrared spectrum identical to that of the
starting material.

**cis-2-Carbethoxycyclopropanecarboxylic acid.** A mixture of isomeric cyclopropane-1,2-dicarboxylic esters was prepared from ethyl chloroacetate, ethyl acrylate and potassium t-butoxide according to M. Mousseron et al. (32). The corresponding acids (2.9 g.) were refluxed for 1½ hours in 20 ml. of acetyl chloride. The excess of acetyl chloride was removed under vacuum and the yellow oil obtained was heated to 220° and distilled at 120°/0.3 mm. The product, which crystallized in the condenser, was heated in methanol and chromatographed on 20 g. of silicic acid. On elution with 3:1 chloroform-ether, there was obtained 1.095 g. of **cis-2-carbethoxycyclopropanecarboxylic acid**, very soluble in organic solvents at room temperature. The analytical sample was recrystallized four times from carbon tetrachloride and melted at 53.6-53.8°.

**Anal.**

Calcd. for C₆H₉O₄: C, 50.00; H, 5.55.

Found: C, 50.01; H, 5.71.

**trans-2-Carbethoxycyclopropanecarboxylic acid.** **cis-2-Carbethoxycyclopropanecarboxylic acid** (0.3397 g.) was refluxed for 2 hours and 20 minutes in 4 ml. of 0.27 N methoxide. A white precipitate was formed, which dissolved when 5.5 ml. of glacial acetic acid was added. Ether (25 ml.) was added and the solution was washed twice with 10 ml. of water. The washings were extracted with 25 ml. of ethyl acetate and the organic solutions were dried. After evaporation of the solvent, the residue was chromatographed on 20 g. of silicic acid and yielded 0.1718 g. (50.5%) of **trans-2-carbethoxycyclopropanecarboxylic acid**, eluted with 1:9 ether-chloroform. With 1:3 ether-chloroform, there was eluted 0.0543 g. (16%) of unreacted **cis-monomethyl ester**, identified
by infrared spectroscopy. The trans-monomethyl ester was extremely soluble in organic solvents at room temperature and hygroscopic. The analytical sample was recrystallized three times from petroleum ether and melted at 45.6-45.7°.

**Anal.**

Calcd. for C₆H₈O₄:  

C, 50.00; H, 5.55.

Found:  

C, 50.05; H, 5.93.

The infrared spectrum in carbon disulfide of this monomethyl ester was identical to that of the material obtained in low yield by partial hydrolysis of dimethyl cyclopropane-trans-1,2-dicarboxylate and used for the acidity constant determination.

**Dimethyl 3-methylene cyclopropane-trans-1,2-dicarboxylate.** Dimethyl 3-methylene cyclopropane-cis-1,2-dicarboxylate (0.168 g.) was refluxed for 5 minutes in 30 ml. of 0.09 N methoxide. After cooling, 10 ml. of glacial acetic acid was added and the solvent was removed under vacuum. No precipitate was formed and the oil obtained was taken up in chloroform and washed with saturated bicarbonate and water. The neutral solution, dried over magnesium sulfate, was concentrated under vacuum and the residue chromatographed on 3.5 g. of silicic acid. One main fraction (0.141 g., m.p. 29-30°) was obtained, which had an infrared spectrum identical to that of authentic dimethyl ester of Feist's acid. trans-2-Carbomethoxy-3-methylene cyclopropanecarboxylic acid. The monomethyl ester of the cis-isomer of Feist's acid was prepared by treating the anhydride with methanol and was purified by chromatography on silicic acid. A solution of 0.1965 g. of this monoester was heated for 15 minutes on the steam bath in 30 ml. of 0.23 N methoxide. The solution was cooled, diluted with 5 ml. of water, acidified to Congo Red with hydrochloric acid and extracted with chloroform. The extract
was dried and evaporated to yield an oil, which was chromatographed on 3 g. of silicic acid. By elution with a 10% solution of ether in chloroform, 0.1413 g. of product was obtained which crystallized on seeding. Its infrared spectrum was identical to that of the monomethyl ester of Feist's acid. By recrystallization, the melting point was raised to 63.8-64.2° (lit. 63.5-64.7°) (28).
-50-

BIBLIOGRAPHY


CHAPTER IV
THE ACID STRENGTH OF
SOME CYCLOPROPANE CARBOXYLIC ACIDS

The dissociation constants in aqueous solution of several
cyclopropane di- and tricarboxylic acids prepared during the course
of this research have been measured electrometrically using a glass
electrode. The results, appearing in Table I, have been corrected
for the ionic strength of the solution by the Debye-Hückel theory
and for the dilution and the interaction of the successive stages
according to Ricci (1). In the literature, these corrections,
leading to the thermodynamic values of the dissociation constants,
have not always been made. It is, however, useful to compare the
values measured in this research with known values of cyclic and
aliphatic carboxylic acids (Table II).

The cyclopropane ring has often been compared to a carbon-
carbon double bond for its electronic effects (2). Cyclopropane-
carboxylic acids indeed have dissociation constants situated between
those of comparable saturated and unsaturated acids but usually
closer to the saturated than to the unsaturated acids. For instance,
cyclopropanecarboxylic acid (pK 4.33) is much closer to propionic
acid (pK 4.33) than acrylic acid (pK 4.25). The same has been found
in a series of trans-2-arylcyclopropanecarboxylic acids compared to
the corresponding substituted β-arylpropionic and cinnamic acids (2).
A similar trend is also noticed for the first acidity constant of
cyclopropane-1,2-diacids.

Brown (3) has recently discussed the factors influencing the
strength of organic acids. The most significant are the polar and
steric effects of the substituents. The acidity constant of an acid
Table I
<table>
<thead>
<tr>
<th>CH$_3$CH$_2$COOH</th>
<th>pK$_1$</th>
<th>pK$_2$</th>
<th>H$_2$C-COOH</th>
<th>pK$_1$</th>
<th>pK$_2$</th>
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<td></td>
<td>3.33</td>
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</tbody>
</table>

Table II

(Values taken from reference 3 except where indicated)
expressed as its pK is a measure of the free energy of the reaction of ionization, \[ \text{HA} + S \rightarrow \text{HS}^+ + \text{A}^- \] where S represents the solvent. The effect of the substituents should be based upon the energies of the substituted acids and ions.

If the electron density in the vicinity of the ionizable proton is decreased by the action of a substituent, it is easier to remove the proton and the pK decreases. The polar effect of a substituent can arise either from a dipole as \( \overset{\sigma^+}{\sigma^-} \text{Cl} \) or \( \overset{\sigma^+}{\sigma^-} \text{C} = \) or from a formal charge. The effect can be transmitted to the ionizing center within the molecule by displacing the electrons in the bonds between the pole and the ionizing center (4). For example, chloroacetic acid (pK 2.36) is a stronger acid than acetic acid (pK 4.76) because of the electron-withdrawing effect of the chlorine.

\[ \overset{\sigma^-}{\text{Cl}} \overset{\sigma^+}{\text{H}_2\text{C}} \overset{\sigma^-}{\text{=O}} \overset{\sigma^+}{\text{H}} \]

However, Bjerrum (5) observed that the effect of the substituents did not decrease as rapidly with chain length as might have been predicted on the basis of this inductive effect. He suggested that there might be a direct action through the solvent between the charge or dipole of a substituent and the ionizing center. This theory can be used to explain that in all cases the ratio \( K_1/K_2 \) of the ionization constants of diacids is greater than the theoretical value of 4 obtained from statistical considerations.

Presumably, the polar effect of the substituents can be exerted both through the molecule and through the solvent and the participation of each action depends on the solvent and the structure of the substance.

The steric effect of substituents on the ionization of carboxylic
acids has been discussed in detail by Brown (3) and Hammond (6). It is especially significant in the case of 1,2-diacids susceptible of cis-trans isomerism. Inspection of Table II shows that in the case of such olefinic and cyclopropanic diacids, the cis-isomer normally has a first acidity stronger and a second acidity weaker than the trans-isomer.

Maleic and fumaric acids have been particularly studied. X-Ray diffraction studies on crystalline maleic acid showed that the distance between the closest oxygen atoms in the molecule was 2.46 Å (7), shorter than twice the Van der Waals radius of oxygen, or 2.7-2.3 Å. This shortening of the oxygen-oxygen distance has been attributed to hydrogen bonding between the acidic hydrogen and the carbonyl oxygen (I).

\[
\text{HO-C=O} \quad \text{[I]} \quad \left[ \begin{array}{c}
\text{O=C=O} \\
\text{H} \\
\text{H}
\end{array} \right] \quad \text{[II]}
\]

The monoion greatly favors hydrogen bonding with the charged oxygen. Infrared spectroscopy (8) has shown that the hydrogen bonded monoion (II) was apparently symmetrical.

The stability of this symmetrical ion II explains that maleic acid is stronger in its first dissociation than fumaric acid. It may also be partly responsible for the weaker acidity of the second dissociation of maleic acid, although the electrostatic repulsion between the carboxylate groups in the maleate dianion (III) is presumably an important factor. The fumarate dianion IV may have no strong electrostatic interaction between the negative charges.
The effect of the hydrogen bonding in the cis-monoion can be evaluated quantitatively by measuring the acid strengths of the half-esters of the diacids (9). In the absence of hydrogen bonding, the dissociation constant for the first acidity of symmetrical diacids should be twice that of the monoester (since two carboxyls can ionize), assuming that the polar effects of a carboxyl and a carbalkoxy group are similar. This assumption is usually satisfactory and for many acids the ratio $K_1/K_E$ of the first acidity constant of the diacid to the constant of the half-ester is found to be 2 (for example fumaric (3), succinic (3) and phthalic (9) acids).

A large value of this ratio indicates strong hydrogen bonding in the monoion, as for maleic acid, $K_1/K_E = 10.6$, or diethylmalonic acid, $K_1/K_E = 32$ (3).

It may be noted that for cyclobutane-, cyclopentane- and cyclohexane-1,2-dicarboxylic acids, the first acidity of the trans-isomer is stronger than that of the cis-isomer. A possible explanation is that a deformation of the ring out of planarity diminishes the hydrogen bonding in the cis-monoion.

Such an effect may also explain that the cis-isomer of 1,2-dimethylcyclopropane-1,2-dicarboxylic acid ($pK_1 3.97$) is weaker than the trans-isomer ($pK_1 3.61$) (12).
Cyclopropane-1,2-dicarboxylic acids

trans-1,2-Cyclopropanedicarboxylic acid (pK₁ 3.70) is a stronger acid than cyclopropanecarboxylic acid (pK 4.83). Taking into account that the dissociation constant of each of the carboxyls is half the value measured for the diacid, the dissociation of one carboxyl corresponds to pK₁ 4.00. The two carboxyls, being trans, have a negligible steric interaction and the increase in acid strength observed by substitution of a trans-carboxyl in the 2-position must be caused by a polar effect.

The electron-withdrawing character of the carboxyl weakens the bond between the oxygen and the hydrogen which will ionize. This ionization is therefore facilitated and results in a lower pK compared to the unsubstituted acid. The monomethyl ester, having pK 4.00, shows that the polar effects of a carboxyl and a carbomethoxy group are equivalent in this series.

When completely dissociated, the trans-diacid gives a dianion possessing two equivalent positions for the return of a proton. The monoion is therefore weakened by a factor of 2 and the real value for the ionization of one carboxyl in the monoion is pK₂ 4.70. The slight difference between this value and that corresponding to cyclopropanecarboxylic acid, pK 4.83, may indicate a small electron-withdrawing character of the carboxylate group. This difference may not be significant, since the older value reported in the literature, pK₂ 5.13, shows no difference in acidity caused by the carboxylate.

cis-1,2-Cyclopropanedicarboxylic acid, pK₁ 3.24, is about three times stronger than the trans-isomer in its first dissociation. The
pK value, 4.12, of the monomethyl ester is very close to that of the trans-monoester and indicates that the polar and steric effects of the carbomethoxy group in both configurations are comparable. It is therefore likely that the same would apply to a carboxyl.

The difference encountered in the first dissociation constants of the isomeric diacids must therefore be caused by another factor and Brown (3) has pointed out the possibility of hydrogen bonding in the monoion, analogous to that found in maleic acid.

Because the bond distance between the carbon atoms bearing the carboxyls is longer in the three-membered ring than in the olefin, the hydrogen bonding in the monoion of cyclopropane-cis-1,2-dicarboxylic acid is not as strong as in the monoion of maleic acid, and is presumably not symmetrical (V).

\[ \text{V} \]

The difference in strength of the second acidity of the isomeric cyclopropane-1,2-diacids may be explained by the same considerations as with maleic and fumaric acids. The proximity of the negative charges in the cis-dianion results in a higher energy than in the trans-isomer where the charges are as far apart as possible.

The introduction of a carbon-carbon double bond exocyclic to the cyclopropane ring lowers the acidity constants of the diacids and their monomethyl esters by about 0.5 pK unit.

This effect is similar to the difference found between propionic
acid, \(pK 4.83\), and vinylacetic acid, \(pK 4.35\) (3), and must therefore be attributed in large part to the electron-withdrawing character of the double bond. A steric effect may be superimposed in the case of the methylenecyclopropanedicarboxylic acids. The double bond, being in the plane of the three-membered ring, favors the approach of solvent molecules whereas in the unsubstituted diacid, the two hydrogens in the 3-position provide some hindrance.

![Diagram](attachment:image.png)

The comparison of cyclopropane-trans-1,2-dicarboxylic acid (VII), 3-methylcyclopropane-trans-1,2-dicarboxylic acid (VIII) and trans-caronic acid (IX) indicates that one methyl group cis to one carboxyl in a 1,2-trans-cyclopropane-diacid has very little effect on the acidity constants. The same may be said of the 1-methyl and 1,2-dimethyl trans-acids.

![Diagram](attachment:image.png)

\[
\begin{align*}
pK_1 & = 3.24 \\
pK_2 & = 6.53 \\
pK_1 & = 3.70 \\
pK_2 & = 5.00 \\
pK_1 & = 3.87 \\
pK_2 & = 5.32 \\
pK_1 & = 3.82 \\
pK_2 & = 5.32 \\
pK_1 & = 3.20 \\
pK_2 & = 6.93
\end{align*}
\]
It is therefore logical that a methyl group trans to cis-carboxyls as in trans-3-methylcyclopropane-cis-1,2-dicarboxylic acid (X) does not have much effect either, and that its dissociation constants are almost those of cyclopropane-cis-1,2-dicarboxylic acid (VI).

The diacid VIII has two monomethyl esters, XI and XII.

\[
\text{CH}_3 \quad \text{COOCH}_3 \\
\text{COOH} \quad \text{pK} 4.10 \quad \text{COOH} \quad \text{pK} 4.03
\]

On a statistical basis only, the sum of the dissociation constants of XI and XII should be equal to the first dissociation constant of VIII, so that the pK of one of these monoesters should have been higher than 4.16 while the other should have been lower than 4.18. The monoester XI, having a less hindered carboxyl, was expected to ionize more easily than XII. Although the constants are nearly equal, the hindered isomer is more acidic. One must conclude that the carbomethoxy group, in at least one of the esters, must have a greater polar effect than a carboxyl.

Brown (3) has discussed the dissociation constants of cis and trans-carboxylic acids (XIII and IX).
He mentioned that since atoms which are bonded can approach closer than nonbonded atoms, the formation of a hydrogen bond effects a decrease in strain and the hydrogen bonded monoion is stabilized relative to the initial acid to a greater extent in cis-caronic acid than in cyclopropane-cis-1,2-dicarboxylic acid (VI) which is a less strained molecule.

He used the same argument to explain the increase in the first acidity of diethylmalonic acid (pK₁ 2.21) over malonic acid (pK₁ 2.33).

It is however questionable whether the difference in strain between the diacid and its hydrogen bonded monoion should be much increased by the presence of another cis-group in the 3-position.

The treatment of Kirkwood and Westheimer (10) offers another interpretation. These authors considered that the substituents modify the solvent in the neighborhood of the polar groups and that the lines of force pass preferentially through the molecule itself, which has a lower dielectric constant than the solvent.

The polar effect of one carboxyl group on the ionization of the other should therefore be greater for cis-caronic acid and cis-3-methylcyclopropane-cis-1,2-dicarboxylic acid (XIV) than for trans-3-methylcyclopropane-cis-1,2-dicarboxylic acid (XV) and cyclopropane-cis-1,2-dicarboxylic acid (VI).

By any theory, 3-methylcyclopropane-trans-1,2-dicarboxylic acid (VIII) should be weaker than XIV and XV since no hydrogen bonding can occur in the monoion. These predictions were confirmed.
The same theory explains that the second acidity varies in the order opposite to that of the first one. The electrostatic repulsion between the negative charges in the dianions is more effective when the amount of substitution of the ring in the neighborhood of the carboxyls increases.

The monomethyl esters of XIV and XV do not show the variation observed for the diacids. The less hindered is the stronger acid. One possible cause is a large difference between the polar effects of carboxyl and carbomethoxy groups in the most crowded system. In the more strained structure (XVI) the configuration of the ester and the carboxylate groups may be fixed in a position favorable to a repulsion between the negative charge and the negative end of the carbon-oxygen dipole. In XVII where the methyl group is trans, the two cis-groups may be free to adopt a electrostatically more favorable configuration, stabilizing the ion and increasing the acidity.

![chemical structures](XVI)(XVII)

The acidity of the most crowded monomethyl ester probably is also weakened by steric hindrance to solvation, which will have most effect when hydrogen bonding (internal solvation) is impossible. The ratio of (first) ionization constants of cis-3-methylcyclopropane-cis-1,2-dicarboxylic acid and its monomethyl ester is 80, the largest such value yet observed for a symmetrical system.
The measurement of the acidity constants of the three 3-methyl-cyclopropane-1,2-dicarboxylic acids elegantly confirms the stereochemical assignments (11).

Cyclopropane-1,2,3-tricarboxylic acids

Compared to cyclopropane-cis-1,2-dicarboxylic acid, pK₁ 3.24, the acidity of cis-cyclopropane-1,2,3-tricarboxylic acid (XVIII), pK₁ 1.93, cannot be explained only by a greater probability of ionization.

\[ \text{XVIII} \]

\[ \text{XIX} \]

If the hydrogen bonded monoions were symmetrical, a statistical factor of 3 in XVIII would lower pK₁ by 0.48, compared to the cis-diacid, or to 2.76. As presumably the monoion of XVIII does not involve a symmetrical hydrogen bond for the same reason as in cyclopropane-cis-1,2-dicarboxylic acid, a statistical factor of 3/2 applies and the triacid should then have pK₁ 3.06. The lower experimental value must therefore be credited to a combination of steric and electrostatic effects.

The first ionization of trans-cyclopropane-1,2,3-tricarboxylic acid (XIX) presumably involves one of the cis-carboxyls in order to form a hydrogen bonded monoion.
The trans-carboxyl group, by its inductive effect, should favor this ionization and the triacid XIX should therefore be stronger than cyclopropane-cis-1,2-dicarboxylic acid, pK$_1$ 3.24, as observed.

Because it is in a trans-configuration, the third carboxyl in XIX does not have as important an effect as in XVIII and the first dissociation constant of the acid XIX is about eight times smaller than that of XVIII.

The second dissociation of the triacids XVIII and XIX involves the carboxyl not bonded to the carboxylate.

In the cis-triacid, the dianion is subject to stronger electrostatic interactions between the negatively charged groups than in the trans-triacid where they are farther apart. The experimental difference is not very large. The net substituent effect of the negatively charged monoion of a cis-1,2-diacid is very similar to that of the neutral system of 1-methyl-cis-2-carboxymethoxy, since the second dissociation constants of XVIII and XIX are respectively equal to the dissociation constants of cis-2-carboxymethoxy-cis-3-methylcyclopropane-carboxylic acid (XX) and trans-2-carboxymethoxy-trans-3-methylcyclopropane-carboxylic acid (XI).
The third ionization of both triacids involves the loss of hydrogen bonds.

The cis-trianion has extremely important electrostatic interactions because of the proximity of the three negative charges. This effect explains the large difference between the third dissociation constants of the isomeric triacids. The trans-dianion has a dissociation constant comparable to the second constant of cyclopropane-cis-1,2-dicarboxylic acid.
EXPERIMENTAL

A Beckman model G pH meter equipped with a Beckman calomel electrode and a Beckman type E glass electrode (high pH) was used throughout this work. The reliability of the equipment was checked before and after each titration against buffer solutions of pH's 4, 7 and 10, having known temperature coefficients.

The base was prepared by diluting standard sodium hydroxide (British Drug Houses) to 500 ml. with freshly boiled distilled water to give a 0.1 N solution, which was used without further standardization.

The acid to be titrated was dissolved in freshly boiled distilled water and a stream of nitrogen was blown over the surface to prevent carbonation. It was checked that no appreciable change in temperature was introduced.

Stirring with a stream of nitrogen was found to be quite unreliable and therefore a magnetic stirrer was used. Several asbestos plates isolated the reaction vessel from the stirrer motor, which did not introduce any appreciable change in temperature. The tip of the buret was always on the level of the surface of the liquid. After each addition of base, stirring was applied sufficiently to homogenize the solution. It was found best to stop stirring for each reading.

The acidity constants were determined from the half neutralization points. When there was discrepancy between the calculated and the experimental values of the end points, the latter were used.

The ionic strength $\mu$ was calculated as $\mu = \frac{1}{2} \sum n_i^2 c_i$

where $n_i$ is the charge of the ion $i$ at concentration $c_i$. In most
cases the effect of the concentration of the hydrogen and hydroxide ions was negligible. The activity coefficients were calculated from the formula 
\[ \log f = \frac{1}{2} \frac{\sqrt{\mu}}{1 + \sqrt{\mu}} \]  
and the correction \( S \) caused by the ionic strength of the solution for the \( m \)th dissociation is 
\[ S = -(2m-1) \log f. \]

In the literature this is usually the only correction applied. When the dissociation constants are close to each other a large error is introduced by assuming the independence of the successive dissociations. This effect and that arising from the dilution on the ionization constants were corrected as indicated by J. S. Ricci (1).

For a triacid the corrections \( D = pK - p\mu - S \) are:

\[ D_1 = -\log \left( \frac{b+D}{a-b-D} \right) + \log \left\{ 1 + \frac{k_2}{K_2} \left( \frac{2a-b-D}{a-b-D} \right) \left[ 1 + \frac{k_3}{K_3} \left( \frac{3a-b-D}{2a-b-D} \right) \right] \right\} \]

\[ D_2 = -\log \left( \frac{b-a+D}{2a-b-D} \right) - \log \left\{ 1 + \frac{Hf^3}{K_1} \left( \frac{b+D}{b-a+D} \right) \left[ 1 + \frac{k_3}{K_3} \left( \frac{3a-b-D}{2a-b-D} \right) \right] \right\} \]

\[ D_3 = -\log \left( \frac{b-2a+D}{3a-b-D} \right) - \log \left\{ 1 + \frac{Hf^3}{K_2} \left( \frac{b-a+D}{b-2a+D} \right) \left[ 1 + \frac{Hf^3}{K_1} \left( \frac{b+D}{b-a+D} \right) \right] \right\} \]

where \( D = H, OH, \) and \( OH \) being the concentrations of the corresponding ions in the solution,

\[ b = \text{concentration of the base (strong monoacidic)}, \]

\[ a = \text{concentration of the acid}. \]

For diacids and monoacids these expressions are simplified accordingly.

Successive approximations are necessary to obtain the dissociation
constants of polyacids.

The accuracy of our determinations is presumably between 0.02
and 0.05 pH units as estimated by the deviations from the mean values.

Cyclopropane-trans-1,2-dicarboxylic acid. A mixture of isomeric cyclo-
propane-1,2-dicarboxylic esters was prepared from ethyl chloracetate,
ethyl acrylate and potassium t-butoxide according to M. Mousseron
et al. (13). Hydrolysis and recrystallization gave the trans-diacid
m.p. 176°.

Titration of 0.0304 g. (0.000234 mole) in 15 ml. of water at 31.5°:

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<th>0.50</th>
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Titration of 0.0304 g. (0.000234 mole) in 15 ml. of water at 31.5°
required 4.62 ml. of base:

Apparent pK_1, 3.62  Apparent pK_2, 4.88

Since the concentration was the same as above, the same corrections
apply.

Corrected values: pK_1, 3.70  pK_2, 4.99.
**trans-2-Carbomethoxycyclopropanecarboxylic acid.** The *trans* diacid was esterified by methanol and sulfuric acid and the diester obtained was partially hydrolyzed in aqueous methanol using one equivalent of base. After crystallization of the diacid formed, the residue was chromatographed on silicic acid. On elution with 33% ether in chloroform, the desired *trans* monomethyl ester was obtained, which was recrystallized from petroleum ether.

Titrination of 0.0297 g. (0.000206 mole) in 15 ml. of water at 31°.

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.20</th>
<th>0.50</th>
<th>0.80</th>
<th>1</th>
<th>1.10</th>
<th>1.20</th>
<th>1.40</th>
<th>1.70</th>
<th>1.90</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.93</td>
<td>3.21</td>
<td>3.55</td>
<td>3.82</td>
<td>3.98</td>
<td>4.06</td>
<td>4.14</td>
<td>4.33</td>
<td>4.73</td>
<td>5.27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>2.00</th>
<th>2.02</th>
<th>2.04</th>
<th>2.10</th>
<th>2.20</th>
<th>2.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.63</td>
<td>9.66</td>
<td>10.06</td>
<td>10.51</td>
<td>10.83</td>
<td>11.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>( \mu )</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.98</td>
<td>0.0062</td>
<td>0.034</td>
<td>-0.01</td>
<td>4.00</td>
</tr>
</tbody>
</table>

Titrination of 0.0465 g. (0.000323 mole) in 24 ml. of water at 31° required 3.13 ml. of base:

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>( \mu )</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.98</td>
<td>0.0061</td>
<td>0.034</td>
<td>-0.01</td>
<td>4.00</td>
</tr>
</tbody>
</table>

**Cyclopropane-cis-1,2-dicarboxylic acid.** The *trans* diacid, m.p. 176°, was refluxed for 3½ hours with an excess of acetyl chloride. The mixed anhydride was decomposed at a temperature higher than 225° under 1.5 mm. pressure. The *cis*-anhydride distilled at about 115° and crystallized in the condenser. Reflux in water gave the *cis*-diacid, m.p. 138°, from ether-petroleum ether, m.p. 140.4-140.8° from nitro-
methane.

Titration of 0.0297 g. (0.000229 mole) in 15 ml. of water at 30°:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.20</th>
<th>0.50</th>
<th>0.80</th>
<th>1.10</th>
<th>1.20</th>
<th>1.40</th>
<th>1.70</th>
<th>2.00</th>
<th>2.10</th>
<th>2.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.57</td>
<td>2.70</td>
<td>2.90</td>
<td>3.10</td>
<td>3.28</td>
<td>3.34</td>
<td>3.50</td>
<td>3.72</td>
<td>4.06</td>
<td>4.23</td>
<td>4.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>2.30</th>
<th>2.40</th>
<th>2.60</th>
<th>2.90</th>
<th>3.20</th>
<th>3.40</th>
<th>3.50</th>
<th>3.80</th>
<th>4.10</th>
<th>4.30</th>
<th>4.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>4.79</td>
<td>5.14</td>
<td>5.54</td>
<td>5.90</td>
<td>6.14</td>
<td>6.29</td>
<td>6.35</td>
<td>6.58</td>
<td>6.84</td>
<td>7.06</td>
<td>7.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>4.46</th>
<th>4.52</th>
<th>4.58</th>
<th>4.60</th>
<th>4.62</th>
<th>4.64</th>
<th>4.66</th>
<th>4.68</th>
<th>4.71</th>
<th>4.80</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.36</td>
<td>7.52</td>
<td>7.78</td>
<td>7.92</td>
<td>8.06</td>
<td>8.34</td>
<td>3.75</td>
<td>9.32</td>
<td>9.70</td>
<td>10.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₁</td>
<td>3.32</td>
<td>0.007</td>
<td>0.04</td>
<td>-0.12</td>
</tr>
<tr>
<td>pK₂</td>
<td>6.35</td>
<td>0.0245</td>
<td>0.18</td>
<td>0</td>
</tr>
</tbody>
</table>

Titration of 0.0311 g. (0.000239 mole) in 15 ml. of water at 30° required 4.92 ml. of base:

<table>
<thead>
<tr>
<th>Apparent</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₁</td>
<td>3.31</td>
<td>0.0074</td>
<td>0.04</td>
<td>-0.12</td>
</tr>
<tr>
<td>pK₂</td>
<td>6.34</td>
<td>0.0256</td>
<td>0.18</td>
<td>0</td>
</tr>
</tbody>
</table>

cis-2-Carbomethoxycyclopropanecarboxylic acid. The anhydride of the cis-1,2-dicarboxylic acid was treated with methanol and the product chromatographed over silicic acid. Elution with 50% ether in chloroform gave the monoester which was crystallized from petroleum ether.
Titration of 0.0324 g. \((0.000225\) mole\) in 15 ml. of water at 30.5\(^\circ\):

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.20</th>
<th>0.50</th>
<th>0.80</th>
<th>1.00</th>
<th>1.10</th>
<th>1.20</th>
<th>1.50</th>
<th>1.80</th>
<th>2.00</th>
<th>2.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.97</td>
<td>3.26</td>
<td>3.61</td>
<td>3.89</td>
<td>4.02</td>
<td>4.10</td>
<td>4.20</td>
<td>4.44</td>
<td>4.71</td>
<td>5.18</td>
<td>5.64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>2.12</th>
<th>2.14</th>
<th>2.16</th>
<th>2.17</th>
<th>2.18</th>
<th>2.20</th>
<th>2.24</th>
<th>2.30</th>
<th>2.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>5.82</td>
<td>6.14</td>
<td>6.76</td>
<td>8.65</td>
<td>9.41</td>
<td>9.90</td>
<td>10.31</td>
<td>10.62</td>
<td>10.90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.09</td>
<td>0.0067</td>
<td>0.04</td>
<td>-0.02</td>
<td>4.11</td>
</tr>
</tbody>
</table>

Titration of 0.0336 g. \((0.000233\) mole\) in 15 ml. of water at 30.5\(^\circ\) required 2.37 ml. of base:

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.09</td>
<td>0.0073</td>
<td>0.04</td>
<td>-0.01</td>
<td>4.12</td>
</tr>
</tbody>
</table>

3-Methylenecyclopropane-trans-1,2-dicarboxylic acid.

Titration of 0.0307 g. \((0.000216\) mole\) in 15 ml. of water at 31\(^\circ\):

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.10</th>
<th>0.20</th>
<th>0.40</th>
<th>0.60</th>
<th>0.80</th>
<th>0.90</th>
<th>1.00</th>
<th>1.10</th>
<th>1.20</th>
<th>1.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.57</td>
<td>2.59</td>
<td>2.65</td>
<td>2.75</td>
<td>2.87</td>
<td>2.97</td>
<td>3.02</td>
<td>3.14</td>
<td>3.20</td>
<td>3.30</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>1.60</th>
<th>1.80</th>
<th>2.00</th>
<th>2.10</th>
<th>2.20</th>
<th>2.40</th>
<th>2.60</th>
<th>2.80</th>
<th>3.00</th>
<th>3.10</th>
<th>3.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>3.44</td>
<td>3.53</td>
<td>3.65</td>
<td>3.71</td>
<td>3.76</td>
<td>3.86</td>
<td>4.00</td>
<td>4.12</td>
<td>4.23</td>
<td>4.29</td>
<td>4.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>3.30</th>
<th>3.50</th>
<th>3.70</th>
<th>3.90</th>
<th>4.00</th>
<th>4.10</th>
<th>4.20</th>
<th>4.24</th>
<th>4.28</th>
<th>4.30</th>
<th>4.32</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>4.42</td>
<td>4.55</td>
<td>4.71</td>
<td>4.92</td>
<td>5.06</td>
<td>5.23</td>
<td>5.52</td>
<td>5.69</td>
<td>5.98</td>
<td>6.22</td>
<td>6.75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>4.34</th>
<th>4.36</th>
<th>4.40</th>
<th>4.50</th>
<th>4.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>9.34</td>
<td>9.76</td>
<td>10.16</td>
<td>10.62</td>
<td>10.96</td>
</tr>
<tr>
<td>Apparent</td>
<td>$\mu$</td>
<td>$S$</td>
<td>$D$</td>
<td>Corrected pK</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>-----</td>
<td>-----</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>$pK_1$</td>
<td>3.13</td>
<td>0.00672</td>
<td>0.035</td>
<td>-0.02</td>
<td>3.15</td>
</tr>
<tr>
<td>$pK_2$</td>
<td>4.38</td>
<td>0.0237</td>
<td>0.176</td>
<td>-0.07</td>
<td>4.49</td>
</tr>
</tbody>
</table>

Titration of 0.0301 g. (0.000212 mole) in 15 ml. of water at 29° required 4.29 ml. of base:

<table>
<thead>
<tr>
<th>Apparent</th>
<th>$\mu$</th>
<th>$S$</th>
<th>$D$</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pK_1$</td>
<td>3.16</td>
<td>0.00665</td>
<td>0.035</td>
<td>-0.02</td>
</tr>
<tr>
<td>$pK_2$</td>
<td>4.42</td>
<td>0.0235</td>
<td>0.176</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

trans-2-Carbomethoxy-3-methylene cyclopropanecarboxylic acid.

Titration of 0.0164 g. (0.000105 mole) in 15 ml. of water at 28°:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
<th>0.45</th>
<th>0.50</th>
<th>0.55</th>
<th>0.60</th>
<th>0.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.78</td>
<td>2.92</td>
<td>3.05</td>
<td>3.19</td>
<td>3.31</td>
<td>3.40</td>
<td>3.46</td>
<td>3.53</td>
<td>3.60</td>
<td>3.76</td>
</tr>
<tr>
<td>ml.</td>
<td>0.80</td>
<td>0.90</td>
<td>0.94</td>
<td>0.98</td>
<td>1.00</td>
<td>1.02</td>
<td>1.04</td>
<td>1.06</td>
<td>1.08</td>
<td>1.12</td>
</tr>
<tr>
<td>pH</td>
<td>3.98</td>
<td>4.23</td>
<td>4.40</td>
<td>4.62</td>
<td>4.80</td>
<td>5.10</td>
<td>5.81</td>
<td>9.55</td>
<td>10.77</td>
<td>10.53</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent $pK$</th>
<th>$\mu$</th>
<th>$S$</th>
<th>$D$</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.50</td>
<td>0.0034</td>
<td>0.026</td>
<td>-0.086</td>
<td>3.44</td>
</tr>
</tbody>
</table>

Titration of 0.0241 g. (0.000154 mole) in 15 ml. of water at 29.5° required 1.51 ml. of base:

<table>
<thead>
<tr>
<th>Apparent $pK$</th>
<th>$\mu$</th>
<th>$S$</th>
<th>$D$</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.44</td>
<td>0.0048</td>
<td>0.03</td>
<td>-0.07</td>
<td>3.40</td>
</tr>
</tbody>
</table>
-72-

Titration of 0.0187 g. (0.000118 mole) in 10 ml. of water at 31° required 1.22 ml. of base:

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.52</td>
<td>0.0057</td>
<td>0.033</td>
<td>-0.05</td>
<td>3.50</td>
</tr>
</tbody>
</table>

3-Methylenecyclopropane-cis-1,2-dicarboxylic acid.

Titration of 0.0721 g. (0.000507 mole) in 15 ml. of water at 29°:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.30</th>
<th>0.70</th>
<th>1.00</th>
<th>1.60</th>
<th>2.10</th>
<th>2.30</th>
<th>2.50</th>
<th>2.80</th>
<th>3.10</th>
<th>3.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.17</td>
<td>2.23</td>
<td>2.34</td>
<td>2.43</td>
<td>2.60</td>
<td>2.74</td>
<td>2.30</td>
<td>2.86</td>
<td>2.94</td>
<td>3.03</td>
<td>3.13</td>
</tr>
<tr>
<td>ml.</td>
<td>3.70</td>
<td>4.00</td>
<td>4.30</td>
<td>4.60</td>
<td>4.80</td>
<td>5.00</td>
<td>5.10</td>
<td>5.20</td>
<td>5.50</td>
<td>5.80</td>
<td>6.10</td>
</tr>
<tr>
<td>pH</td>
<td>3.26</td>
<td>3.40</td>
<td>3.56</td>
<td>3.80</td>
<td>4.03</td>
<td>4.38</td>
<td>4.56</td>
<td>4.75</td>
<td>5.10</td>
<td>5.33</td>
<td>5.49</td>
</tr>
<tr>
<td>ml.</td>
<td>6.70</td>
<td>7.00</td>
<td>7.20</td>
<td>7.30</td>
<td>7.60</td>
<td>3.00</td>
<td>3.60</td>
<td>9.00</td>
<td>9.60</td>
<td>9.90</td>
<td>10.00</td>
</tr>
<tr>
<td>pH</td>
<td>5.73</td>
<td>5.32</td>
<td>5.90</td>
<td>5.93</td>
<td>6.04</td>
<td>6.16</td>
<td>6.40</td>
<td>6.56</td>
<td>6.96</td>
<td>7.34</td>
<td>7.60</td>
</tr>
<tr>
<td>ml.</td>
<td>10.05</td>
<td>10.08</td>
<td>10.10</td>
<td>10.14</td>
<td>10.16</td>
<td>10.20</td>
<td>10.30</td>
<td>10.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35</td>
<td>5.06</td>
<td>3.30</td>
<td>9.36</td>
<td>9.70</td>
<td>10.10</td>
<td>10.54</td>
<td>10.92</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₁</td>
<td>2.87</td>
<td>0.015</td>
<td>0.049</td>
<td>-0.086</td>
</tr>
<tr>
<td>pK₂</td>
<td>5.04</td>
<td>0.045</td>
<td>0.223</td>
<td>negl.</td>
</tr>
</tbody>
</table>

Titration of 0.0297 g. (0.000209 mole) in 15 ml. of water at 29° required 4.1 ml. of base:

<table>
<thead>
<tr>
<th>Apparent</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₁</td>
<td>2.90</td>
<td>0.0064</td>
<td>0.0345</td>
<td>-0.187</td>
</tr>
<tr>
<td>pK₂</td>
<td>6.09</td>
<td>0.023</td>
<td>0.173</td>
<td>negl.</td>
</tr>
</tbody>
</table>
Titration of 0.0278 g. (0.000196 mole) in 20 ml. of water at 29\(^\circ\) required 4.08 ml. of base:

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>(\mu)</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>(pK_1)</td>
<td>2.97</td>
<td>0.0054</td>
<td>0.025</td>
<td>-0.21</td>
<td>2.78</td>
</tr>
<tr>
<td>(pK_2)</td>
<td>6.12</td>
<td>0.0177</td>
<td>0.158</td>
<td>neglig.</td>
<td>6.28</td>
</tr>
</tbody>
</table>

**cis-2-Carbomethoxy-3-methylenecyclopropanecarboxylic acid.** This material was prepared by treatment of the anhydride with methanol, followed by chromatography (the material was presumably not completely free of ether).

Titration of 0.0440 g. (0.000282 mole) in 15 ml. of water at 29\(^\circ\):

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.20</th>
<th>0.40</th>
<th>0.80</th>
<th>1.00</th>
<th>1.20</th>
<th>1.30</th>
<th>1.50</th>
<th>1.70</th>
<th>2.10</th>
<th>2.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.80</td>
<td>3.02</td>
<td>3.16</td>
<td>3.47</td>
<td>3.59</td>
<td>3.71</td>
<td>3.77</td>
<td>3.93</td>
<td>4.07</td>
<td>4.52</td>
<td>5.00</td>
</tr>
<tr>
<td>ml.</td>
<td>2.40</td>
<td>2.42</td>
<td>2.44</td>
<td>2.46</td>
<td>2.50</td>
<td>2.60</td>
<td>2.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>5.86</td>
<td>7.66</td>
<td>9.36</td>
<td>9.70</td>
<td>10.11</td>
<td>10.48</td>
<td>10.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Apparent (pK)</th>
<th>(\mu)</th>
<th>S</th>
<th>D</th>
<th>Corrected (pK)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.72</td>
<td>0.0075</td>
<td>0.037</td>
<td>-0.024</td>
<td>3.73</td>
</tr>
</tbody>
</table>

**cis-3-Methylenecyclopropane-cis-1,2-dicarboxylic acid.**

Titration of 0.0305 g. (0.000212 mole) in 15 ml. of water at 23\(^\circ\):

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.40</th>
<th>0.70</th>
<th>0.90</th>
<th>1.00</th>
<th>1.10</th>
<th>1.40</th>
<th>1.60</th>
<th>1.80</th>
<th>2.00</th>
<th>2.04</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.22</td>
<td>2.33</td>
<td>2.50</td>
<td>2.60</td>
<td>2.66</td>
<td>2.72</td>
<td>2.92</td>
<td>3.10</td>
<td>3.36</td>
<td>3.90</td>
<td>4.13</td>
</tr>
<tr>
<td>ml.</td>
<td>2.06</td>
<td>2.08</td>
<td>2.10</td>
<td>2.14</td>
<td>2.16</td>
<td>2.20</td>
<td>2.30</td>
<td>2.50</td>
<td>2.80</td>
<td>3.00</td>
<td>3.10</td>
</tr>
<tr>
<td>pH</td>
<td>4.30</td>
<td>4.52</td>
<td>4.86</td>
<td>5.75</td>
<td>6.06</td>
<td>6.39</td>
<td>6.83</td>
<td>7.22</td>
<td>7.58</td>
<td>7.75</td>
<td>7.83</td>
</tr>
</tbody>
</table>
ml.  3.20  3.50  3.80  4.00  4.10  4.15  4.20  4.25  4.30  4.35  4.40  4.60

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th></th>
<th>S</th>
<th></th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₁</td>
<td>2.70</td>
<td>0.0076</td>
<td>0.037</td>
<td>-0.30</td>
<td>2.44</td>
<td></td>
</tr>
<tr>
<td>pK₂</td>
<td>7.88</td>
<td>0.0233</td>
<td>0.176</td>
<td>neglig.</td>
<td>8.06</td>
<td></td>
</tr>
</tbody>
</table>

Titration of another 0.0305 g. sample in 15 ml. of water at 28° required 4.24 ml. of base. The apparent values were pK₁ 2.72, pK₂ 7.95.

Titration of 0.0287 g. (0.000199 mole) in 15 ml. of water at 29.2° required 4.06 ml. of base:

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th></th>
<th>S</th>
<th></th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₁</td>
<td>2.74</td>
<td>0.0072</td>
<td>0.036</td>
<td>-0.247</td>
<td>2.53</td>
<td></td>
</tr>
<tr>
<td>pK₂</td>
<td>7.90</td>
<td>0.0224</td>
<td>0.173</td>
<td>neglig.</td>
<td>8.07</td>
<td></td>
</tr>
</tbody>
</table>

**trans-3-Methylcyclopropane-cis-1,2-dicarboxylic acid.**

Titration of 0.0325 g. (0.000226 mole) in 15 ml. of water at 28.5°:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>0.20</th>
<th>0.50</th>
<th>1.00</th>
<th>1.10</th>
<th>1.20</th>
<th>1.40</th>
<th>1.70</th>
<th>2.00</th>
<th>2.10</th>
<th>2.15</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.52</td>
<td>2.54</td>
<td>2.83</td>
<td>3.15</td>
<td>3.21</td>
<td>3.28</td>
<td>3.43</td>
<td>3.69</td>
<td>4.10</td>
<td>4.32</td>
<td>4.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2.20</th>
<th>2.22</th>
<th>2.26</th>
<th>2.30</th>
<th>2.36</th>
<th>2.40</th>
<th>2.40</th>
<th>2.60</th>
<th>2.80</th>
<th>3.10</th>
<th>3.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>4.69</td>
<td>4.78</td>
<td>5.01</td>
<td>5.20</td>
<td>5.44</td>
<td>5.56</td>
<td>5.76</td>
<td>5.93</td>
<td>6.16</td>
<td>6.43</td>
<td>6.60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>3.40</th>
<th>3.50</th>
<th>3.70</th>
<th>4.00</th>
<th>4.20</th>
<th>4.36</th>
<th>4.40</th>
<th>4.46</th>
<th>4.48</th>
<th>4.52</th>
<th>4.54</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>6.66</td>
<td>6.73</td>
<td>6.90</td>
<td>7.17</td>
<td>7.43</td>
<td>7.75</td>
<td>7.89</td>
<td>8.19</td>
<td>8.33</td>
<td>8.87</td>
<td>9.50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>4.56</th>
<th>4.60</th>
<th>4.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>9.81</td>
<td>10.19</td>
<td>10.61</td>
</tr>
</tbody>
</table>
-75-

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>( p )</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>( pK_1 )</td>
<td>3.24</td>
<td>0.0070</td>
<td>0.036</td>
<td>-0.074</td>
<td>3.20</td>
</tr>
<tr>
<td>( pK_2 )</td>
<td>6.65</td>
<td>0.0246</td>
<td>0.179</td>
<td>neglig.</td>
<td>6.83</td>
</tr>
</tbody>
</table>

Titration of 0.0327 g. (0.000227 mole) in 15 ml. of water at 30\(^\circ\) required 4.53 ml. of base:

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>( p )</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>( pK_1 )</td>
<td>3.23</td>
<td>0.007</td>
<td>0.036</td>
<td>-0.074</td>
<td>3.19</td>
</tr>
<tr>
<td>( pK_2 )</td>
<td>6.65</td>
<td>0.0246</td>
<td>0.179</td>
<td>neglig.</td>
<td>6.83</td>
</tr>
</tbody>
</table>

3-Methylcyclopropane-\textit{trans}-1,2-dicarboxylic acid.

Titration of 0.0243 g. (0.0001685 mole) in 15 ml. of water at 28\(^\circ\):

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.20</th>
<th>0.40</th>
<th>0.60</th>
<th>0.80</th>
<th>0.90</th>
<th>1.10</th>
<th>1.40</th>
<th>1.60</th>
<th>2.00</th>
<th>2.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.88</td>
<td>3.22</td>
<td>3.38</td>
<td>3.61</td>
<td>3.80</td>
<td>3.84</td>
<td>4.00</td>
<td>4.22</td>
<td>4.36</td>
<td>4.70</td>
<td>5.02</td>
</tr>
<tr>
<td>ml.</td>
<td>2.60</td>
<td>2.70</td>
<td>3.00</td>
<td>3.15</td>
<td>3.20</td>
<td>3.25</td>
<td>3.30</td>
<td>3.35</td>
<td>3.50</td>
<td>3.60</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>5.20</td>
<td>5.35</td>
<td>5.68</td>
<td>6.06</td>
<td>6.31</td>
<td>6.70</td>
<td>9.61</td>
<td>10.32</td>
<td>10.95</td>
<td>11.07</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>( p )</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>( pK_1 )</td>
<td>3.80</td>
<td>0.0052</td>
<td>0.031</td>
<td>+0.017</td>
<td>3.85</td>
</tr>
<tr>
<td>( pK_2 )</td>
<td>5.20</td>
<td>0.0188</td>
<td>0.161</td>
<td>-0.051</td>
<td>5.31</td>
</tr>
</tbody>
</table>

Titration of 0.0499 g. (0.0346 mole) in 10 ml. of water at 29\(^\circ\) required 6.76 ml. of base:

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>( p )</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>( pK_1 )</td>
<td>3.80</td>
<td>0.0145</td>
<td>0.049</td>
<td>+0.044</td>
<td>3.89</td>
</tr>
<tr>
<td>( pK_2 )</td>
<td>5.17</td>
<td>0.0449</td>
<td>0.223</td>
<td>-0.054</td>
<td>5.34</td>
</tr>
</tbody>
</table>
**cis-2-Carbomethoxy-cis-3-methylcyclopropanecarboxylic acid.**

Titration of 0.0579 g. (0.000366 mole) in 20 ml. of water at 29.2°C:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.20</th>
<th>0.60</th>
<th>1.02</th>
<th>1.40</th>
<th>1.60</th>
<th>1.70</th>
<th>1.80</th>
<th>1.90</th>
<th>2.10</th>
<th>2.60</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>3.04</td>
<td>3.30</td>
<td>3.70</td>
<td>3.98</td>
<td>4.19</td>
<td>4.26</td>
<td>4.32</td>
<td>4.36</td>
<td>4.41</td>
<td>4.50</td>
<td>4.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>3.00</th>
<th>3.20</th>
<th>3.40</th>
<th>3.50</th>
<th>3.58</th>
<th>3.60</th>
<th>3.64</th>
<th>3.66</th>
<th>3.68</th>
<th>3.70</th>
<th>3.80</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>5.03</td>
<td>5.22</td>
<td>5.52</td>
<td>5.75</td>
<td>6.12</td>
<td>6.30</td>
<td>6.96</td>
<td>7.66</td>
<td>8.71</td>
<td>9.52</td>
<td>10.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.38</td>
<td>0.0084</td>
<td>0.039</td>
<td>neglig.</td>
<td>4.42</td>
</tr>
</tbody>
</table>

Titration of 0.0266 g. (0.000168 mole) in 15 ml. of water at 26.5°C required 1.62 ml. of base:

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.46</td>
<td>0.0051</td>
<td>0.031</td>
<td>-0.009</td>
<td>4.48</td>
</tr>
</tbody>
</table>

**cis-2-Carbomethoxy-trans-3-methylcyclopropanecarboxylic acid.**

Titration of 0.0283 g. (0.000179 mole) in 15 ml. of water at 28°C:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.10</th>
<th>0.30</th>
<th>0.50</th>
<th>0.70</th>
<th>0.80</th>
<th>0.90</th>
<th>1.00</th>
<th>1.20</th>
<th>1.40</th>
<th>1.60</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>3.00</td>
<td>3.19</td>
<td>3.50</td>
<td>3.73</td>
<td>3.95</td>
<td>4.05</td>
<td>4.15</td>
<td>4.23</td>
<td>4.43</td>
<td>4.68</td>
<td>5.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>1.70</th>
<th>1.74</th>
<th>1.76</th>
<th>1.78</th>
<th>1.80</th>
<th>1.82</th>
<th>1.86</th>
<th>1.90</th>
<th>2.00</th>
<th>2.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>5.44</td>
<td>5.75</td>
<td>6.01</td>
<td>6.50</td>
<td>8.33</td>
<td>9.71</td>
<td>10.30</td>
<td>10.54</td>
<td>10.90</td>
<td>11.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.15</td>
<td>0.0060</td>
<td>0.033</td>
<td>-0.011</td>
<td>4.17</td>
</tr>
</tbody>
</table>
Titration of 0.0301 g. (0.000190 mole) in 15 ml. of water at 29°
required 1.91 ml. of base:

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.20</td>
<td>0.0060</td>
<td>0.033</td>
<td>-0.010</td>
<td>4.22</td>
</tr>
</tbody>
</table>

trans-2-Carbomethoxy-trans-3-methylcyclopropanecarboxylic acid.

Titration of 0.0339 g. (0.000214 mole) in 20 ml. of water at 29.5°:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.50</th>
<th>0.80</th>
<th>0.90</th>
<th>1.00</th>
<th>1.10</th>
<th>1.20</th>
<th>1.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>3.02</td>
<td>3.16</td>
<td>3.23</td>
<td>3.40</td>
<td>3.61</td>
<td>3.86</td>
<td>3.94</td>
<td>4.01</td>
<td>4.09</td>
<td>4.16</td>
<td>4.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>1.50</th>
<th>1.70</th>
<th>1.90</th>
<th>2.00</th>
<th>2.04</th>
<th>2.06</th>
<th>2.08</th>
<th>2.10</th>
<th>2.14</th>
<th>2.16</th>
<th>2.20</th>
<th>2.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>4.43</td>
<td>4.64</td>
<td>4.98</td>
<td>5.28</td>
<td>5.46</td>
<td>5.60</td>
<td>5.80</td>
<td>6.11</td>
<td>9.55</td>
<td>9.94</td>
<td>10.29</td>
<td>10.70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.06</td>
<td>0.0050</td>
<td>0.031</td>
<td>-0.015</td>
<td>4.08</td>
</tr>
</tbody>
</table>

Titration of 0.0380 g. (0.000240 mole) in 15 ml. of water at 29.5°
required 2.35 ml. of base:

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.06</td>
<td>0.0073</td>
<td>0.036</td>
<td>-0.011</td>
<td>4.08</td>
</tr>
</tbody>
</table>

Titration with a "Radiometer" automatic titrator of 5.969 mg. (0.0000378 mole) in 6 ml. of water at 25° required 0.385 ml. of base:

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.135</td>
<td>0.0031</td>
<td>0.025</td>
<td>-0.025</td>
<td>4.135</td>
</tr>
</tbody>
</table>
trans-2-Carbomethoxy-cis-3-methylcyclopropanecarboxylic acid.

Titration of 0.0380 g. (0.0002405 mole) in 15 ml. of water at 29.5°:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.20</th>
<th>0.40</th>
<th>0.80</th>
<th>1.00</th>
<th>1.10</th>
<th>1.20</th>
<th>1.30</th>
<th>1.70</th>
<th>1.90</th>
<th>2.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.92</td>
<td>3.18</td>
<td>3.40</td>
<td>3.73</td>
<td>3.86</td>
<td>3.95</td>
<td>4.02</td>
<td>4.12</td>
<td>4.42</td>
<td>4.62</td>
<td>4.86</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>2.20</th>
<th>2.26</th>
<th>2.30</th>
<th>2.34</th>
<th>2.36</th>
<th>2.38</th>
<th>2.40</th>
<th>2.42</th>
<th>2.50</th>
<th>2.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>5.10</td>
<td>5.30</td>
<td>5.48</td>
<td>5.84</td>
<td>6.23</td>
<td>8.44</td>
<td>9.73</td>
<td>10.06</td>
<td>10.55</td>
<td>11.01</td>
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</tbody>
</table>

<table>
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<th>μ</th>
<th>S</th>
<th>D</th>
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</tr>
</thead>
<tbody>
<tr>
<td>4.01</td>
<td>0.0074</td>
<td>0.037</td>
<td>-0.013</td>
<td>4.03</td>
</tr>
</tbody>
</table>

Titration of 0.0491 g. (0.000311 mole) in 20 ml. of water at 29° required 3.09 ml. of base:

<table>
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<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.00</td>
<td>0.0072</td>
<td>0.036</td>
<td>-0.011</td>
<td>4.03</td>
</tr>
</tbody>
</table>

Titration of 0.006548 g. (0.0000414 mole) in 6 ml. of water at 24° with a "Radiometer" automatic titrator required 0.423 ml. of base:

<table>
<thead>
<tr>
<th>Apparent pK</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.04</td>
<td>0.0033</td>
<td>0.026</td>
<td>-0.025</td>
<td>4.04</td>
</tr>
</tbody>
</table>

Cyclopropane-cis-1,2,3-tricarboxylic acid.

Titration of 0.0495 g. (0.000285 mole) in 15 ml. of water at 31°:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.20</th>
<th>0.60</th>
<th>1.10</th>
<th>1.20</th>
<th>1.30</th>
<th>1.40</th>
<th>1.60</th>
<th>2.00</th>
<th>2.40</th>
<th>3.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>1.99</td>
<td>2.03</td>
<td>2.13</td>
<td>2.25</td>
<td>2.30</td>
<td>2.34</td>
<td>2.38</td>
<td>2.45</td>
<td>2.63</td>
<td>2.88</td>
<td>3.60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>3.50</th>
<th>4.00</th>
<th>4.20</th>
<th>4.30</th>
<th>4.40</th>
<th>4.60</th>
<th>5.00</th>
<th>5.40</th>
<th>5.52</th>
<th>5.60</th>
<th>5.64</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>3.91</td>
<td>4.14</td>
<td>4.25</td>
<td>4.31</td>
<td>4.37</td>
<td>4.50</td>
<td>4.76</td>
<td>5.20</td>
<td>5.42</td>
<td>5.69</td>
<td>5.88</td>
</tr>
<tr>
<td>ml.</td>
<td>5.68</td>
<td>5.70</td>
<td>5.72</td>
<td>5.74</td>
<td>5.76</td>
<td>5.80</td>
<td>5.88</td>
<td>6.00</td>
<td>6.40</td>
<td>6.80</td>
<td>7.18</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
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<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>pH</td>
<td>6.19</td>
<td>6.44</td>
<td>6.80</td>
<td>7.34</td>
<td>7.61</td>
<td>8.00</td>
<td>8.30</td>
<td>8.59</td>
<td>9.03</td>
<td>9.32</td>
<td>9.55</td>
</tr>
<tr>
<td>ml.</td>
<td>7.60</td>
<td>8.00</td>
<td>8.40</td>
<td>8.60</td>
<td>8.80</td>
<td>9.00</td>
<td>9.20</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>9.80</td>
<td>10.06</td>
<td>10.39</td>
<td>10.60</td>
<td>10.80</td>
<td>10.97</td>
<td>11.15</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>µ</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK1</td>
<td>2.38</td>
<td>0.013</td>
<td>0.046</td>
<td>-0.484</td>
<td>1.94</td>
</tr>
<tr>
<td>PK2</td>
<td>4.31</td>
<td>0.030</td>
<td>0.192</td>
<td>-0.009</td>
<td>4.49</td>
</tr>
<tr>
<td>PK3</td>
<td>9.54</td>
<td>0.058</td>
<td>0.406</td>
<td>+0.006</td>
<td>9.95</td>
</tr>
</tbody>
</table>

Titration of 0.0247 g. (0.000142 mole) in 15 ml. of water at 30° required 4.30 ml. of base for total neutralization:

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>µ</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK1</td>
<td>2.545</td>
<td>0.008</td>
<td>0.037</td>
<td>-0.69</td>
<td>1.89</td>
</tr>
<tr>
<td>PK2</td>
<td>4.37</td>
<td>0.017</td>
<td>0.154</td>
<td>-0.015</td>
<td>4.51</td>
</tr>
<tr>
<td>PK3</td>
<td>9.70</td>
<td>0.034</td>
<td>0.338</td>
<td>-0.014</td>
<td>10.05</td>
</tr>
</tbody>
</table>

Titration to the second equivalent value of 0.1756 g. (0.00101 mole) in 12 ml. of water at 29.5° required 20.30 ml. of base:

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>µ</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK1</td>
<td>2.13</td>
<td>0.038</td>
<td>0.070</td>
<td>-0.250</td>
<td>1.95</td>
</tr>
<tr>
<td>PK2</td>
<td>4.23</td>
<td>0.074</td>
<td>0.264</td>
<td>-0.008</td>
<td>4.49</td>
</tr>
</tbody>
</table>
Cyclopropane-trans-1,2,3-tricarboxylic acid.

Titrations of 0.0258 g. (0.000148 mole) in 15 ml. of water at 28°:

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.30</th>
<th>0.60</th>
<th>0.70</th>
<th>0.80</th>
<th>1.00</th>
<th>1.10</th>
<th>1.30</th>
<th>1.40</th>
<th>1.60</th>
<th>1.80</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.48</td>
<td>2.64</td>
<td>2.82</td>
<td>2.89</td>
<td>2.99</td>
<td>3.10</td>
<td>3.19</td>
<td>3.31</td>
<td>3.39</td>
<td>3.53</td>
<td>3.69</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>2.00</th>
<th>2.20</th>
<th>2.40</th>
<th>2.70</th>
<th>3.00</th>
<th>3.30</th>
<th>3.50</th>
<th>3.80</th>
<th>4.00</th>
<th>4.20</th>
<th>4.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>3.84</td>
<td>4.00</td>
<td>4.20</td>
<td>4.59</td>
<td>5.12</td>
<td>5.60</td>
<td>5.86</td>
<td>6.20</td>
<td>6.44</td>
<td>6.78</td>
<td>7.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ml.</th>
<th>4.34</th>
<th>4.38</th>
<th>4.40</th>
<th>4.44</th>
<th>4.60</th>
<th>5.00</th>
<th>6.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.23</td>
<td>7.50</td>
<td>7.78</td>
<td>9.00</td>
<td>9.50</td>
<td>9.99</td>
<td>10.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₁</td>
<td>2.92</td>
<td>0.006</td>
<td>0.034</td>
<td>-0.129</td>
<td>2.92</td>
</tr>
<tr>
<td>pK₂</td>
<td>4.03</td>
<td>0.0172</td>
<td>0.156</td>
<td>-0.074</td>
<td>4.11</td>
</tr>
<tr>
<td>pK₃</td>
<td>6.09</td>
<td>0.0356</td>
<td>0.343</td>
<td>-0.008</td>
<td>6.43</td>
</tr>
</tbody>
</table>

Titrations of 0.0219 g. (0.000126 mole) in 15 ml. of water at 28° required 3.72 ml. of base:

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>μ</th>
<th>S</th>
<th>D</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₁</td>
<td>2.93</td>
<td>0.005</td>
<td>0.032</td>
<td>-0.163</td>
<td>2.80</td>
</tr>
<tr>
<td>pK₂</td>
<td>4.02</td>
<td>0.0149</td>
<td>0.148</td>
<td>-0.078</td>
<td>4.09</td>
</tr>
<tr>
<td>pK₃</td>
<td>6.06</td>
<td>0.0313</td>
<td>0.326</td>
<td>-0.01</td>
<td>6.38</td>
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</table>
BIBLIOGRAPHY


CHAPTER V
A STEREOSELECTIVE MICHAEL ADDITION

Introduction

The Michael addition is one of the reactions most commonly used in organic synthesis. It involves nucleophilic attack on a carbon-carbon double bond substituted by an electron withdrawing group R (R = -COOC₂H₅, -CO-, -CN etc.). The nucleophile X⁻ becomes attached to the carbon atom situated β to the substituent, and the resulting anion may be written as a hybrid of contributing structures.

Because of the stabilizing resonance, the anion has been commonly believed to have a relatively long life, which would allow it to attain configurational equilibrium. When cis and trans-isomers are treated with the same nucleophile, the same anion would therefore be expected, which upon protonation should give the same product.

No stereospecific Michael reaction has been reported in the literature and no general study of the steric course of this reaction had been undertaken before Kennedy (1) discovered that the products of the reaction of diethyl sodiomalonate with ethyl α-bromocrotonate and ethyl α-bromoisocrotonate in ethanol were not identical. He studied the reaction in aprotic solvents, ether and petroleum ether, in order to show that the protonation of the anion was the important step. He
also attempted to prove that the reaction commenced with a Michael addition and that the substitution of the bromine by the malonate ion was not the first step.

Because of the importance of the problem, a careful restudy was desired, using more precise analytical methods.
Structure of the isomeric α-bromocrotonic acids

Treatment of crotonic acid dibromide with hot pyridine (2) or with aqueous sodium hydroxide (3) yields α-bromocrotonic acid or α-bromoisocrotonic acid respectively. The accepted structures I and II were proposed by Michael (4) and based on his observation (5) that the addition of halogen acids and halogens to acetylenic acids occurred in a trans fashion and that elimination also proceeded in a trans manner. Crotonic acid was considered to possess a trans configuration, and upon bromination and dehydrobromination in trans processes should give rise to α-bromoisocrotonic acid. Along the same lines, isocrotonic acid upon bromination and dehydrobromination should provide α-bromocrotonic acid. In both cases, the predicted results were observed. Formation of I from crotonic acid and pyridine is presumed to occur through rearrangement of II.

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{Br} \\
\text{H} & \quad \text{C} = \text{C} \quad \text{COOH} \\
\text{I} & \\
\text{H} & \quad \text{C} = \text{C} \quad \text{COOH} \\
\text{CH}_3 & \quad \text{Br} \\
\text{II} &
\end{align*}
\]

Confirmatory information is given by the relative stability of the ethyl esters. It has been observed (1) that ethyl α-bromoiso
crotonate isomerized readily under the influence of oxygen to ethyl
α-bromocrotonate. It is likely that the smaller steric interaction
is for cis methyl-bromine rather than cis methyl-carboethoxy.
Ultra violet spectra also support this formulation. α-Bromoisocrotonic
acid exhibits an absorption maximum of lower intensity at longer wave
length than does α-bromocrotonic acid (1).
Further evidence concerns the ease of esterification of the isomeric acids. α-Bromocrotonic acid was reported (1) to be much more easily esterified than α-bromoisocrotonic acid, suggesting that the carboxyl group was less hindered in the former. The rates of esterification of the isomeric acids have not been measured, but the extent of their esterification in identical homogeneous conditions was determined in the present work.

Reflux for 2 hours with 2% sulfuric acid in ethanol gave a 46% yield of ethyl α-bromocrotonate from α-bromocrotonic acid and only 10% of ethyl α-bromoisocrotonate from α-bromoisocrotonic acid, thus showing clearly that the carboxyl is more hindered in the latter series.

Another good way to determine the environment of the carboxyl groups is to measure their acidity constants and to compare these values with those of the parent crotonic (III) and isocrotonic acids (IV) of known configuration (6).

The introduction of the bromine at the α-position must result in the same inductive effect and therefore approximately the same increase of the acidity of the two isomers.

The acidity constants for the isomeric α-bromo acids have been found to be: α-bromocrotonic acid, pK 3.22; α-bromoisocrotonic acid, pK 2.76. The literature (7) gives for crotonic acid, pK 4.69, and isocrotonic acid, pK 4.44.
The differences are:

crotonic - α-bromocrotonic \( \Delta pK 1.47 \)
isocrotonic - α-bromoisocrotonic \( \Delta pK 1.68 \).

These values are of the same order of magnitude as for the pair acetic acid - bromoacetic acid, \( \Delta pK 1.90 \) (7), and therefore fit the structural assignment.
The reaction of diethyl sodiomalonate with the isomeric ethyl α-bromocrotonates

The reaction of ethyl α-bromocrotonate (V) with diethyl sodiomalonate in ethanol was found to yield triethyl 3-methylcyclopropane-1,1,2-tricarboxylate containing at least 92% of the cis-isomer (VI), whereas in the same conditions ethyl α-bromoisocrotonate (VII) gave a mixture containing 63% of the trans-triester (VIII).

\[ \text{H} \quad \text{C} = \text{C} - \text{COOC}_2\text{H}_5 \quad \text{H}_3\text{C} \quad \text{C} = \text{C} - \text{COOC}_2\text{H}_5 \]

\[ \text{CH}_3 \quad \text{VI} \quad \text{H} \quad \text{COOC}_2\text{H}_5 \quad \text{H} \quad \text{COOC}_2\text{H}_5 \]

\[ \text{CH}_3 \quad \text{VII} \quad \text{COOC}_2\text{H}_5 \quad \text{CH}_3 \quad \text{COOC}_2\text{H}_5 \]

It was verified that the cis-triester was stable under the conditions of the reaction.

The stereospecificity, although not perfect, is remarkable and indicates that a long-lived ionic intermediate was not produced in at least one of the reactions. Otherwise, both isomeric bromoesters V and VII would give the same ion IX, which would be protonated to a common mixture of products (X).
It may be noted that dehydrobromination of the bromoesters VII and VIII prior to the addition of the malonic ester group could lead through ethyl tetrolate only to olefinic esters and is hence ruled out. Direct displacement of the bromine by the nucleophile in VII or VIII would be unusual because of the lack of reactivity of vinyl bromides. It is, however, possible that a base-catalyzed isomerization would give the unconjugated bromoester XI, in which the doubly activated bromine would be displaced with ease. Base isomerization of XII could then lead to two isomeric unsaturated triesters, XIII and XIV.
Baker (3) has reported the cyclization of trimethyl 2-propene-1,1,2-tricarboxylate (XV) in alkali.

\[
\begin{align*}
\text{CH}_3 &\text{CH}_2\text{CH} &\text{COOC}_2\text{H}_5 &\quad \text{CH}_3 &\text{CH}_2\text{CH} &\text{COOC}_2\text{H}_5 \\
\text{CH} &\text{(COOC}_2\text{H}_5)_2 &\quad \text{Br} &\text{C} &\text{(COOC}_2\text{H}_5)_2 &\quad \text{CH}_3 &\text{CH}_2\text{CH} &\text{COOC}_2\text{H}_5 \\
&\quad \text{XVI} & &\quad \text{XVII} & &\quad \text{XVIII}
\end{align*}
\]

Malachowski (9), however, described the preparation of the two isomeric triethyl propene-1,1,2-tricarboxylates and could treat them with bases, including diethyl sodiomalonate, without effecting their cyclization.

A careful examination of the homologs XIII and XIV was therefore necessary to decide whether they could cyclize and lead to VI and VIII.

Triethyl butane-1,1,2-tricarboxylate (XVI) was prepared by the reaction of diethyl sodiomalonate with ethyl \( \lambda \)-bromobutyrate (10). Upon bromination, it yielded triethyl 1-bromobutane-1,1,2-tricarboxylate (XVII).

Sodium ethoxide did not dehydrobrominate XVII but reduced it back to XVI. This reduction can be explained by the large amount of polar character in the bromine-malonic ester bond. In presence of base, a positive bromine ion is abstracted and the stable malonate anion formed is protonated in working up the reaction.
Dehydrobromination of XVII occurred readily in pyridine. The first product of the reaction can be expected to be triethyl 1-butene-1,1,2-tricarboxylate (XVIII). The crowding among the substituents on the double bond tends to bring them out of planarity and diminishes the stabilization of the product by resonance. It is therefore not surprising that under the influence of the base, the double bond migrated to reach a less substituted and more stable arrangement. A conjugated system was present, indicated by the ultraviolet spectrum ($\lambda_{\text{max}}$ 211 m$\mu$, $\varepsilon$ 8200 in 10% aqueous ethanol).

The product of the reaction of XVII with pyridine was analyzed by proton magnetic resonance spectroscopy using tetramethysilane as reference (figure 1).

In carbon tetrachloride as solvent, a quadruplet centered at -250 cycles indicated an olefinic hydrogen split by the adjacent methyl group. In dimethyl itaconate the doubly bonded methylene peaks are centered at -252 cycles. The presence of these olefinic peaks demonstrates the rearrangement of XVIII in presence of pyridine giving XIII or XIV, but only one of them, as shown by treating this material with sodium ethoxide. Another olefinic quadruplet appeared, centered at -284 cycles, its relative intensity depending on the conditions of the treatment. This latter quadruplet was the only olefinic hydrogen bond present when the product from pyridine dehydrobromination had been refluxed with one equivalent of ethoxide for almost 5 hours. In this last product ($\lambda_{\text{max}}$ 213 m$\mu$, $\varepsilon$ 8550 in 10% methanol) the methyl group on the double bond gave two strong peaks at -70 and -78 cycles, whereas before ethoxide treatment they were at -82 and -89 cycles.

Both unsaturated triesters gave ethylidenesuccinic acid on acid
P.M.R. Spectra of Triethyl 2-butene-1,1,2-tricarboxylate

A. From dehydrobromination in pyridine.
B. Treated with ½ equivalent ethoxide at room temperature.
C. Treated with 1 equivalent ethoxide at reflux.
hydrolysis. The proton magnetic resonance spectrum of dimethyl ethyldene-
succinate was identical to that of the more stable unsaturated triester
in the olefinic region. It had a quadruplet centered at -280 cycles
(olefinic hydrogen) and a doublet at -70 and -78 cycles (C-methyl).

\[
\begin{align*}
\text{XIII and XIV} & \xrightarrow{H^+} \text{H}^+ \\
\text{H}_2\text{O} & \quad \text{CH}_3\text{-CH=}[\text{C}-\text{COOH}]
\end{align*}
\]

\[
\text{CH}_2\text{-COOH}
\]

The stereochemistry of the more stable isomer of the unsaturated
triesters XIII and XIV can be assigned on the basis of the proton mag-
netic resonance data. The shifts of the methyl peaks to higher field
and of the olefinic hydrogen band to lower field on treatment with
ethoxide indicate that the more stable product is XIII, where the
carboethoxy and methyl groups are cis. Both proton magnetic resonance
and vapor phase chromatography indicated that no cyclization occurred
during the treatment of XIII and XIV with sodium ethoxide.

The unsaturated triester XIII, stabler to base, was found re-
markably unstable to heat. When examined by vapor phase chromatography,
it underwent cleavage under conditions so mild that its analysis in
mixture with its isomer required low temperatures (about 140°) resulting
in long retention times and poor resolution. The other isomer was found
stable at temperatures as high as 190°.

Since the unsaturated triesters XIII and XIV were found not to
cyclize to the isomeric cyclopropane triesters, they were not interme-
diates in the reaction of the \(\text{X}\)-bromocrotonic esters with diethyl sodio-
malonate. Therefore, the malonic ester residue first attacked the
\( \beta \) -carbon atom of the bromocrotonates.

It has already been mentioned that the ion obtained by addition of the diethyl malonate ion to a bromo ester must have a short life in order to account for the stereospecificity of the reaction. Because of the resonance with the ester group, the configuration at the \( \alpha \)-carbon must be planar (XIX).

![Chemical Structure](image)

The carbonyl group must lie in the plane, with two possible orientations. The probability or effects of differing orientations cannot, unfortunately, be readily estimated.

One fate of XIX would be rapid protonation cis to the malonate residue, either by 1,3 proton transfer or from solvent, followed by displacement of the bromine with inversion.

![Chemical Structure](image)

This scheme is however in conflict with the experimental results that the group originally cis to the ester group in the olefins becomes mainly trans in the cyclopropane triesters.

The probable conclusion is that rapid protonation by solvent occurs trans.
to the malonate group in XIX. The more acidic hydrogen is then ionized and cyclization occurs with inversion to yield the observed products.

In order to account for the good stereospecificity of the reaction an effectively concerted mechanism must be postulated in which the nucleophile generates a negative charge on the $\alpha$-carbon of the unsaturated bromoester, immediately neutralized by a solvent molecule.

Because of the intervention of an external proton source, it was likely that solvents that did not possess any acidic hydrogen would not be suitable for a stereospecific Michael addition and would lead to the most stable carbanion configuration from either ethyl $\alpha$-bromocrotonate. The reaction could stop at this stage, when acidification would yield the open-chain bromotriester X, or proceed further to yield the cyclopropane triesters, thus proving that the initial carbanion XIX had been protonated and that dehydrobromination occurred in the manner previously described.
Kennedy (1) had used ether and petroleum ether as media for the reaction, but since diethyl sodiomalonate was insoluble in these solvents, the reaction was heterogeneous and the result could not be safely compared to that obtained in homogeneous ethanol solution.

Several aprotic solvents in which the salts were soluble have now been used, and the results are recorded in Table I.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric constant</th>
<th>Ethyl α-bromo-crotonate</th>
<th>Ethyl α-bromo-isocrotonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,4-dioxane</td>
<td>2.2</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>tetrahydrofuran</td>
<td>8</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>dimethylformamide</td>
<td>36.7</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td>1-methyl-2-pyrrolidinone</td>
<td></td>
<td>66</td>
<td>56</td>
</tr>
<tr>
<td>dimethyl sulfoxide</td>
<td>45</td>
<td>78</td>
<td>73</td>
</tr>
</tbody>
</table>

It is apparent from these results that:

1. Only a slight amount of stereospecificity is retained, thus proving the mechanism indicated for the reaction in ethanol, which required an acidic hydrogen from the solvent.

2. There is a stereoselectivity in the reaction, related to the solvent.

As the cis-triester was stable under the experimental conditions, these results may be explained if a common intermediate was obtained from both bromo esters. This intermediate would be the ionic adduct
XIX in its most stable conformation, obtained by rotation around the single bond generated between the original α- and β-carbon atoms of the bromo ester. The reaction can proceed further as described above to yield a cyclopropane derivative.

Among the possible conformations of XIX, the probable ones have the substituents of the planar α-carbon atom as far as possible from the bulky malonate residue.

Irreversible protonation of this ion fixes the structure of the cyclopropane triester. Since in all cases a mixture of isomers was obtained, the protonation had occurred from both sides of the plane of the α-carbon atom, in proportion depending on the solvent.

It is possible, however, that there are two stable configurations for the ion XIX in equilibrium.

Protonation of these ions will account for the lack of stereospecificity. As internal 1,3 shift of a proton is not very likely, the protonation occurs presumably externally and most likely the proton source approaches the ion from the opposite side from the malonate.
group. It is therefore possible for this protonation to occur to some extent in a concerted manner, as described when ethanol was the solvent. Because the solvent is not the proton source this concerted protonation cannot be a major path. It may however occur as shown by the results in Table I. The cyclopropane triesters obtained were richer in the cis-isomer when ethyl Κ-bromocrotonate was the starting material than when it was ethyl Κ-bromoisocrotonate. Such a distribution was also found when ethanol was used as solvent.

Further proof for the mechanism of the concerted reaction was obtained by using t-butyl alcohol as solvent. In the concerted step of the reaction in ethanol, the proton is given by the solvent to the anion being formed. It can be predicted that the t-butylate ion is a base stronger than any of the ions formed in the reaction, and therefore t-butyl alcohol will not act as a ready proton source. The experimental results confirmed this prediction. The mixture of cyclopropane triesters from ethyl Κ-bromocrotonate contained 65% of the cis-isomer, that from ethyl Κ-bromoisocrotonate contained 62% of the cis-isomer.

From the results in aprotic solvents, one can distinguish a trend for the mixtures of cyclopropane triesters to be richer in cis-isomer when the dielectric constant of the solvent is higher. t-Butyl alcohol does not follow this rule.

Solvent effects in the course of reactions involving carbanions have been reported in the cleavage of (-)-3,4-dimethyl-4-phenyl-3-hexanol in base which yields 2-phenylbutane through a carbanion intermediate (11). The ratio between the rate constants of the reaction leading to the inverted configuration to that leading to the retained configuration
varies in the same order as the dielectric constant of the solvent used.

One case of stereoselectivity of a base-catalyzed reaction yielding a cis conformation has been reported. The two stereoisomeric \( \alpha \)-phenyl-benzalacetones, treated with hydrogen peroxide in base, give a single epoxide which has the two phenyl groups cis (12).

Several cyclizations leading predominantly to a less stable cis configuration have been described. For instance, on treatment of ethyl acrylate with \( \alpha \)-substituted propionates in presence of base, a mixture of cyclopropane diesters is obtained which contains 35% of cis-isomer when \( X = Cl \), 70% when \( X = Br \) and only 10% when \( X = C_6H_5SO_2 \) (13).  

\[
\text{CH}_2=\text{CH}-\text{COOC}_2\text{H}_5 + \text{CH}_3-\text{CH}-\text{COOC}_2\text{H}_5 \xrightarrow{\text{Kot-bu}^+} \begin{array}{c}
\text{H} \\
\text{COOC}_2\text{H}_5
\end{array} \]

\[
\begin{array}{c}
\text{COOC}_2\text{H}_5 \\
\text{CH}_3
\end{array}
\]

Stereoselectivity has also been observed in the addition of morpholine to cis and trans \( \alpha \)-bromo-\( \alpha \)-unsaturated ketones in benzene. A single product is obtained, stereoisomeric to that obtained from the addition of \( \alpha \)-bromomorpholine to the corresponding \( \alpha \)-unsaturated ketones (14). The solvent effect in this reaction has not been studied.

The reaction of isomeric methyl \( \alpha \)-bromocinnamates with piperidine gives different methyl 2,3-dipiperidylidihydrocinnamates (16), but although some mechanistic studies have been made (17), the configuration of the products has not been established.

It has recently been shown (15) that nucleophilic addition across a triple bond occurs in a trans fashion, but it had never been shown previously that nucleophilic addition across a double bond was also
trans process. However, this fact was expected, since base catalyzed eliminations are known to occur in a trans manner. The study of the reaction of diethyl sodiomalonate with the isomeric ethyl \( \alpha \)-bromo-crotonates offers the first evidence that nucleophilic addition across a double bond in a Michael reaction is a trans process.
Preparation of the pure isomeric triethyl 3-methylcyclopropane-1,1,2-tricarboxylates and analysis of their mixtures.

In order to analyze the products of the reaction discussed, pure samples of triethyl 3-methylcyclopropane-1,1,2-tricarboxylates were needed.

The reaction of sodiomalonic ester with ethyl α-bromocrotonate in ethanol was found to yield mostly the cis isomer. When this mixture of isomers was hydrolyzed to the mixture of acids, their separation by fractional crystallization was extremely difficult. Partial hydrolysis to a monoester diacid, however, permitted easy purification by crystallization, and the cis isomer, treated with diazomethane yielded the pure cis triester.

Three structures are possible for the cis monoester diacid.

![Structures XX, XXI, XXII](image)

A chemical distinction between the structures XX, XXI and XXII would be to study the ability of the diacid to form an anhydride.

A simpler method is to measure the dissociation constants and compare them with the known values for related systems.
The experimental values found were $pK_1$ 2.90, $pK_2$ 4.96, strongly indicating that the product has a trans-1,2-diacid structure and therefore is XXII. The lowering of the first acidity constant as compared to XXV results from the inductive effect of the carboethoxy group which, being electron withdrawing, favors more strongly the ionization of the acid group situated on the same carbon atom.

The pure triethyl trans-3-methylcyclopropane-1,1,2-tricarboxylate was prepared from mixtures of the two isomers. Treatment with sodium ethoxide solution isomerized the cis isomer almost completely to trans. The purification was carried out by fractional crystallization of the triacids obtained by hydrolysis of the isomerized esters. The pure trans triacid was easily obtained, and on treatment with diazomethane yielded the pure trans triethyl ester.

The triesters obey the v.Auwers-Skita rule: $d_{cis} = 1.038$, $d_{trans} = 1.079$.

The refractive indices of the esters were:

- Pure trans: $n_D^{26.75} = 1.4424$, $n_D^{28} = 1.4416$, $n_D^{30.25} = 1.4405$;
- Pure cis: $n_D^{26.75} = 1.4459$, $n_D^{28} = 1.4452$, $n_D^{30.25} = 1.4441$.

Analysis of mixtures could be performed by measuring their refractive indices. This method may be subject to fairly large errors because of the relatively small difference between the indices of the pure isomers and because the indices have a large temperature coefficient. Furthermore, the presence of small amounts of unsaturated impurities of high
refractive index may have a significant effect.

The most accurate method of analysis was found to be vapor phase chromatography. Despite the similarity of the structures of the two triesters and the closeness of their boiling points (cis, 116°/0.75 mm.; trans, 118°/1.05 mm.) resolution good enough for analytical work was obtained.

Calibration curves were made by preparing known mixtures of the two isomers and recording the height of the peaks given by samples of similar size. The sum of the two peaks was taken as 100 and the % cis calculated from the peak heights was plotted against the % cis known in the mixtures. (Usually the experimental agreed with the calculated values within 10%). Two straight lines were obtained, depending on which isomer had the larger peak height, and interpolation for unknown mixtures was straightforward.

Results obtained by this method with a packed column of silicone D.C.550 on Chromosorb at 190° were in good agreement with those obtained with a capillary column (Apiezon L in 200 feet of stainless steel, interior diameter 0.01 inch) used by kindness of Dr. A. Zlatkis, which gave a perfect resolution of the components.
EXPERIMENTAL

α-Bromoisocrotonic acid. A solution of 14.7 g. of sodium hydroxide (0.366 mole) in 150 ml. of water was added to 90 g. (0.366 mole) of α,β-dibromobutyric acid (m.p. 34-36°) with cooling in ice. Another portion of 14.7 g. of sodium hydroxide in 350 ml. of water was added, the temperature being kept around 22°. After standing for 2 hours at room temperature, the reaction mixture was acidified with 42 ml. of concentrated hydrochloric acid (with cooling). The thick precipitate was filtered and recrystallized from water. There was obtained 43.45 g. (71.4%) of α-bromoisocrotonic acid, m.p. 90.2-91.2°, \( \lambda_{max} \) 207 mµ (\( \varepsilon \) 3935), 242 mµ (\( \varepsilon \) 3935) in 0.1 M sulfuric acid.

Titration of 0.0740 g. (0.000449 mole) in 15 ml. of water at 34° with 0.1 N sodium hydroxide. (For detailed procedure see Chapter IV).

<table>
<thead>
<tr>
<th>ml.</th>
<th>0</th>
<th>0.40</th>
<th>1.00</th>
<th>1.40</th>
<th>2.00</th>
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<td>3.40</td>
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<th>4.40</th>
<th>4.44</th>
<th>4.46</th>
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<table>
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<th>p</th>
<th>S</th>
<th>D</th>
<th>Corrected pK</th>
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<td>2.33</td>
<td>0.0138</td>
<td>0.047</td>
<td>-0.107</td>
<td>2.77</td>
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</table>

Another titration of 0.0753 g. (0.0004565 mole) in 15 ml. of water at 34° required 4.50 ml. of 0.1 N base. The apparent pK was 2.31, corrected 2.75.
Ethyl α-bromoisocrotonate. The procedure of Moureu and Chovin (16) was followed and from 42 g. of α-bromoisocrotonic acid, 600 ml. of dry ethanol and 36 ml. of concentrated sulfuric acid there was obtained 39.21 g. (30%) of ester, b.p. 92.5°/34 mm., λmax 242 mμ (ε 4330), 207 mμ (ε 4390) in 1% aqueous methanol. The ethyl α-bromoisocrotonate was kept in the ice box with 0.1232 g. of diphenylamine.

α-Bromocrotonic acid. The recrystallized acid had m.p. 107-107.2°, λmax 233 mμ (ε 3330) in 3.1 N sulfuric acid.

Titration of 0.0751 g. (0.000455 mole) in 15 ml. of water at 34° with 0.1 N sodium hydroxide:

<table>
<thead>
<tr>
<th>ml.</th>
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<th>1.40</th>
<th>1.30</th>
<th>2.20</th>
<th>2.40</th>
<th>3.00</th>
<th>3.50</th>
<th>4.00</th>
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<tbody>
<tr>
<td>pH</td>
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<td>2.53</td>
<td>2.82</td>
<td>3.07</td>
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<td>3.25</td>
<td>3.51</td>
<td>3.79</td>
<td>4.05</td>
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<table>
<thead>
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<th>ml.</th>
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<th>4.56</th>
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<tbody>
<tr>
<td>pH</td>
<td>4.83</td>
<td>5.23</td>
<td>6.20</td>
<td>7.50</td>
<td>9.75</td>
<td>10.40</td>
</tr>
</tbody>
</table>

\[
\begin{array}{cccc}
\text{Apparent pH} & \mu & \delta & \xi \\
3.24 & 0.0137 & 0.047 & -0.041 & 3.25 \\
\end{array}
\]

Another titration of 0.0742 g. (0.00045 mole) in 15 ml. of water at 34° required 4.5 ml. of 0.1 N sodium hydroxide.
The apparent pH was 3.20, the corrected pH 3.20.

Partial exterification of α-bromoisocrotonic acid. A solution of 10.003 g. of α-bromoisocrotonic acid in 200 ml. of dry ethanol was refluxed 2 hours with 4 ml. of concentrated sulfuric acid. After cooling, 500 ml. of ether was added. The solution was washed with 200 ml. of water, two 125 ml.-fractions of 5% bicarbonate and 100 ml. of
brine. After drying over magnesium sulfate, the solution was concentrated and distilled to yield 1.340 g. (15.75%), b.p. 91°/33 mm., of ethyl α-bromoisoisocrotonate. Diphenylamine (9.7 mg.) was added to stabilize the ester and an ultraviolet spectrum in 1% aqueous methanol showed λ<sub>max</sub> = 235 mμ (ε 6650) and 240 mμ (ε 4130). Esterification of α-bromoisoisocrotonic acid in similar conditions for 5 hours yielded 33.9% of the ester. Esterification for 5 hours with a ratio of sulfuric acid to ethanol of 5% yielded 53% of the ester.

Partial esterification of α-bromocrotonic acid. A solution of 10.005 g. of α-bromocrotonic acid in 200 ml. of dry ethanol was refluxed 2 hours with 4 ml. of concentrated sulfuric acid. After working up exactly as described for the isomeric acid, there was obtained 5.349 g. (45.7%) of ethyl α-bromocrotonate, b.p. 95°/35 mm., λ<sub>max</sub> = 235 mμ (ε 6650) (1% aqueous methanol). Esterification of 5 g. of α-bromocrotonic acid with 100 ml. of ethanol and 5 ml. of concentrated sulfuric acid for 5 hours yielded 65% of ester.

Cyclization with ethyl α-bromoisoisocrotonate in ethanol. A solution of 7.0632 g. (0.0441 mole) of diethyl malonate in 10 ml. ethanol was added to a solution of 0.9995 g. (0.0433 mole) of sodium in 25 ml. of ethanol. After stirring for 1½ hours to complete the formation of sodiomalonic ester, this solution (with an additional 10 ml. of solvent) was added slowly with stirring to a solution of 8.3609 g. (0.0433 mole) of ethyl α-bromoisoisocrotonate in 15 ml. of ethanol. The rate of addition was controlled in such a way that the reaction mixture was neutral before each new addition (phenolphthalein was used as indicator). The addition required 1 hour and 35 minutes and the reaction mixture was stirred for another 1 hour and 15 minutes. Ether (200 ml.) was
added and the medium was acidified with 30 ml. of 3 N nitric acid.
The dark yellow ether layer was washed with 30 ml. of brine, five 50-ml.
portions of saturated sodium bicarbonate (until the washings were
colorless), and two 50-ml. portions of brine. The washings were ex-
tracted with ether and the ether solutions, light yellow in color,
were dried over magnesium sulfate and distilled. The yellow product
obtained, b.p. 116°/0.7 mm., n\textsubscript{D}^{20.5} 1.4423, was saturated to permanganate
and after a treatment with norite in ether yielded 7.3859 g., b.p.
109°/0.35 mm., n\textsubscript{D}^{29.25} 1.4420, and 0.5334 g. n\textsubscript{D}^{23.75} 1.4426, obtained
by heating the column with a microburner. Both fractions were colorless.
The main fraction was found to contain 60% of the trans-isomer from vapor phase chromatography and 61% from refractive indices.
Another reaction performed in similar conditions and analyzed before distillation was shown to contain 62% of trans-isomer. When the reaction was performed in more dilute solution its rate became ex-
tremely slow. Furthermore the product was slightly unsaturated to permanganate and extremely difficult to purify.

Cyclization of ethyl α-bromocrotonate in ethanol. A solution of 6.22 g.
of malonic ester in 10 ml. of ethanol was added to 30 ml. of ethanol which had dissolved 0.394 g. of sodium and the mixture was stirred for 1 hour.
To this solution, a solution of 7.5 g. of ethyl α-bromocrotonate in 25 ml. of ethanol was added with stirring during 1 hour and 15 minutes and stirred for 1 hour and 45 minutes after completion of the addition. After working up as before, distillation yielded 7.0313 g. (66.4%),
b.p. 123°/0.3 mm., n\textsubscript{D}^{28.5} 1.4448, colorless and slightly unsaturated to permanganate. This material was treated with potassium permanganate in acetone and distilled to yield 5.5756 g., b.p. 110°/0.3 mm.
n$_D^{28}$ 1.4447 saturated to permanganate, and 0.6831 g. recovered by heating the column with a microburner. The main fraction contained from 92 to 99% of the cis isomer from vapor phase chromatography, 36% from refractive indices.

The cyclization performed by addition of the sodiomalonate ester to the \( \alpha \)-bromocrotonate in presence of an excess of sodium bromide yielded a product of similar composition, n$_D^{23}$ 1.4446, saturated to permanganate.

**Stability of triethyl 3-methylcyclopropane-cis-1,1,2-tricarboxylate.**

Diethyl malonate (0.130 g., 0.00031 mole) was stirred for 40 minutes in a solution of sodium ethoxide prepared by dissolving 0.0203 g. of sodium (0.00033 mole) in 13 ml. of dry ethanol. To this solution was added 2.2236 g. (0.0735 mole) of cis triester, with 4 ml. of ethanol. The solution was stirred for 3 hours at room temperature, diluted with 100 ml. of ether and washed successively with 30 ml. of 3 N nitric acid, 30 ml. of water, two 30-ml. portions of saturated sodium bicarbonate and 30 ml. of water. After drying, the solvent was removed under vacuum and by vapor phase chromatography the crude product was shown to be the unchanged cis-triester. Distillation gave a saturated material, n$_D^{26.2}$ 1.4454, identical to the starting triester.

**Partial hydrolysis of the cis triester.** An homogeneous solution was obtained by stirring for 20 hours 43.64 g. of triester (90% cis) in 1\( \frac{1}{2} \) liters of 2% potassium hydroxide. The unreacted ester was extracted with two 250-ml. portions of ether. The aqueous solution was acidified to Congo Red and extracted with four 250-ml. portions of ether. After drying over magnesium sulfate and removal of the solvent, 31.5 g. of oily material was obtained, which crystallized on scratching.
Two recrystallizations from ether-petroleum ether followed by drying in vacuum at 110° gave the anhydrous *cis* monoester diacid, m.p. 150.4-151°. A sample was esterified with diazoethane to obtain the pure *cis* triester. After distillation (b.p. 116°/0.75 mm.) it had $n_D^{26.75}$ 1.4459. A solution of 3.963 mg. of the monoester diacid (0.00001037 mole) in 5 ml. of water at 25 ° was titrated with 0.1 M sodium hydroxide using a "Radiometer" automatic titrator. The complete neutralization required 0.37 ml. of base.

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>μ</th>
<th>3</th>
<th>2</th>
<th>Corrected</th>
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<td>0.018</td>
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<tr>
<td>$pK_2$</td>
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<td>0.028</td>
<td>-0.012</td>
<td>4.56</td>
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</table>

**Isomerization of triethyl 3-methylcyclopropane-**cis-1,1,2-tricarboxylate.

A solution of sodium ethoxide was prepared by dissolving 0.5075 g. of sodium in 50 ml. of ethanol. In this solution, 6.6320 g. of triester containing about 90% of the *cis* isomer ($n_D^{25}$ = 1.4461) was refluxed for 4 hours. Acidification with glacial acetic acid gave, after working up, a neutral fraction which was distilled. There was obtained 4.2874 g., b.p. 114°/0.8 mm., $n_D^{25}$ 1.4412, saturated to permanganate. Analysis with vapor phase chromatography showed that it was the almost pure *trans* isomer.

**Hydrolysis of triethyl 3-methylcyclopropane-trans-1,1,2-tricarboxylate.**

Some *trans* triester obtained as described above (10.3345 g.) was refluxed for 12 hours in a solution of 10 g. of potassium hydroxide in 100 ml. of water. After cooling and extraction of the neutral fraction with ether, the solution was acidified strongly to Congo Red with hydrochloric acid, concentrated under vacuum until the salt began to
precipitate and extracted with three 33-ml. portions of ether, followed
by three 30-ml. portions of ethyl acetate. Upon concentration of the
dry organic solution there was obtained 5.6 g. of white crystals which
after three recrystallizations from acetone-chloroform yielded 4.5219 g.
(60%), m.p. 215.4-216.2° dec. This trans triacid was esterified by
diazoethane and distilled to yield the pure trans triester, b.p. 113°/
1.05 mm., nD 26.75 1.4424.

Triethyl butane-1,1,2-tricarboxylate. A solution of sodium ethoxide was
prepared from 4.353 g. of sodium metal and 100 ml. of dry ethanol. This
solution was stirred for 30 minutes with 34.3 g. of diethyl malonate.
The sodiomalonic ester was added during 45 minutes to 41.7925 g. of
ethyl α-bromobutyrate in 50 ml. of ethanol. After standing 2½ days
at room temperature, 150 ml. of ether was added, followed by enough
3 N nitric acid to dissolve the precipitate. The ether layer was washed
with two 50-ml. portions of brine, two 50-ml. portions of saturated
sodium bicarbonate and two 50-ml. portions of brine. The dried ether
solution was distilled and yielded 44.69 g. (76%) of triethyl butane-
1,1,2-tricarboxylate, b.p. 112-113/0.3 mm., which was pure by vapor
phase chromatographic analysis.

Triethyl 1-bromobutane-1,1,2-tricarboxylate. The triethyl butane-1,1,2-
tricarboxylate was dissolved in 50 ml. of carbon tetrachloride in a
500-ml. 3-neck flask and placed over a 250-W. light bulb close enough
that reflux occurred. Bromine (8.5 ml.) was added with stirring over
a 20-minute period. After the addition, the stirring was continued
for one more hour over light. The solution was washed with 40 ml. of
water, two 40-ml. portions of saturated bicarbonate, a small amount of
dilute sodium bisulfite (which was later found to reduce the bromo-
triester to starting material), and 50 ml. of brine. The colorless solution was dried over magnesium sulfate and distilled, giving 16.3 g., b.p. 126-136°/1 mm., containing about 15% of starting material as shown by vapor phase chromatography, and 36.44 g., b.p. 136°/1 mm., of essentially pure triethyl 1-bromobutane-1,1,2-tricarboxylate. These fractions turned yellow on standing overnight at room temperature but stayed colorless when kept in the ice box.

Treatment of triethyl 1-bromobutane-1,1,2-tricarboxylate with sodium ethoxide. A solution of 13.9959 g. (0.0397 mole) of pure triethyl 1-bromobutane-1,1,2-tricarboxylate in 20 ml. of ethanol was added to a solution of sodium ethoxide prepared by dissolving 0.9207 g. (0.0401 mole) of sodium in 50 ml. of ethanol. After reflux for 2 hours and 40 minutes the dark brown reaction mixture was neutral. Ether (400 ml.) was added, the precipitate formed was dissolved with 3 N nitric acid, and after washing with water, bicarbonate and brine, the organic solution was dried. The solvent was evaporated and the residue was analyzed by vapor phase chromatography at 190°. One peak at 5.3 minutes constituted the major part of the product. Among other peaks were small ones at 5.4, 3.4 and 9.0 minutes (not well resolved). These peaks, with the same relative intensity, were found on analysis of the main fraction after distillation which yielded 4.5135 g., (44%), b.p. 110-115°/0.75 mm., nD^27.5 1.4381. Under the same conditions the starting material had its peak at 14 minutes and the trans and cis cyclopropane triesters at 7.5 and 5 minutes respectively. This material (0.0166 mole) was treated with a solution of 0.0580 g. of sodium metal (0.00252 mole) in 45 ml. of ethanol. After 5 hours and 40 minutes of reflux the reaction mixture was worked up as above and distilled at 120-126°/1.3 mm. to yield
3.0395 g., (63%), \( n_\text{o}^{25.5} = 1.4310 \), of triethyl butane-1,1,2-tricarboxylate, \( \lambda_{\text{max}} = 210.5 \, \mu \), \( \epsilon = 375 \) (10% aqueous methanol). Analysis by vapor phase chromatography showed that only the peak at 6.8 minutes remained.

**Treatment of triethyl 1-bromobutane-1,1,2-tricarboxylate in pyridine.**

In 30 ml. of pyridine distilled over barium oxide, 4.1744 g. of triethyl 1-bromobutane-1,1,2-tricarboxylate was refluxed for 1½ hours. The reaction mixture became black and a precipitate was formed. Ether (200 ml.) and water (50 ml.) were added. The ether solution was washed twice with 25 ml. of 6 H hydrochloric acid and 50 ml. of water. The aqueous extracts were washed with ether and the ether extracts were combined and dried. Distillation yielded 2.2703 g., b.p. 126-127/1 mm.; 
\[ n_\text{o}^{25.6} = 1.4493; \lambda_{\text{max}} = 211 \, \mu, \epsilon = 3200 \) (10% ethanol). Analysis by vapor phase chromatography at 139° showed that it possessed one major component (7 minutes) but had a small peak corresponding to the triethyl butane-1,1,2-tricarboxylate (about 10% of the total) at 6 minutes. Under these conditions the isomeric cyclopropane triesters had their peaks at 7 and 7.5 minutes.

The analytical sample had b.p. 128°/0.35 mm., \( n_\text{o}^{25} = 1.4495 \).

**Anal.** Calcd. for C\(_{13}\)H\(_{20}\)O\(_6\): C, 57.34; H, 7.40.

**Found:** C, 57.34; H, 7.54

**Treatment of triethyl 2-butene-1,1,2-tricarboxylate with sodium ethoxide.**

1. The unsaturated triester obtained in pyridine (3.0471 g., 0.01103 mole) was refluxed for 4 hours and 15 minutes in a solution of sodium ethoxide obtained by dissolving 0.0193 g. (0.00036 mole) of sodium metal in 20 ml. of ethanol. After cooling, the reaction mixture was neutralized with glacial acetic acid. Ether (150 ml.) was added and the solution was washed with 30 ml. of water, 25 ml. of saturated bicarbonate
solution and 50 ml. of brine. After drying, the solvent was evaporated. Distillation yielded 2.2633 g., b.p. 117-121°/0.3 mm., nD25 1.4488, \(\lambda_{\text{max}}\) 211.5 m\(\mu\), \(\varepsilon\) 3000 (10% aqueous methanol).

2. A solution of sodium ethoxide was prepared by dissolving 0.0470 g. (0.00204 mole) of sodium metal in 25 ml. of ethanol. A solution in 10 ml. of ethanol of 2.2100 g. (0.00312 mole) of unsaturated triester obtained in pyridine was added and the mixture stirred at room temperature for 13½ hours. After acidification with glacial acetic acid, 100 ml. of ether was added and the solution washed successively with 30-ml. portions of water, saturated bicarbonate and brine. After drying, the solvent was evaporated. Distillation yielded 1.5689 g., b.p. 112-120°/0.6 mm., nD24.5 1.4493; \(\lambda_{\text{max}}\) 211.5 m\(\mu\), \(\varepsilon\) 7925 (10% aqueous methanol).

3. A solution of sodium ethoxide was prepared by dissolving 0.2309 g. (0.01 mole) of sodium metal in 25 ml. of ethanol. To this was added a solution of 2.7250 g. (0.01 mole) of unsaturated triester obtained in pyridine, in 10 ml. of ethanol. After stirring at room temperature for 14 hours the reaction mixture was acidified with 3 ml. of glacial acetic acid and worked up as above. Distillation yielded 1.6614 g., b.p. 121-122°/0.6 mm.; nD24.3 1.4504; \(\lambda_{\text{max}}\) 211 m\(\mu\), \(\varepsilon\) 6925 (10% aqueous methanol).

4. A solution of sodium ethoxide was prepared by dissolving 0.2644 g. of sodium metal (0.0115 mole) in 30 ml. of ethanol. The unsaturated triester obtained in pyridine (3.0403 g., 0.0111 mole) was added and the solution was refluxed for 4 hours and 40 minutes. After neutralization with glacial acetic acid, 120 ml. of ether was added and the solution worked up as above. Distillation yielded 0.3261 g. of forerun and 2.1008 g., b.p. 132-134°/1.3 mm.; nD29 1.4490; \(\lambda_{\text{max}}\) 213 m\(\mu\), \(\varepsilon\) 8550
(10% aqueous methanol).

The proton magnetic resonance data were obtained on a Varian 40 Mc spectrometer from 30% solutions in carbon tetrachloride with tetramethylsilane as internal standard.

**Vapor phase chromatography.** The vapor phase chromatographic analyses reported in this chapter were performed in a commercial Perkin-Elmer model 154-C fractometer, with helium as carrier. A commercial Perkin-Elmer type C (Silicone) column, 2 meters in length, used at 165° under 20 pounds, gave retention times of 42.3 minutes for triethyl 3-methylcyclopropane-1,1,2-trans-tricarboxylate and 45.8 minutes for the cis-isomer (top of the peaks) but did not permit the analysis of mixtures containing less than 25% of the trans-isomer.

A 2-meter column was prepared with 10% of silicone DC. 550 by weight of Chromosorb, and was used under 10 pounds pressure. The temperature was usually 189-190°, where the calibration was performed. The retention times were 8.5 minutes for the trans and 9.1 minutes for the cis-isomer (top of the peaks). At 146° under 25.7 pounds pressure, the 1,1,2-tricarbethoxy-2-butene obtained in pyridine had a retention time of 20.8 minutes, its isomer 24 minutes (top of the peaks). No sign of aging of the column was noticed. However, we found it impossible to duplicate the results of this column using a silicone DC. 550 from another container, all other conditions being identical.

**Hydrolysis of triethyl 2-butene-1,1,2-tricarboxylate.** The unsaturated triester obtained in pyridine (1.3804 g.) was refluxed for 5 hours in 30 ml. of 6 N hydrochloric acid. The solution was concentrated in vacuum to half its volume and extracted three times with 30 ml. of ethyl acetate. The organic solution was dried and the solvent evaporated.
The residue, which crystallized on standing, was recrystallized from ether-petroleum ether. There was obtained 0.3662 g., m.p. 130-143°, which after recrystallization from ethyl acetate-chloroform melted at 172.5°. Authentic ethyldenedisuccinic acid had m.p. 172° and a mixture m.p. 172.3°. The infrared spectra of the product and of the authentic ethyldenedisuccinic acid were superimposable.

**Cyclization with ethyl α-bromocrotonate in dimethylformamide.** Sodium hydride, (0.8775 g., 0.03655 mole) was added by portions and with cooling to a solution of 5.3524 g. (0.0366 mole) of diethyl malonate in 50 ml. of dimethylformamide. After stirring for 45 minutes a clear solution was obtained, which, with an additional 5 ml. of solvent, was added to a solution of 7.0717 g. (0.0366 mole) of ethyl α-bromocrotonate in 15 ml. of dimethylformamide. The reaction mixture was stirred during the addition at room temperature. The addition was adjusted to such a rate that the reaction mixture was always very slightly basic or neutral, as indicated by phenolphthalein. The addition lasted 50 minutes and the stirring was continued for 2 hours and 15 minutes. The yellow reaction mixture yielded a white precipitate upon addition of 250 ml. of ether and became colorless when washed with 50 ml. of 1.6 M nitric acid. The ether solution was then washed with 50 ml. of brine, three 50-ml. portions of saturated bicarbonate and 50 ml. of brine. After evaporation of the dried solvent, distillation of the yellow residue yielded 7.4298 g., b.p. 119°/0.7-0.9 mm., \( n_D^{29} 1.4430 \), slightly unsaturated to permanganate. Treatment with permanganate in acetone and with Norite yielded 5.2071 g., b.p. 115°/0.65 mm., \( n_D^{29} 1.4430 \), shown to contain from 60 to 65% of the cis cyclopropane triester by vapor phase chromatography, 62% by refractive indices.
Another run performed in similar conditions but analyzed by vapor phase chromatography prior to distillation was shown to contain 68% of the cis isomer in the mixture of cyclopropane triesters.

Cyclization with ethyl α-bromoisocrotonate in dimethylformamide. After reaction of 0.7849 g. (0.0326 mole) of sodium hydride with 5.2655 g. (0.0329 mole) of diethyl malonate in 55 ml. of dimethylformamide, the solution was added to 6.3380 g. (0.0329 mole) of ethyl α-bromoisocrotonate in 20 ml. of dimethylformamide over a 30-minute period, with stirring. The stirring was continued for 2½ hours. Ether (200 ml.) was added and the organic solution was washed successively with 30 ml. of 3 N nitric acid, 50 ml. of brine, two 30-ml. portions of saturated bicarbonate and 50 ml. of brine. The aqueous extracts were washed with 100 ml. of ether which was again treated with brine. After drying, the ether extracts were evaporated and the residue was distilled to yield 6.3352 g., b.p. 115⁰/0.7 mm., nD26.75 1.4445, saturated to permanganate.

This mixture of cyclopropane triesters was shown to contain 56% of the cis isomer by vapor phase chromatography and ca. 57% from refractive indices (average between determination at different temperatures).

Another cyclization performed in similar conditions but analyzed before distillation was shown to contain 63.5% of the cis isomer in the mixture of cyclopropane triesters.

Stability of triethyl 3-methylcyclopropane-cis-1,1,2-tricarboxylate in dimethylformamide. Diethyl malonate (0.100 g., 0.000625 mole) was allowed to react with 0.0139 g. (0.000557 mole) of sodium hydride in 8 ml. of dimethylformamide. Pure cis cyclopropane triester, (1.4290 g.) was added and the solution was stirred at room temperature for 3 hours and 15 minutes. Ether (200 ml.) was added and the organic solution was washed successively with 30 ml. of 3 N nitric acid, 30 ml. of brine,
two 30-ml. portions of saturated bicarbonate and 30 ml. of brine. After drying, the solvent was removed under vacuum. Vapor phase chromatography on this material and on that obtained after distillation (1.4290 g., \( n_2^D \) 1.4452) showed that no isomerization had taken place.

**Cyclization with ethyl \( \alpha \)-bromocrotonate in tetrahydrofuran.** In 25 ml. of dry tetrahydrofuran, 0.10 g. (0.00417 mole) of sodium hydride was allowed to react with 0.74 g. (0.00461 mole) of diethyl malonate. This solution was slowly added with stirring to a solution of 0.3817 g. (0.00457 mole) of ethyl \( \alpha \)-bromocrotonate in 15 ml. of tetrahydrofuran. At the beginning the reaction was extremely fast and a white precipitate was formed. The rate then dropped and the addition was completed after 3 hours. The reaction mixture was stirred overnight and acidified with 0.1 ml. of glacial acetic acid. Ether (100 ml.) was added and the solution was washed with two 20-ml. portions of water, 20 ml. of saturated bicarbonate, 20 ml. of water and dried. Distillation yielded 0.4332 g., b.p. \( 110^\circ/0.4 \text{ mm.} \), \( n_2^D \) 1.4443. Vapor phase chromatography showed that the mixture of cyclopropane triesters contained 40% of the cis isomer.

**Cyclization with ethyl \( \alpha \)-bromoisocrotonate in tetrahydrofuran.** In 10 ml. of tetrahydrofuran, 0.11 g. of sodium hydride (0.00459 mole) was allowed to react with 0.74 g. (0.00461 mole) of diethyl malonate. This solution was added with stirring to a solution of 0.3909 g. (0.00461 mole) of ethyl \( \alpha \)-bromoisocrotonate in 15 ml. of tetrahydrofuran. The rate of reaction was extremely slow and the addition was performed over a 9-hour period, followed by 11 hours of stirring at room temperature. A white precipitate had been formed but the solution was still basic. It was neutralized by 0.2 ml. of glacial acetic acid added at once,
100 ml. of ether was added, and the solution was washed with two 50-ml. portions of water, 25 ml. of saturated bicarbonate and 30 ml. of water. After drying, the solvent was removed and vapor phase chromatography of the residue showed that the mixture of the cyclopropane triesters contained 36% of the cis isomer. Distillation yielded 0.6913 g., b.p. 110°/0.4 mm., n_D^20 1.4442.

**Stability of triethyl 3-methylcyclopropane-cis-1,1,2-tricarboxylate in tetrahydrofuran.** In 20 ml. of dry tetrahydrofuran, 0.2250 g. of sodium hydride (0.0010 mole) was allowed to react with 0.1753 g. (0.00113 mole) of diethyl malonate. A solution of 0.3923 g. of cis triester (containing 10% of trans isomer) in 10 ml. of tetrahydrofuran was added and the mixture stirred for 12 hours at room temperature. Ether (100 ml.) was added after acidification with 1 ml. of glacial acetic acid and the solution was washed with two 20-ml. portions of water, 20 ml. of saturated bicarbonate and 20 ml. of water. After drying, the solvent was evaporated and vapor phase chromatography showed that no isomerization had taken place.

**Cyclization with ethyl α-bromocrotonate in dioxane.** In 27 ml. of dioxane distilled over sodium hydride, 0.1342 g. (0.0056 mole) of sodium hydride was allowed to react with 0.95 g. (0.0059 mole) of diethyl malonate. After 1 hour of stirring a clear colorless solution was obtained, which was added (with 5 ml. more solvent) to a solution of 1.0763 g. (0.0056 mole) of ethyl α-bromocrotonate in 20 ml. of dioxane. The reaction mixture was stirred during the addition which lasted 4 hours and 45 minutes, and for 6 hours after its completion. A yellow precipitate was formed during the reaction. The solution was acidified with 0.1 ml. of glacial acetic acid and 100 ml. of ether was
added. The organic solution was washed with two 25-ml. portions of water, 25 ml. of saturated bicarbonate, 25 ml. of water and dried. Distillation at 0.4 mm. yielded 0.7340 g., b.p. 110°, n^25 D 1.4441. Vapor phase chromatography showed that it contained 41% of the cis isomer in the mixture of the cyclopropane triesters.

Cyclization with ethyl α-bromoiso-crotonate in dioxane. After reaction of 0.1037 g. (0.00432 mole) of sodium hydride with 0.3 g. (0.005 mole) of diethyl malonate in 25 ml. of dry dioxane, the solution was added dropwise to a solution of 0.8413 g. (0.00435 mole) of ethyl α-bromoiso-crotonate in 10 ml. of dioxane. The reaction mixture was stirred during the addition which lasted 4 hours and 45 minutes and for 4½ hours thereafter. A white precipitate was formed during the addition. Since the reaction mixture was slightly basic, 0.1 ml. of glacial acetic acid was added. After addition of 100 ml. of ether, the organic solution was washed with two 25-ml. portions of water, 25 ml. of saturated bicarbonate, 25 ml. of water and dried. Distillation yielded 0.5371 g., b.p. 110°/0.4 mm., n^25 D 1.4438, containing 33% of the cis isomer in the mixture of cyclopropane triesters as shown by vapor phase chromatography.

Stability of triethyl 3-methylcyclopropane-1,1,2-tricarboxylate in dioxane. In 25 ml. of dioxane, 0.0636 g. of sodium hydride (0.00265 mole) was allowed to react with 0.5 g. (0.00312 mole) of diethyl malonate. To this solution was added 0.3 g. (0.00292 mole) of cis cyclopropane triester (containing 10% of the trans isomer) in 10 ml. of dioxane and the solution was stirred at room temperature for 12 hours. After acidification with glacial acetic acid, addition of ether and working up as previously described, vapor phase chromatography showed that no isomerization had taken place.
Cyclization with ethyl α-bromocrotonate in 1-methyl-2-pyrrolidinone.
The solvent was dried overnight over sodium hydride and distilled at
atmospheric pressure (b.p. 203°). A clear solution was obtained after
stirring for one hour 0.1092 g. (0.00455 mole) of sodium hydride with
0.85 g. (0.0053 mole) of diethyl malonate in 15 ml. of N-methyl-
pyrrolidone. The solution, with 5 ml. of additional solvent, was
added dropwise to a solution of 0.8471 g. (0.00439 mole) of ethyl
α-bromocrotonate in 10 ml. of N-methylpyrrolidone while stirring.
The reaction occurred very rapidly but no precipitate was formed
during the addition which lasted 1 hour and 35 minutes. The stirring
was continued for 6½ hours, when the reaction mixture was neutral.
Glacial acetic acid (0.1 ml.) was added to the dark yellow solution,
followed by 100 ml. of ether, and the solution was washed with two 25-
ml. portions of water, 25 ml. of saturated bicarbonate, and two 25-ml.
portions of water. The solution was dried and the solvent evaporated.
Distillation yielded 0.5012 g., b.p. 110°/0.42 mm., nD²⁴ 1.4445, slightly
yellow. Vapor phase chromatography showed that the mixture of cyclo-
propane triesters contained 66% of the cis-isomer.

Cyclization with ethyl α-bromoisoocrotonate in 1-methyl-2-pyrrolidinone.
In 20 ml. of dry N-methylpyrrolidone, 0.1097 g. (0.00456 mole) of
sodium hydride was allowed to react with 0.85 g. (0.0053 mole) of diethyl
malonate. This solution was added dropwise with stirring over a 2-hour
period to 0.8631 g. (0.00447 mole) of ethyl α-bromoisoocrotonate in 10
ml. of N-methylpyrrolidone. Stirring was continued for 7 hours, 0.1
ml. of glacial acetic acid was added and the solution worked up exactly
as above. Distillation yielded 0.5910 g., b.p. 110°/0.42 mm.,
nD²⁴ 1.4440. Vapor phase chromatography showed that the mixture of
cyclopropane triesters contained 56% of the cis-isomer.

**Stability of triethyl 3-methylcyclopropane-1,1,2-tricarboxylate in 1-methyl-2-pyrrolidinone.** In 5 ml. of N-methylpyrrolidone, 0.0032 g. (0.000341 mole) of sodium hydride was allowed to react with 0.0655 g. (0.000409 mole) of diethyl malonate. A solution of 0.1301 g. (0.000479 mole) of cis cyclopropane triester (containing 10% of the trans isomer) in 5 ml. of the same solvent was added and stirred for 12 hours.

Glacial acetic acid (0.2 ml.) was added, followed by 50 ml. of ether. The solution was washed twice with 10 ml. of water, then with 10 ml. of saturated bicarbonate and with 10 ml. of water. After drying, the solvent was evaporated and analysis of the residue with vapor phase chromatography showed that no isomerization had taken place.

**Cyclization with ethyl α-bromocrotonate in dimethyl sulfoxide.** The solvent was distilled over barium oxide at 37° and 25 mm. A slightly yellow, clear solution was obtained after stirring for one hour 0.1002 g. (0.00418 mole) of sodium hydride with 0.6302 g. of diethyl malonate (0.00424 mole) in 12 ml. of dimethyl sulfoxide. The solution was added dropwise to 0.3054 g. (0.00413 mole) of ethyl α-bromocrotonate in 3 ml. of dimethyl sulfoxide. During the addition which lasted 40 minutes the reaction mixture turned dark yellow but no precipitate was formed.

Stirring was continued for 8 hours when the solution was almost neutral. Glacial acetic acid (0.1 ml.) was added, followed with 100 ml. of ether. Two phases were formed but no salt precipitated. Water (25 ml.) was added and the ether solution was washed with 25 ml. of water, 25 ml. of saturated sodium bicarbonate and 25 ml. of water, and the washings were extracted with 25 ml. of ether. After drying, the solvent was removed and distillation of the residue yielded 0.5944 g., b.p. 110°/0.45 mm.
$n_D^{24}$ 1.4446. Analysis by vapor phase chromatography showed that 73% of the cis isomer was present in the mixture of cyclopropane triesters.

**Cyclization with ethyl α-bromoisocrotonate in dimethyl sulfoxide**

Sodium hydride (0.0034 g, 0.00347 mole) was allowed to react with 0.5674 g. (0.00355 mole) of diethyl malonate in 12 ml. of dimethyl sulfoxide. This solution was added dropwise with stirring to 0.5074 g. (0.00263 mole) of ethyl α-bromoisocrotonate in 10 ml. of solvent. The addition took 30 minutes and the stirring was continued for 2½ hours. No precipitate was formed. The reaction mixture was worked up exactly as described above. Distillation yielded 0.3955 g., b.p. 110°/0.45 mm., $n_D^{24}$ 1.4459. Analysis by vapor phase chromatography showed that the mixture of cyclopropane triesters contained 73% of the cis-isomer.

**Stability of triethyl 3-methylcyclopropane-1,1,2-tricarboxylate in dimethyl sulfoxide.** In 4 ml. of dimethyl sulfoxide, 0.3097 g. (0.000404 mole) of sodium hydride was allowed to react with 0.0763 g. (0.00050 mole) of diethyl malonate. This solution was added to 0.1036 g. (0.000395 mole) of cis-cyclopropane triester (containing 10% of the trans-isomer) in 4 ml. of solvent and stirred for 18 hours. After acidification and working up, vapor phase chromatography showed that no isomerization had taken place.

**Cyclization with ethyl α-bromocrotonate in t-butyl alcohol.** Sodium hydride (0.0715 g, 0.00298 mole) was allowed to react with 0.6355 g. of diethyl malonate in 20 ml. of $t$-butyl alcohol. This solution was added with stirring over a 70-minute period to a solution of 0.5737 g. (0.00297 mole) of ethyl α-bromocrotonate in 10 ml. of $t$-butyl alcohol. A white precipitate was formed during the addition. The stirring was continued for 6 hours and 50 minutes after completion of the addition.
The reaction mixture was very slightly basic. Glacial acetic acid (0.1 ml.) was added, followed with 100 ml. of ether and the solution was washed with two 25-ml. portions of water, 25 ml. of saturated bicarbonate, 25 ml. of water and dried. Distillation yielded 0.3165 g., b.p. 110°/0.45 mm., n_D^23.6 1.4454. Vapor phase chromatography showed that the mixture of cyclopropane triesters contained 68.5% of the cis isomer.

Cyclization with ethyl K-bromoisocrotonate in t-butyl alcohol. Sodium hydride (0.0737 g. 0.00326 mole) was allowed to react with 0.6589 g. of diethyl malonate in 20 ml. of t-butyl alcohol. This solution was added with stirring to 0.6519 g. (0.00328 mole) of ethyl K-bromoisocrotonate in 10 ml. of t-butyl alcohol. The addition lasted 1 hour during which a white precipitate was formed. The stirring was con-
tinued for 11 1/2 hours. The reaction mixture was almost neutral. The addition of 0.1 ml. of glacial acetic acid was followed by 100 ml. of ether and the solution was worked up as above. Distillation yielded 0.3653 g. of yellow product, b.p. 110°/0.45 mm., n_D^24 1.4447. Vapor phase chromatography showed that the mixture of cyclopropane triesters contained 66% of the cis isomer.

Stability of triethyl 3-methylcyclopropane-1,1,2-tricarboxylate in t-butyl alcohol. Sodium hydride (0.0131 g. 0.000546 mole) reacted with 0.1200 g. (0.00075 mole) of diethyl malonate in 6 ml. of t-butyl alcohol. This solution was added to 0.1467 g. (0.00076 mole) of cyclopropane cis triester (containing 10% of the trans isomer) in 12 ml. of t-butyl alcohol and the mixture was stirred for 11 hours. The solution was acidified with 0.2 ml. of glacial acetic acid, 50 ml. of ether was added and the solution was washed twice with 10 ml. of water, with 10 ml. of saturated bicarbonate and 10 ml. of water. After drying and
evaporation of the solvent, vapor phase chromatography showed that no isomerization had taken place.
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