PART I THE SYNTHESIS OF SPIRO(3,5)NONANE

PART II THE PRESUMED SYNTHESIS OF 1,3-CYCLOBUTANE-DICARBOXYLIC ACID BY MARKOWNIKOFF AND KRESTOWNIKOFF

PART III THE SYNTHESIS OF CIS AND TRANS-1,3-CYCLO-BUTANEDICARBOXYLIC ACIDS

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ABSTRACT

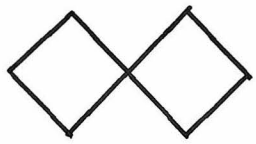
Spiro(3,5)nonane was prepared by methods indicative of structure.

The historically important acid reported in 1881 by Markownikoff and Krestownikoff and assigned the structure 1,3-cyclobutanedicarboxylic acid (a structure which has never subsequently been questioned) was shown to be 1-methyl-1,2-cyclopropanedicarboxylic acid. The mechanism of the formation of the Markownikoff-Krestownikoff acid is discussed.

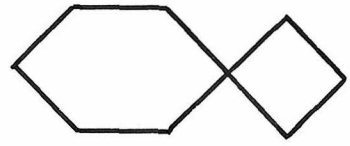
The previously unknown cis- and trans-1,3-cyclobutanedicarboxylic acids were synthesized. After numerous unsuccessful attempts the synthesis was achieved starting from pentaerythritol. The reaction between the benzylidene derivative of 2,2-bis(bromomethyl)-1,3-propandiol and sodium malonic ester gave a condensation product which after hydrolysis and oxidation with nitric acid yielded 1,1,3,3-cyclobutanetetracarboxylic acid. On decarboxylation of the latter, the desired acids were obtained.

THE SYNTHESIS OF SPIRO(3,5)NONANE (1)

The synthesis of spirane hydrocarbons containing the cyclobutane ring is a part of the general investigation of cyclobutane chemistry now in progress in this laboratory. Spiro(3,3)heptane (I), the first cyclobutane spiro-hydrocarbon to be described, was recently synthesized in this laboratory (2). In continuing this work spiro-(3,5)nonane (II) was synthesized by two different methods.



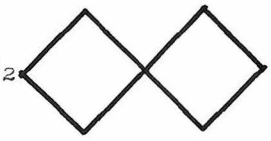
I



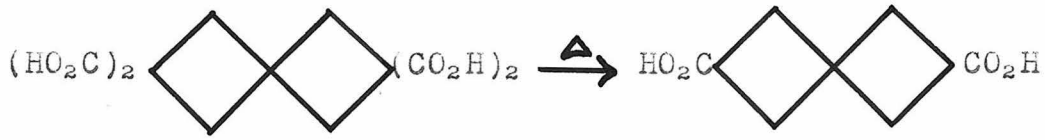
II

Relatively few preparative routes exist for the practical synthesis of spiranes containing the cyclobutane ring. Fecht's (3) early synthesis of 2,6-spiro-(3,3)heptanedicarboxylic acid (III), an extension of the Perkin (4) synthesis, illustrates one mode of spirane formation:

$$C(CH_2Br)_4 + 2CH_2(CO_2C_5H_{11})_2 + 4NaO\,C_5H_{11} \longrightarrow$$

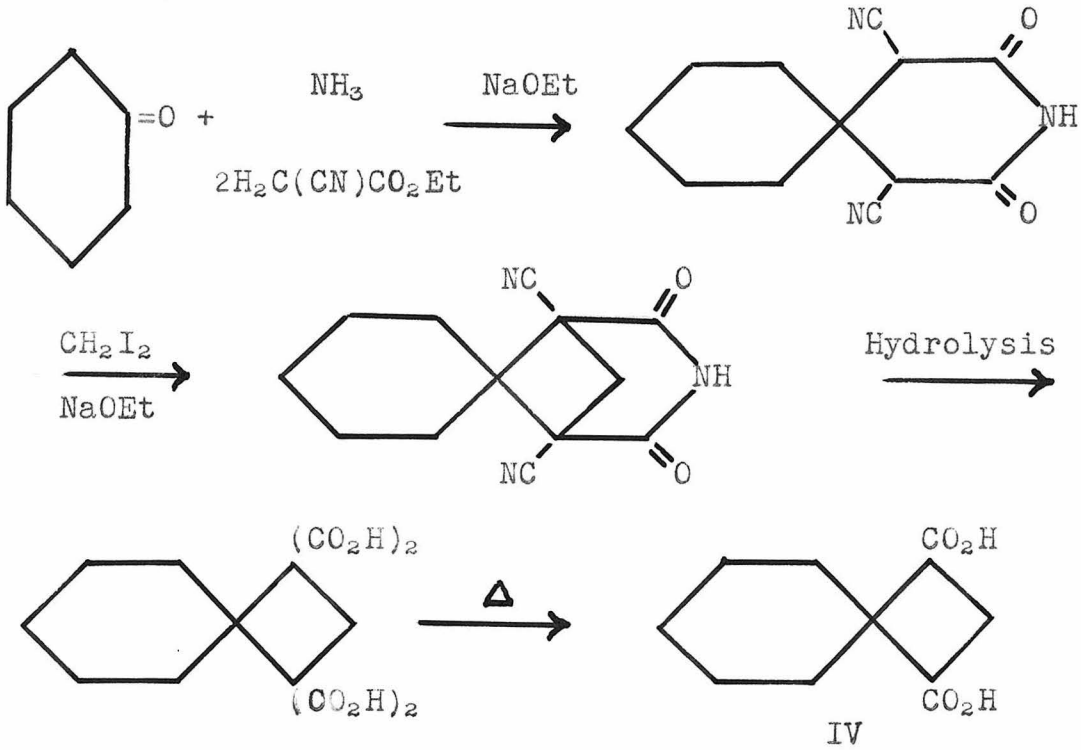


$$(H_{11}C_5O_2C)_2 \qquad (CO_2C_5H_{11})_2 \xrightarrow{\text{Hydrolysis}}$$



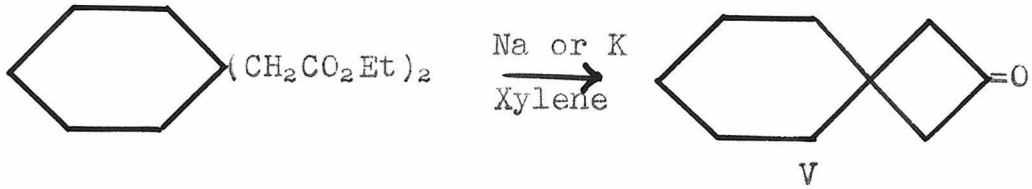
III

A variety of 1,3-spiro-cyclobutanedicarboxylic acids have been prepared through a Guareschi-type imide (5). Paul (6) synthesized 1,3-spiro(3,5)nonanedicarboxylic acid (IV) by the following reactions:



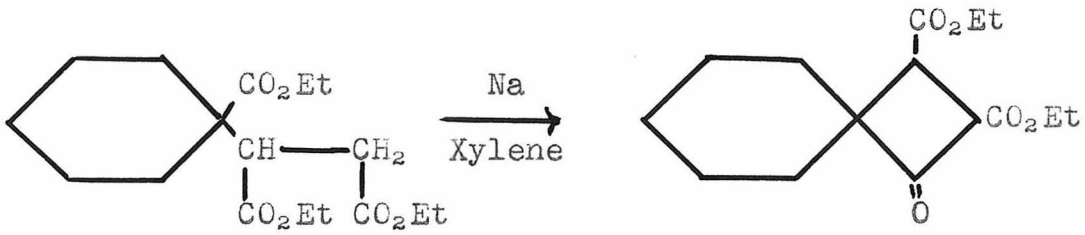
IV

Kon (7) prepared spiro(3,5)nonan-3-one, in very poor yield, by the reaction.



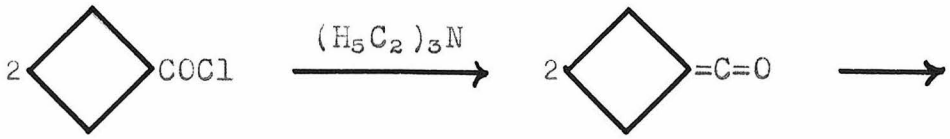
V

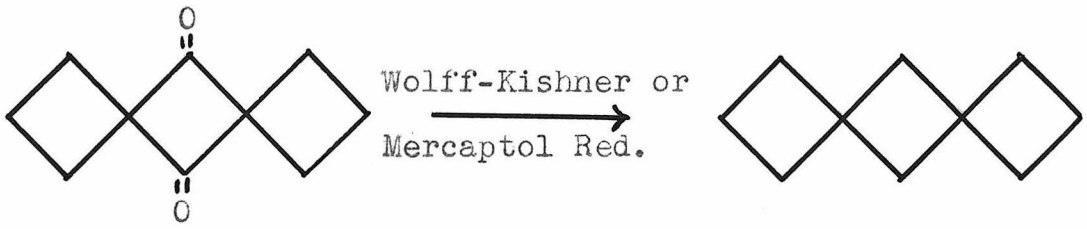
The synthesis of ethyl 1,2-spiro(3,5)nonan-3-one-dicarboxylate (VI), in very small yield, was reported by Chatterjee (8) :

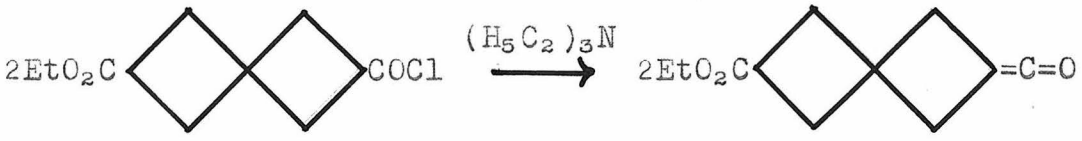


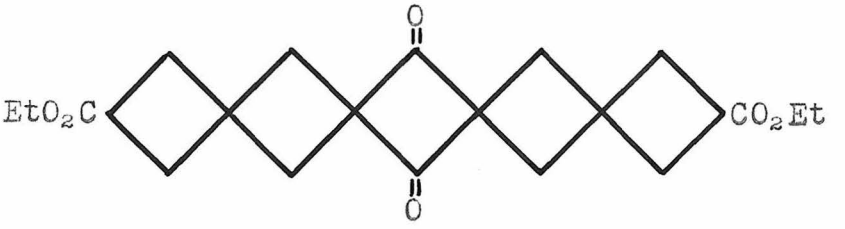
VI

Poly-spiro cyclobutanes have been prepared in this laboratory (9) by ketene dimerization (10) followed by Wolff-Kishner or mercaptol reduction:

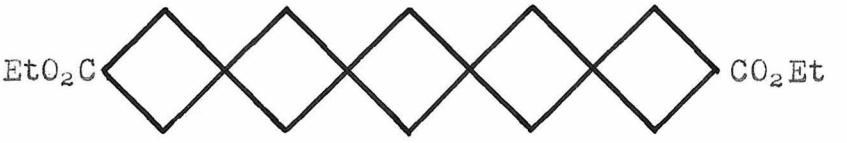




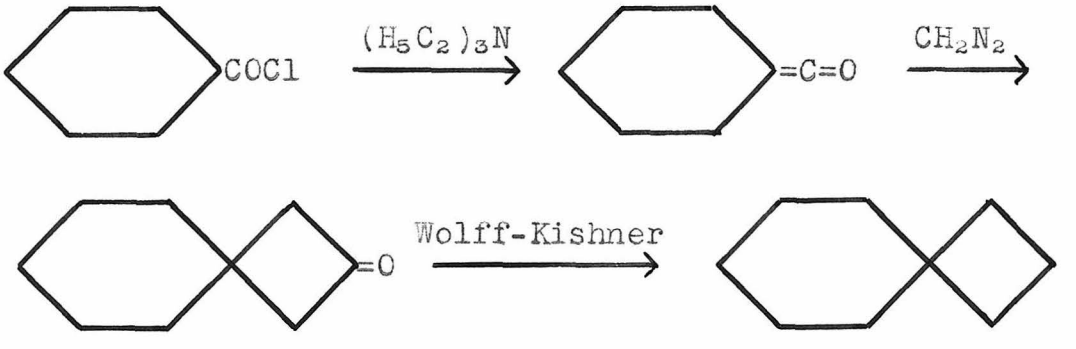




Wolff-Kishner →



Fujimoto (1), in this laboratory, prepared spiro-(3,5)nonane (II), in low yield, by the following reactions:

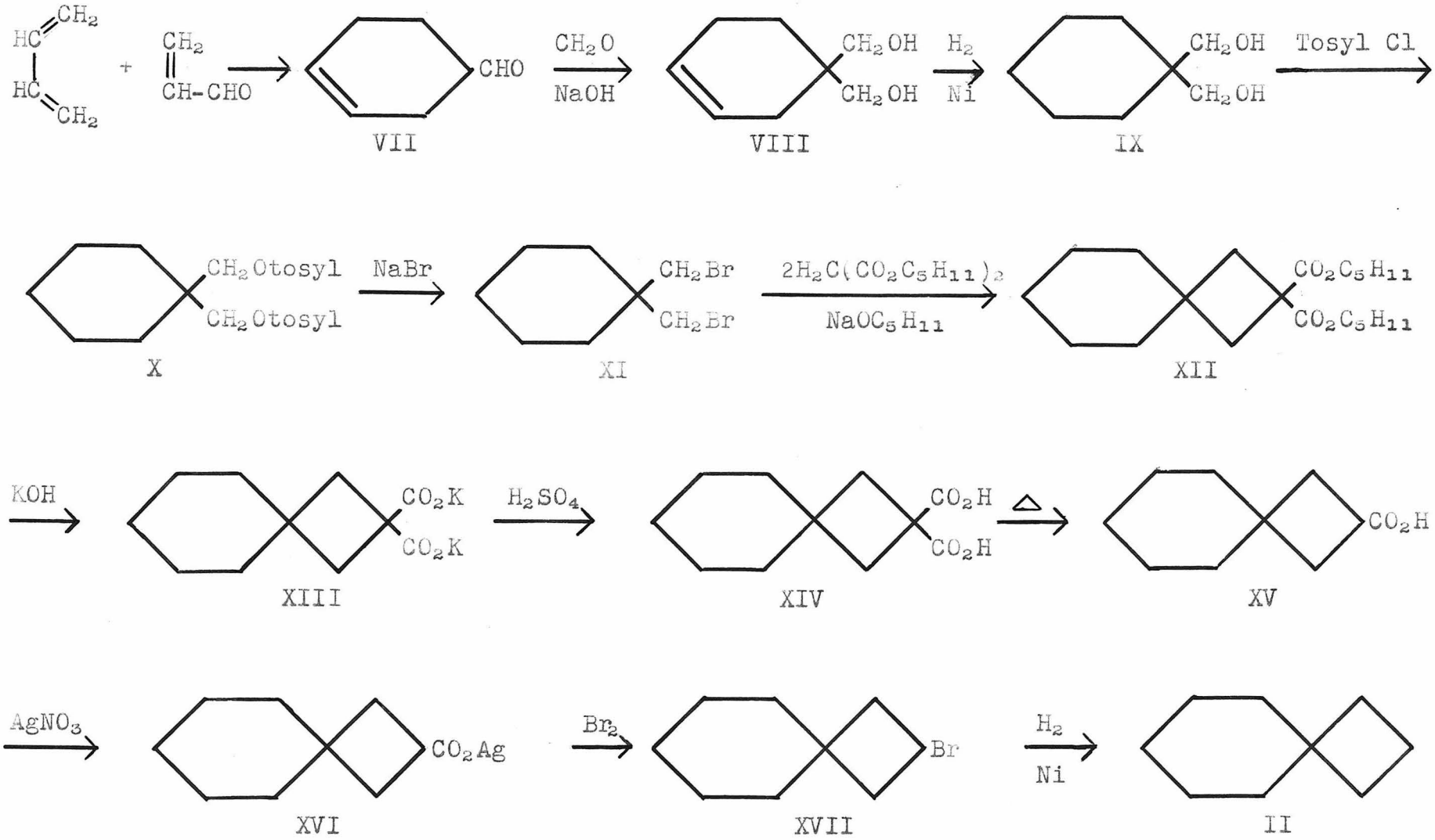


II

The synthesis of spiro(3,5)nonane (II), effected by the writer, is outlined in Table I. Bis(hydroxymethyl)-cyclohexane (IX) was prepared by the method of Boord and co-workers (11). Conversion of (IX) to bis(bromomethyl)-cyclohexane (XI) through the tosylate (X) gave yields of

Table 1

The Synthesis of Spiro(3,5)nonane



50-70%, compared to the 27% yield reported by Boord (11) using phosphorus tribromide. All the subsequent steps were carried out in good yield.

Isoamyl 2,2-spiro(3,5)nonanedicarboxylate (XII), resulting from the malonic ester synthesis carried out in isoamyl alcohol (cf.3), was saponified and decarboxylated in the usual manner. The 2-spiro(3,5)nonanecarboxylic acid (XV) was degraded to 2-bromospiro(3,5)nonane (XVII) by the Hunsdiecker reaction (12). Spiro(3,5)nonane (II) was subsequently prepared by catalytic hydrogenation of the bromide (XVII) in sodium methoxide-methanol (13).

The physical constants of the spiro(3,5)nonane (II) prepared by these two different routes agreed as did the analysis. The identity of these two samples was conclusively demonstrated by comparing their infra-red absorption spectra (Fig. 1).

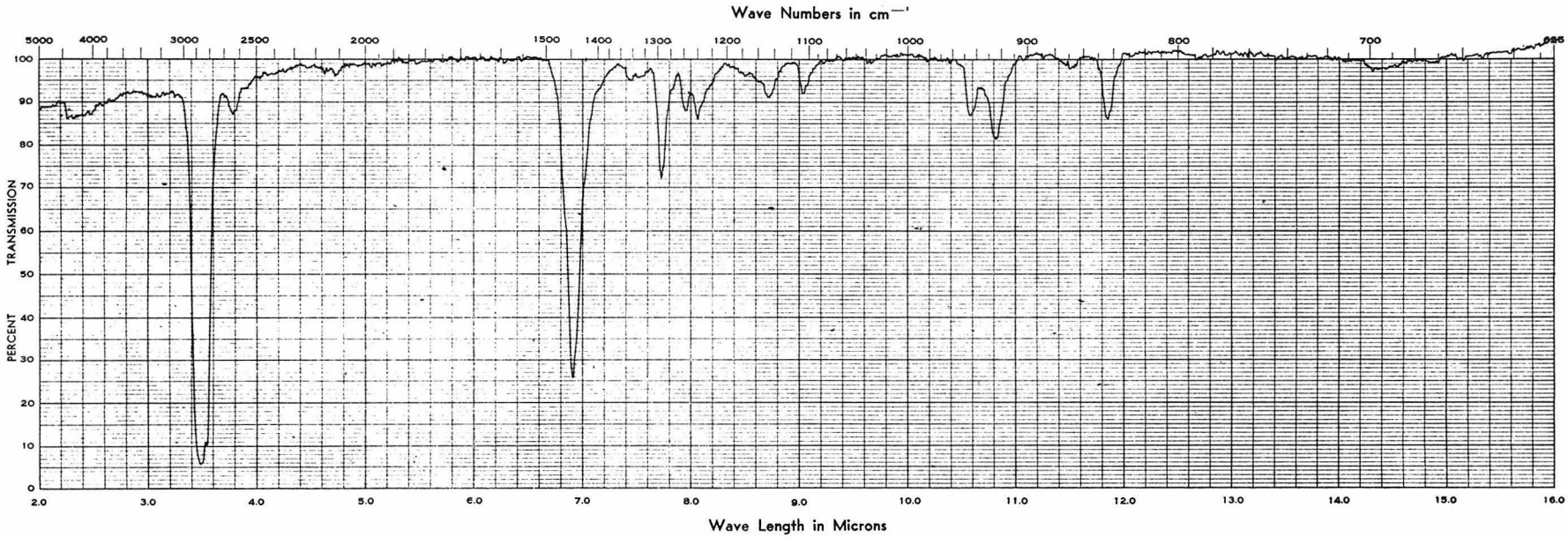


Fig. 1

Infrared absorption spectrum of spiro(3,5)nonane. Cell thickness, 0.01 mm. Courtesy Samuel P. Sadtler & Son, Inc. (Philadelphia, Pa.).

EXPERIMENTAL

3-Cyclohexene-1-carboxaldehyde (VII)

The procedure used was patterned after that described by Chayanov (14) and Boord and co-workers (11). Five moles each of acrolein (Eastman Kodak Co.) and 1,3-butadiene were placed in a one-liter bomb (American Instrument Co.) previously cooled overnight in a dry ice chest. After the addition of 5 g. of hydroquinone, the bomb was sealed and heated as rapidly as possible to 115°. The temperature rose slowly to 130°, then jumped suddenly to 230°. After the bomb was cooled, the contents were distilled through an 18-inch column. The product (VII), b.p. 89° at 75 mm., was obtained in yields of 65-75%.

4,4-Bis(hydroxymethyl)-1-cyclohexene (VIII)

Following the method of Whitmore and co-workers (15), 520 g. (4.73 moles) of 3-cyclohexene-1-carboxaldehyde (VII) was mixed with one liter of 40% formaldehyde and sufficient alcohol to form a homogeneous solution. Over a one-hour period this solution was run into 600 g. of sodium hydroxide in 2.5 l. of 95% alcohol in a 5-l. three-necked flask provided with a mechanical stirrer, reflux condenser, and dropping funnel. After refluxing for 20 hours, the alcohol was stripped off on a steam bath, and the residual black solution was continuously extracted with ether for four days. The ether was stripped off from the extract and the product (VIII) was distilled (b.p. 130° at 3-4 mm.) after the addition of two grams of Raney nickel. The pure white diol (VIII) contained traces of

oil (m.p. 89°). After one crystallization from methyl alcohol it melted at 90.5° (literature values (11) 92.0°; (16) 92.5°). The yield of (VIII) was 67%.

1,1-Bis(hydroxymethyl)-cyclohexane (IX)

4,4-Bis(hydroxymethyl)-1-cyclohexene was dissolved in methyl alcohol (40 g. per 100 ml.) and placed in a steel bomb along with 10% Raney nickel (17). Hydrogenation was carried out at 1000 p.s.i. and 70-80°. When the hydrogenation was completed, the solution was filtered free of Raney nickel; the methyl alcohol was distilled off; and the diol (IX) was dried in vacuo over sodium hydroxide; m.p. 97-98° (literature value (11) 98.5°), yield,88%.

1,1-Bis(tosyloxymethyl)-cyclohexane (X)

Three hundred sixty-eight grams (2.55 moles) of 1,1-bis(hydroxymethyl)-cyclohexane (IX) was dissolved in 2100 ml. of pyridine (Barrett Co., redistilled over barium oxide) and then cooled for 30 minutes in an ice bath. To this solution 1075 g. (6.1 moles) of tosyl chloride (Eastman Kodak Co. practical, recrystallized from petroleum ether) was then added over a twenty-five-minute period while the solution was kept cold in an ice bath and swirled occasionally. When the reaction subsided, the mixture was allowed to stand overnight at room temperature. The product was then poured into dilute hydrochloric acid. A light yellow liquid separated and quickly solidified. The tosylate (X) was filtered, washed with dilute hydrochloric acid, and crystallized twice from methyl alcohol; large prisms, m.p. 74.0-74.5°, yield,778 g.

(67%). On smaller scale (using Eastman Kodak Co. white label tosyl chloride) nearly quantitative yields were obtained.

Anal. Calcd. for $C_{22}H_{28}O_6S_2$: C, 58.38; H, 6.24. Found: C, 58.54; H, 6.39.

1,1-Bis(bromomethyl)-cyclohexane (XI)

A mixture of 778 g. (1.72 moles) of tosylate (X), 426 g. (4.13 moles, 20% excess) of sodium bromide (reagent), and 1200 ml. of diethylene glycol (Eastman Kodak Co., yellow label) was heated for three hours at 150-170° in a 5-l. flask, provided with a very efficient Hershberg stirrer. Considerable frothing took place. After the mixture was cooled to room temperature 2.5 l. of water was added. The lower organic layer was separated and the aqueous phase was extracted four times with carbon tetrachloride. The combined carbon tetrachloride extracts and dibromide were washed with water and dried over sodium sulfate. After the solvent was stripped off under a water pump, the residue was distilled through an 18-inch Vigreux column. The dibromide (XI), b.p. 110° at 5-6 mm., n_D^{25} 1.5355 (literature values (11), b.p. 117° at 6 mm., n_D^{25} 1.5390), was obtained in 79% yield (366 g.). The yield of dibromide (XI) based on diol was 53%. When Eastman Kodak Co. white label tosyl chloride was used on a smaller scale, the yield of dibromide was 65-70% based upon diol.

Isoamyl 2,2-spiro(3,5)nonanedicarboxylate (XII)

A solution of 85.0 g. (3.7 moles, 25% excess) of sodium in three liters of isoamyl alcohol (previously

dried by distilling from magnesium turnings) was prepared in a 5-l. flask. To this, 594 g. (3.7 moles) of ethyl malonate (Eli Lilly Co., dried by distillation) was added and the mixture was refluxed for one hour, during which time ethyl alcohol was distilled off. The flask was cooled and 404 g. (1.48 moles) of the dibromide (XI) and a handful of porous chips were added. The mixture was refluxed gently for 44 hours. After the flask was cooled, ice water was poured in, and the solution was neutralized with hydrochloric acid. The organic phase was separated, and the aqueous phase was extracted with ether. The combined ether extract and organic phase were dried over sodium sulfate, and the bulk of the ether and isoamyl alcohol was distilled off under reduced pressure from a steam bath. Fractionation of the residue, nearly 2 l., gave 241 g. of material, b.p. 165° at 4mm. to 180° at 1-2 mm., n_D^{25} 1.4590. Redistillation gave 151.5 g. (30%) of ester (XII), b.p. 195° at 4-5 mm., n_D^{25} 1.4564, d_4^{22} 0.9611.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 71.55; H, 10.29. Found: C, 71.65; H, 10.33.

2,2-Spiro(3,5)nonanedicarboxylic Acid (XIV)

To 133.5 g. (0.377 mole) of the ester (XII) in a 1-l. flask[+], 84 g. (1.5 moles) of potassium hydroxide dissolved in 500 ml. of absolute alcohol (filtered to clarify)

[+]The hydrolysis could be more conveniently carried out in a beaker.

was added all at once with swirling. A heavy white precipitate formed after a few minutes. The mixture was heated on a steam cone for twenty minutes and cooled to room temperature. The resultant cake was broken up and transferred to a sintered glass funnel. After as much of the liquid as possible was pressed out, the precipitate was air dried overnight in an open beaker. The potassium salt (XIII) had a slight yellow color and smelled strongly of isoamyl alcohol. The product was then triturated with absolute alcohol, filtered, and dried on a steam cone to constant weight, 102 g. (white and odorless). This salt (XIII) was dissolved in 200 ml. of cold water and 38 g. (0.4 mole) of sulfuric acid, diluted with an equal volume of water, was added slowly with stirring. 2,2-Spiro(3,5)nonanedicarboxylic acid (XIV) precipitated as a white solid. After being filtered and washed with cold water, the product was dried overnight in vacuo over sodium hydroxide; crude yield, 89.6 g. (theory 88.5 g.). A small portion of the acid was crystallized twice from water; m.p. 200° (dec.).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.29; H, 7.60.
Found: C, 62.35; H, 7.76.

2-Spiro(3,5)nonanecarboxylic Acid (XV)

For decarboxylation, 97.5 g. of the crude acid (XIV) was placed in a 500-ml. Claisen flask and heated to 220°. When the evolution of carbon dioxide ceased (ten minutes), the bath temperature was lowered and the 2-spiro(3,5)nonanecarboxylic acid was distilled; b.p.163° at 15 mm., d_4^{24} 1.0363,

n_D^{25} 1.4793, m.p. 21°; yield, 45.6 g. (67% based upon the ester (XII)).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.53.

The amide of 2-spiro(3,5)nonanecarboxylic acid (XV) was prepared in the usual manner from thionyl chloride, the acid, and ammonium hydroxide. After three crystallizations from water-methanol the amide melted at 156.0-156.5°.

Anal. Calcd. for $C_{10}H_{17}ON$: C, 71.81; H, 10.25. Found: C, 71.87; H, 10.27.

Silver 2-spiro(3,5)nonanecarboxylate (XVI)

A solution of 41.6 g. (0.248 mole) of the spirane acid in 300 ml. of water containing two drops of phenolphthalein was prepared. To this, a 15% aqueous potassium hydroxide solution was added until the solution just turned red. The solution was then made slightly acid with one drop of the spirane acid (XV); whereupon, the color faded completely. After this potassium salt solution was heated to 50°, it was slowly added to a mechanically stirred solution of 42.2 g. (0.248 mole) of silver nitrate in 168 ml. of water heated to 40°. The silver salt (XVI) came down as a fine white precipitate. After the mixture was cooled, the silver salt was filtered and washed with 150 ml. of water in which it was quite insoluble. (XVI) was suspended in and filtered from acetone, methyl alcohol and absolute ether in that order. The product was air-dried overnight, powered in a mortar, and transferred to a 300-ml. round-bottom flask. The flask was

evacuated with an oil pump; and after the gas evolution ceased, the flask was heated on a steam cone in vacuo for 90 minutes. After 15 minutes the visible gas evolution ceased. The yield of silver salt (XVI) was 65.0 g. (nearly quantitative).

2-Bromospiro(3,5)nonane (XVII)

Forty grams of bromine (reagent), previously dried over sulfuric acid, was dissolved in 200 ml. of carbon tetrachloride, previously dried over calcium sulfate. The bromine solution was placed in a dry 500-ml. three-necked flask provided with a reflux condenser (protected with a calcium chloride tube), a mercury-sealed Hershberg stirrer, and a short length of wide rubber tubing for the addition of the silver salt. After the flask was cooled in an ice-bath, 65.0 g. of the silver salt (XVI) was slowly added over a 45-minute period. A vigorous evolution of carbon dioxide ensued. The ice-bath was removed and the mixture was heated to reflux for 15 minutes. After the product was cooled, the solid silver bromide was filtered off and washed with carbon tetrachloride until the filtrate came through colorless (approximately 200 ml.). The combined filtrates (deep red) were washed with aqueous sodium bisulfite (color faded), and dried over sodium sulfate. After the solvent was stripped off, the 2-bromospiro(3,5)nonane (XVII) was distilled, b.p. 103-104° at 13-14 mm., n_D^{25} 1.5015, d_4^{21} 1.2544; yield, 57%.

Anal. Calcd. for $C_9H_{15}Br$: C, 53.22; H, 7.44.
Found: C, 53.58; H, 7.69.

Spiro(3,5)nonane (II)

To an ice cold solution of 4.6 g. (0.2 mole) of sodium dissolved in 150 ml. of absolute methyl alcohol, there was added 28.3 g. (0.139 mole) of 2-bromospiro(3,5)nonane (XVII). Fifteen grams of Raney nickel (17) was added and hydrogen was passed in at atmospheric pressure and room temperature. The hydrogen uptake was 92% of theory over a six-hour period. Some water was inadvertently allowed to enter the flask during the hydrogenation, but apparently it had no effect other than slowing down the rate of hydrogenation. Additional portions of 1-2 g. of catalyst were added from time to time during the hydrogenation. The resulting solution was filtered through an asbestos mat, and the residue was washed three times with ether. After the filtrate was washed three times with water and once with 6N hydrochloric acid, the ether-hydrocarbon solution was dried over potassium carbonate and then over sodium for 18 hours. The resulting solution was filtered and the ether was stripped off under reduced pressure. Distillation of the residue at atmospheric pressure (750 mm.) gave 11.83 g. of product b.p. 156-157°, which did not decolorize an aqueous or acetone solution of potassium permangenate. Redistillation of this material yielded 7.70 g. of pure spiro(3,5)nonane (II), b.p. 157.5-157.7°, d_4^{23} 0.8512, n_D^{25} 1.4580.

Anal. Calcd. for C_9H_{16}: C, 87.02; H, 12.98.
Found: C, 86.94; H, 13.11.

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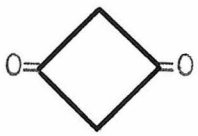
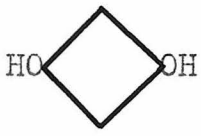
THE PRESUMED SYNTHESIS OF 1,3-CYCLOBUTANEDICARBOXYLIC ACID BY MARKOWNIKOFF AND KRESTOWNIKOFF(1)+

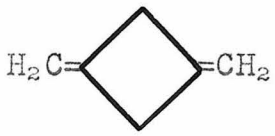
cis- and trans-1,3-Cyclobutanedicarboxylic acids (I) and (II) are of considerable interest in this laboratory as possible intermediates for the synthesis of cyclobutadiene (III). Several possible routes from (I) or (II) to (III) are given in Table I. Acids (I) and (II) are also potential sources of such interesting compounds as cyclobutan-1,3-dione (IV), cyclobutan-1,3-diol (V), and 1,3-dimethylenecyclobutane (VI).



IV



V



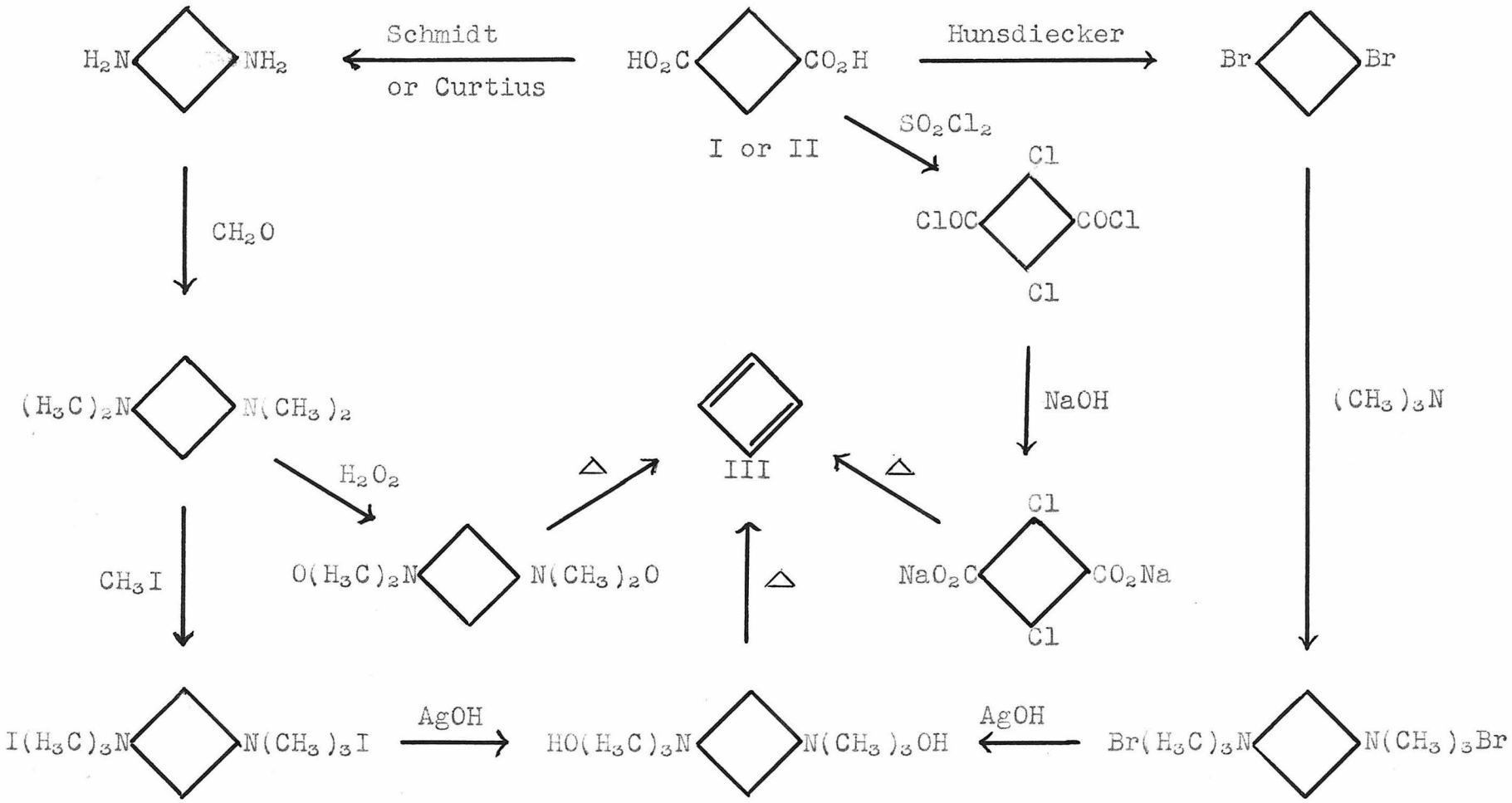
VI

An acid which was assigned the structure trans-1,3-cyclobutanedicarboxylic acid (II) was reported by Markownikoff and Krestownikoff (1) in 1881. This preparation has been accepted as the first correctly interpreted alicyclic synthesis (2). The Markownikoff-Krestownikoff synthesis was especially important to this laboratory since it had previously been shown here (3) that other syntheses of 1,3-cyclobutanedicarboxylic acid described in the literature did not furnish this compound and thus the Markownikoff-Krestownikoff synthesis appeared to be the only route to the desired acid.

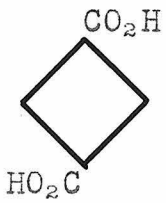
+ D. H. Deutsch and E. R. Buchman, in press.

Table 1

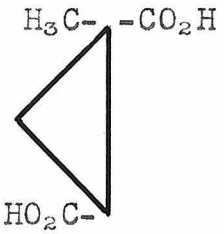
Proposed Syntheses of Cyclobutadiene from 1,3-Cyclobutanedicarboxylic Acid



As a consequence of the work presented in this section of the thesis, it was discovered that the acid prepared by Markownikoff and Krestownikoff (1) was not trans-1,3-cyclobutanedicarboxylic acid (II) but its isomer, trans-1-methyl-1,2-cyclopropanedicarboxylic acid (VII)[+]. It is indeed sur-



II



VII

prising that (despite the historical importance of this acid) this incorrect formulation had been accepted for nearly seventy years. It may be of interest to the reader to be given a resume of the literature pertaining to the Markownikoff-Krestownikoff acid.

In 1881 Markownikoff and Krestownikoff (1) reported that, by the action of alcohol free sodium ethoxide on ethyl α-chloropropionate, a small yield of ester, formulated as (VIII), was obtained which on hydrolysis gave an acid melting at 170°. On the basis of its saturated properties and elementary analysis they assigned this acid the structure (II). These authors postulated that (VIII) resulted from

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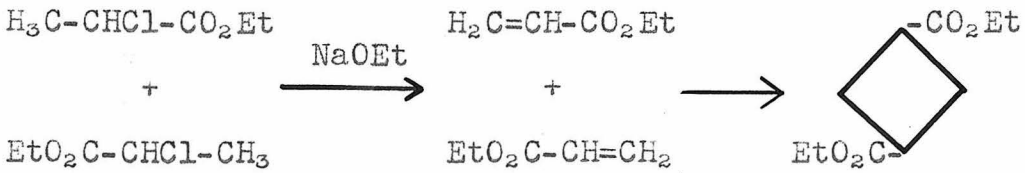
[+]Historical Note. As a result of these findings it follows that the first correctly interpreted synthesis of an alicyclic compound was Freund's (4) synthesis of cyclopropane (1882), and that ethyl 1,1-cyclobutanedicarboxylate (Perkin, jun., (5) (1883)) was the first cyclobutane derivative to be synthesized.

the symmetrical dimerization of ethyl acrylate formed from ethyl α-chloropropionate.



VIII

At a later date, Markownikoff (6) reported the conversion of his trans acid into a cis anhydride and thence into cis-1,2-cyclobutanedicarboxylic acid (IX), melting point 138-139°. Authentic (IX), having a melting point of 138°, had been synthesized a few years earlier by Perkin, jun. (7). Haworth and Perkin jun. (8) in 1898 reinvestigated the matter and agreed that Markownikoff's trans acid was represented by (II), but showed that his cis acid was not identical with (IX) since their anhydrides melted 25° apart. From this they concluded that no position isomerization had occurred and that Markownikoff's cis acid was cis-1,3-cyclobutanedicarboxylic acid (I).

The scientific world accepted the conclusions of Perkin, jun. and no further communication relating to the Markownikoff-Krestownikoff acid appeared until 1925. In connection with his studies on the relative ease of formation of small-ring compounds, Ingold (9) investigated the products of the reaction of ethyl α-bromo-γ-methylglutarate[+] (X) with potassium hydroxide. Among these were found cis-

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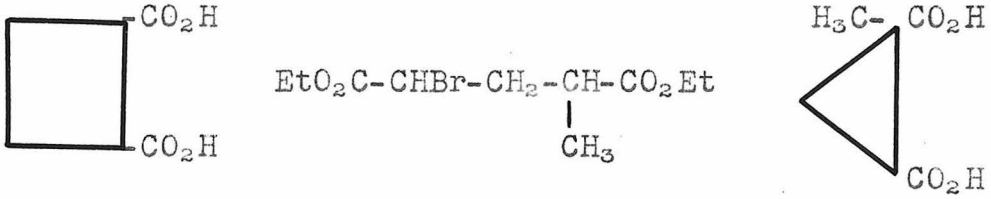
[+]The reactions of the iodo and chloro analogs of (X) were also investigated.

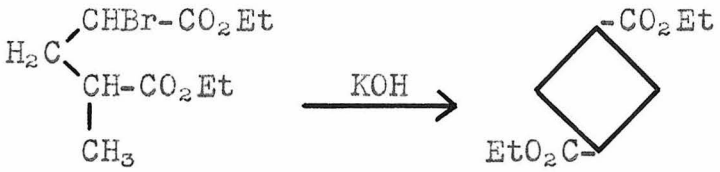
and trans-1-methyl-1,2-cyclopropanedicarboxylic acids (XI) and (VII) with melting points 142° and 168° respectively and a search was made for 1,3-cyclobutanedicarboxylic acids.



IX X XI

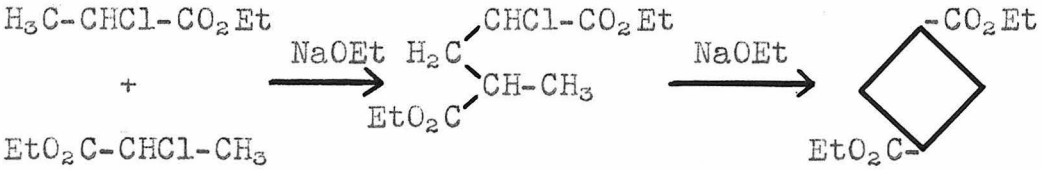
The following is a quotation from Ingold's article:

"It remains to be added that no trace of 1,3-cyclobutanedicarboxylic acid could be detected, although its formation from the bromo-ester (IV) might be expected to take place according to the scheme:



IV

If the mechanism of the formation of cyclobutane-1:3 dicarboxylic ester from α-chloropropionic ester by the action of sodium ethoxide (Markownikoff and Krestownikoff, Annalen 1881,208 333) is, as might naturally be supposed, the following:



XXII XXIII

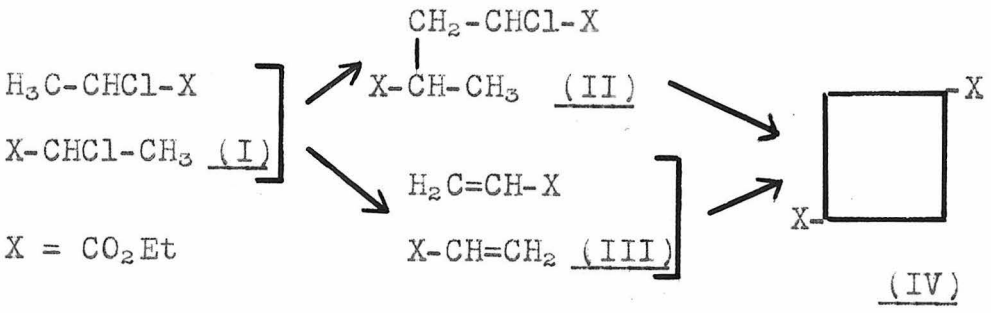
for the hypothetical intermediate product (XXII) is the chloro analogue of the bromo-ester (IV). Moreover, the chlorine compound (XXII) has been prepared synthetically, by the chlorination of α-methylglutaric acid, and all attempts to convert it into the cyclobutane ester (XXIII) by

the agency of sodium ethoxide have hitherto failed.

It has been thought right to mention these negative results here, as, although the mechanism of the Markownikoff-Krestownikoff reaction is at present under investigation, the matter is of such complexity that it may well baffle enquiry for a considerable time."

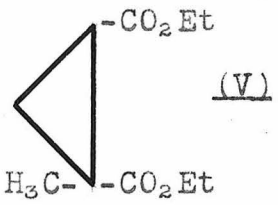
In the same year that the above article appeared, Goss and Ingold (10) wrote a stimulating article, "The Possible Enhanced Activity of Newly Formed Molecules". These authors had noted that numerous cases have arisen where chemists have been unable to confirm apparently obvious reaction mechanisms by preparing supposed intermediate products and subjecting them to the conditions of the original experiment: the substances remain unaltered or behave differently from expectation. In this connection Goss and Ingold cited:

"Two mechanisms suggest themselves for the formation of the cyclobutane ester (IV) (Markownikov and Krestownikov, Annalen 1880, 208 334) from chloropropionic ester (I) and sodium ethoxide: the elimination of hydrogen chloride is either inter-molecular, in which case α-chloro-γ-methyl glutaric ester (II) is the intermediate product, or intra-molecular, ethyl acrylate (III) being first formed

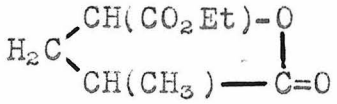


The chloro-ester (II) has been prepared and subjected to the action of sodium ethoxide under the same conditions. It gave no detectable quantity of the cyclobutane ester, but on the other hand, yielded the cyclopropane ester (V) together with the lactone ester (VI), the unsaturated ester (VII) and the

ethoxy-ester (VIII).



(V)

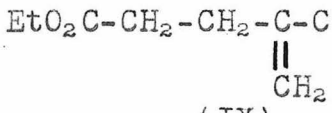


(VI)

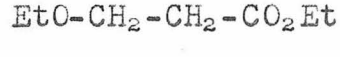
$EtO_2C-CHMe-CH=CH-CO_2Et$ (VII)

$EtO_2C-CHMe-CH_2-CH(OEt)-CO_2Et$ (VIII)

Acrylic ester (III) was treated in a similar method. Again no cyclobutane ester could be detected, but only its unsaturated isomeride, α-methyleneglutaric ester (IX)



(IX)



(X)

which was the chief product apart from β-ethoxypropionic ester (X)."

The experimental section of this paper, consisting of the following three parts, is particularly noteworthy: (a) Repetition of the original Markownikoff-Krestownikoff procedure gave the suppo sed trans-1,3-cyclobutanedicarboxylic acid (II), melting point 170°. (b) Treatment of ethyl α-chloro-γ-methylglutarate under the Markownikoff-Krestownikoff conditions gave trans-1-methyl-1,2-cyclopropanedicarboxylic acid (VII), melting point 168°, together with α-methyleneglutaric acid and α-ethoxy-γ-methylglutaric acid. (c) Ethyl acrylate under the Markownikoff-Krestownikoff conditions gave 10% of α-methyleneglutaric acid and 90% of β-ethoxypropionic acid. How the identifications of trans-1,3-cyclobutanedicarboxylic acid (II) and trans-1-

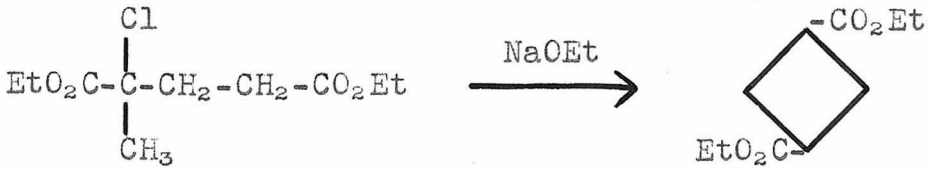
methyl-1,2-cyclopropanedicarboxylic acid (VII) were arrived at was not stated.

The last published work on the Markownikoff-Krestownikoff acid came from this laboratory when Buchman, Reims and Schlatter (3) corroborated Markownikoff and Krestownikoff's synthesis and assumed the product to be 1,3-cyclobutanedicarboxylic acid.

In the hands of this author, the preparation of the Markownikoff acid proved very unsatisfactory. Modifications in the Markownikoff-Krestownikoff procedure were carried out with the hope of devising a better synthesis of 1,3-cyclobutanedicarboxylic acid through an elucidation of the reaction mechanism. Despite the fact that ethyl acrylate under the Markownikoff-Krestownikoff conditions gave no four-member ring compound (10) and ethyl α-chloropropionate gave only 5% of the Markownikoff-Krestownikoff acid, the writer considered it likely that an equimolar mixture of these two esters under the Markownikoff-Krestownikoff conditions might give a higher yield of the desired acid. The result of this experiment was a 30% yield of an acid identical with that obtained by the original Markownikoff-Krestownikoff procedure.

Dr. Saul Winstein of the University of California at Los Angeles had proposed (11) that the intermediate in the Markownikoff-Krestownikoff reaction, resulting from the condensation of ethyl α-chloropropionate and ethyl acrylate, (formed from ethyl α-chloropropionate by the action of sodium

ethoxide) might be ethyl α-chloro-α-methylglutarate (XII). Although a satisfactory mechanism for the reaction:



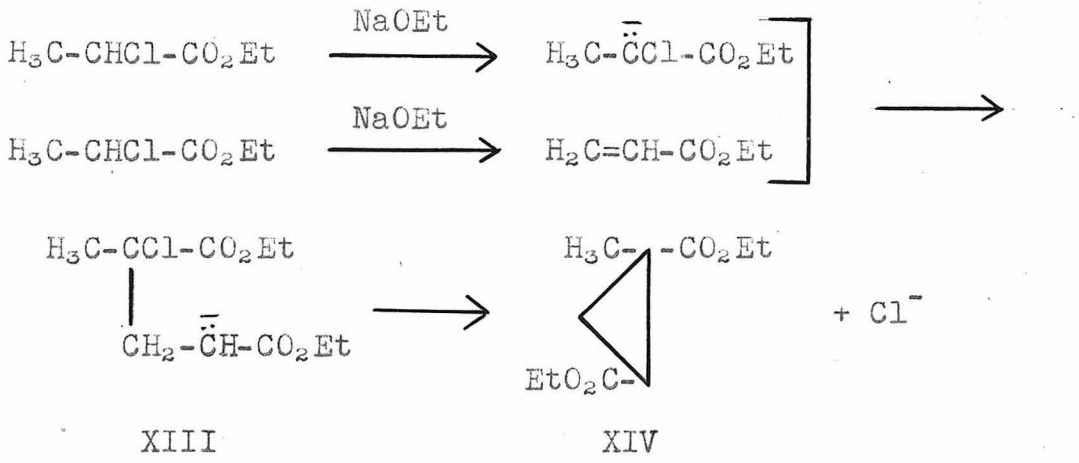
XII VIII

could not be devised, the experiment just described strengthened the case for (XII) as an intermediate in the Markownikoff-Krestownikoff reaction.

Since it was not clear how (XII) could give (VIII), I proceeded to re-examine whether the structure of the Markownikoff-Krestownikoff acid had been correctly assigned. It immediately became apparent, from a close study of the literature, that no absolute structure proof had ever been adduced. In fact, all the previous work on the Markownikoff-Krestownikoff acid gave no positive indication that a four-membered ring was present. A previously known finding which favored a three-membered ring over a four-membered ring was the instability of the cis form of the Markownikoff-Krestownikoff acid noted by Haworth and Perkin, jun. (8), and verified by Buchman, Reims and Schlatter (3) during attempts to convert the supposed cis-1,3-cyclobutanedicarboxylic acid to the trans form by heating with concentrated hydrochloric acid at 180° for several hours.

An important additional consideration led the writer to the trans-1-methyl-1,2-cyclopropanedicarboxylic acid (VII) structure as a probable formulation of the Markownikoff-Krestownikoff acid. This was that it was possible in an ortho-

dox manner to explain the formation of (VII) from the Markownikoff-Krestownikoff starting materials. The course of the reaction may be represented as follows:

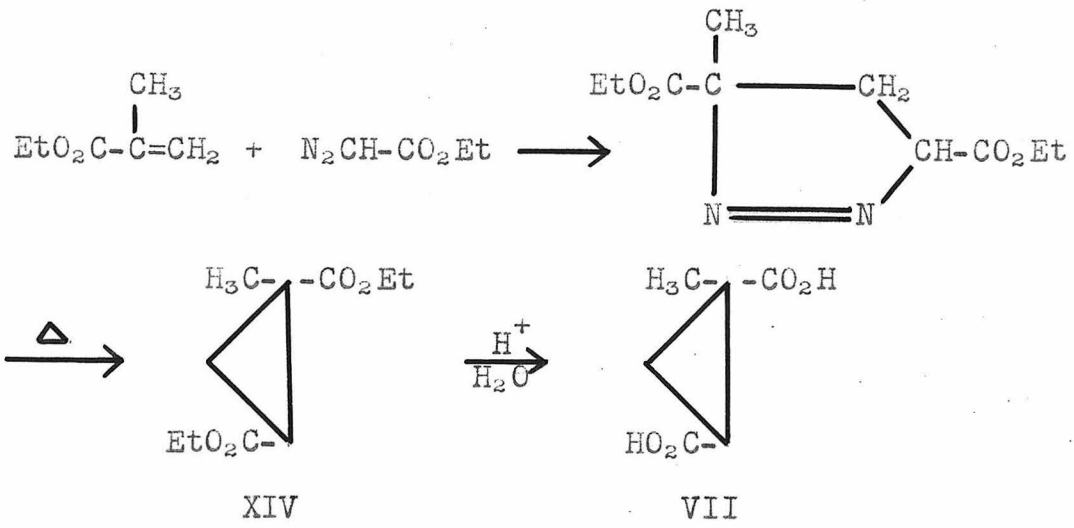


XIII XIV

A search of the literature substantiated the above formulation. The reported melting point (169°) of trans-1-methyl-1,2-cyclopropanedicarboxylic acid (VII) (9,12,14,15) agreed with the melting point (170-173°) of the Markownikoff-Krestownikoff acid (1,3,6,8,10); the melting point (141-142°) reported for cis-1-methyl-1,2-cyclopropanedicarboxylic acid (XI) (9,12,13) coincided with the melting point (142-143°) of the cis form of the Markownikoff-Krestownikoff acid (3, cf. 6,8); and the melting point (37-42°) reported for the anhydride of cis-1-methyl-1,2-cyclopropanedicarboxylic acid (12) was in reasonable agreement with the melting point (47.5-48.0°) found for the anhydride of the cis form of the Markownikoff-Krestownikoff acid (3,8).

The Markownikoff-Krestownikoff acid and the acid obtained from ethyl acrylate and ethyl α-chloropropionate under the Markownikoff-Krestownikoff conditions were conclusively demonstrated to be identical with trans-1-methyl-1,2-cyclopropanedicarboxylic acid (VII). Authentic (VII) was unambig-

uously synthesized from ethyl methacrylate and diazoacetic ester followed by acid hydrolysis (cf. 12,13).

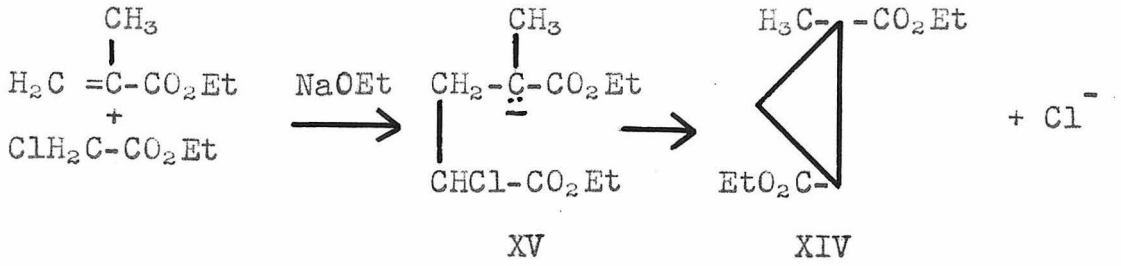


XIV VII

The trans-1-methyl-1,2-cyclopropanedicarboxylic acid (VII) thus obtained melted at 172.2-172.7° and gave no depression when mixed with either of the samples of the Markownikoff-Krestownikoff acid. The p-toluidide of each of these samples of acid had melting points of 205-206.5° and 211-212° +.

From an understanding of the Markownikoff-Krestownikoff reaction mechanism it follows that a 1:1 mixture of ethyl methacrylate and ethyl chloroacetate under the Markownikoff-Krestownikoff reaction conditions could likewise give ethyl trans-1-methyl-1,2-cyclopropanedicarboxylate (XIV) by the following reaction:

+Two enantiotropic forms of the p-toluidide exist.



XV XIV

This was experimentally realized. The lower yield (10%) obtained by this last method resulted from the difference in structure of the intermediate ions (XIII) and (XV). In ion (XIII) the chlorine is on a tertiary carbon and hence is considerably more reactive than in ion (XV) where the corresponding carbon is secondary. Also, the carbon bearing the negative charge in (XIII) is secondary and hence will form more easily than the corresponding ion (XV) where the electron donating methyl group tends to repel the negative charge on the adjoining α carbon atom.

An attempt to synthesize (XIV) by subjecting ethyl α-chloro-α-methylglutarate (XII) to the Markownikoff-Krestownikoff conditions was unsuccessful, perhaps due to the inability to obtain (XII) in a pure state (cf. 16,17). Also, it should be noted that the ion (XIII), postulated as an intermediate in the Markownikoff-Krestownikoff reaction, may not be formed from (XII).

EXPERIMENTAL

trans-1-Methyl-1,2-cyclopropanedicarboxylic acid (VII)

From ethyl acrylate and ethyl α-chloropropionate

Twenty-six grams (1.13 moles) of sodium was dissolved in 500 ml. of absolute alcohol, and the excess alcohol was distilled off under reduced pressure. The last trace of alcohol was removed by heating at 180° for forty-five minutes under the full vacuum of an oil pump. After the flask was cooled to 50°, nitrogen was admitted. A total reflux partial take-off head and a dropping funnel were connected to the sodium ethoxide flask, and a mixture of 100 g. (1.0 moles) of ethyl acrylate and 137 g. (1.0 mole) of ethyl α-chloropropionate was slowly added to the sodium ethoxide from the dropping funnel. By maintaining the reaction flask bath temperature at 120-130°, the reaction proceeded briskly. Ethyl alcohol distilled out (the temperature at the top of the column was 78-80°) as the mixed esters were added. After the addition was completed (thirty minutes), the reaction mixture was maintained at 130° for an additional thirty minutes. The product was cooled in an ice bath and then poured into 400 ml. of water containing 20 ml. of 12N hydrochloric acid. The organic phase which separated was washed with aqueous sodium bicarbonate and combined with the ether extract of the aqueous phase. After the ether solution was dried over sodium sulfate, the ether was stripped off, and the residue was distilled. The following fractions were collected:

A	55-115° at 20 mm.[+]		
B	115-124° at 20 mm.	n_D^{26} 1.436	62.8 g.
C	124° at 20 mm. (center cut)	n_D^{26} 1.437	4.1 g.
D	124-128° at 20 mm.	n_D^{25} 1.436	16.8 g.

Fractions B and D distilled mainly at 124° at 20 mm. The yield of crude ethyl 1-methyl-1,2-cyclopropanedicarboxylate was 83.7 g. (41.8%). Fractions B, C, and D were combined and hydrolyzed by refluxing with 1 l. of 6N hydrochloric acid for sixteen hours. The resulting solution was boiled with Norite for ten minutes to remove the color, filtered, and evaporated down to dryness on a steam cone under reduced pressure. Two recrystallizations of the white crystalline residue from hot water gave 41.4 g. (28.5%) of pure trans-1-methyl-1,2-cyclopropanedicarboxylic acid (VII), m.p. 172-173°. The moderate amount of cis isomer (XI) which remained in the mother liquors was not worked up.

The p-toluidide of (VII) was prepared by refluxing 0.5 g. of (VII) with 1.5 g. of p-toluidine for seventy-five minutes, bath temperature 210°. After cooling, the residue was triturated with dilute hydrochloric acid and recrystallized three times from absolute alcohol, clusters of thin prisms. The p-toluidide had two enantiotropic modifications α and β m.p. 205.5-206.0° and 211.0-212.0° respectively. When the rate of heating was one degree per minute or less, modification α was observed; but when the rate of heating was three degrees or more per minute, modification β was noted. At an

[+] α and β-ethoxypropionic esters were formed as by-products.

intermediate rate of heating, softening was noted at the melting point of α.

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.50; H, 6.88. Found: C, 74.46; H, 6.87.

From ethyl methacrylate and diazoacetic ester (cf. 12, 13)

A mixture of 57 g. (0.5 mole) of ethyl methacrylate and 52 g. (0.5 moles) of diazoacetic ester (Org. Syn., 24, 56) was slowly added to 110 ml. of refluxing xylene. The nitrogen evolution became vigorous after approximately one-third of the mixture was added. Refluxing was continued for three hours after the addition was completed. After the bulk of the xylene was stripped, the esters of (VII) and (IX) were distilled, b.p. 120-125° at 20 mm.; yield, 34.5 g. (34.5%). Basic sponification of these ester with 100% excess of alcoholic potassium hydroxide, followed by acidification and ether extraction gave a mixture of the cis and trans acids (XI) and (VII). Repeated recrystallization from water and then from acetone-benzene yielded the pure trans-1-methyl-1,2-cyclopropanedicarboxylic acid (VII), m.p. 172.2-172.7°. The melting point of a sample of this acid showed no depression when mixed with a sample of (VII) which was prepared from ethyl acrylate and ethyl α-chloropropionate.

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.60. Found: C, 50.10; H, 5.57.

The p-toluidide of (VII) was prepared as above, m.p. 205.0-205.7° and 211.5° respectively for the α and β forms.

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.50; H, 6.88. Found: C, 74.36; H, 6.96.

From ethyl chloroacetate and ethyl methacrylate

Starting from ethyl chloroacetate and ethyl methacrylate, (VII) was prepared by the same procedure as was employed when starting from ethyl α-chloropropionate and ethyl acrylate. The yield of (VII), m.p. 172.5-172.7°, was 10% (estimated). The mixed melting point of this sample of the trans acid and one prepared from ethyl methacrylate and diazoacetic ester showed no depression.

From ethyl α-chloropropionate (1)

Starting from ethyl α-chloropropionate, (VII) was prepared by essentially the same procedure as was employed starting from ethyl α-chloropropionate and ethyl acrylate. This is the Markownikoff-Krestownikoff synthesis of (VII). The yield of (VII), m.p. 172-173° was 2-4%.

The p-toluidide of (VII) was prepared as described above. The α and β forms melted at 206.5° and 211.6° respectively.

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.50; H, 6.88.
Found: C, 74.42; H, 6.86.

The attempted preparation of ethyl α-chloro-κ-methylglutarate (XII).

A 250-ml. flask provided with a reflux condenser, a calcium chloride tube, and a hydrogen chloride trap was cooled in a dry ice bath. To the flask were added 150 ml. of dry chloroform, 21.4 g. (0.147 mole) of γ-carboxy-γ-valerolactone[+] (m.p. 70.5-71.5°) and 62.5 g. of phosphorus pentachloride.

[+]γ-Carboxy-γ-valerolactone was prepared by the procedure of J.Block, K.Kreckler, and B.Tollens (18, cf. 17).

The dry ice bath was removed, and the temperature was slowly raised until the chloroform refluxed. A vigorous evolution of hydrogen chloride ensued, and all of the phosphorus pentachloride dissolved. After the gas evolution ceased, the chloroform, phosphorus oxychloride, and excess phosphorus pentachloride were removed in vacuo. The residue was cooled to 0°, and 50 ml. of absolute alcohol was added. After standing overnight, the solution was poured into ice-cold aqueous sodium bicarbonate whereupon a light yellow liquid separated. The aqueous phase was extracted twice with ether; the ether extract combined with the product, was dried over sodium sulfate and the ether was stripped off in vacuo. Distillation of the residue through an 8-inch column gave 13.1 g. of material, b.p. 98-100° at 0.5 mm., n_D^{25} 1.4460. Redistillation yielded two fractions: A, b.p. 102-105° at 0.5 mm., n_D^{25} 1.4481 and B, b.p. 105-107° at 0.5 mm., n_D^{25} 1.4471. A portion of fraction B was analyzed.

Anal. Calcd. for $C_{10}H_{17}O_4Cl$: C, 50.74; H, 7.24; Cl, 14.98. Found: C, 51.04; H, 6.55; Cl, 10.81.

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(8) E. Haworth and W. H. Perkin, jun., ibid., 73, 332 (1898).

(9) C. K. Ingold, ibid., 127, 387 (1925).

(10) F.R. Goss and C. K. Ingold, ibid., 127, 2776 (1925).

(11) Private communication from Dr. Saul Winstein. Cf. B. Keilin, Thesis for the degree of Master of Science, Calif. Inst. of Tech., 1945, p.22.

(12) K. v. Auwers and F. König, Ann., 490, 276 (1932).

(13) K. v. Auwers and E. Cauer, ibid., 470, 304 (1929).

(14) H. Staudinger, O. Mutwyler, L. Ruzicka and S. Seibt, Helv. Chim. Acta, 7, 401 (1924).

(15) K. E. Wilzbach, F. R. Mayo and R. Van Meter, J. Amer. Chem. Soc., 70, 4069 (1948).

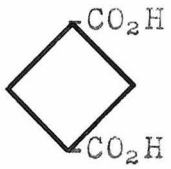
(16) J. Brent, Ber., 19, 513 (1886).

(17) J. W. Baker, Proc. Leeds Phil. and Lit. Soc., Sci. Sec., 2, 115 (1930).

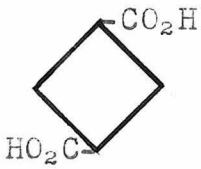
(18) J.Block, K.Kreckeler and B.Tollens, Ann.,238, 287 (1887).

THE SYNTHESIS OF CIS- AND TRANS-1,3-CYCLOBUTANEDICARBOXYLIC ACIDS

The synthesis of cis- and trans-1,3-cyclobutanedicarboxylic acids (I) and (II) became a problem of prime importance once it was established that the Markownikoff acids were cis- and trans-1-methyl-1,2-cyclopropanedicarboxylic acids (III) and (IV) (cf. preceeding section). Hence authentic 1,3-cyclobutanedicarboxylic acid had not previously been prepared. A



I



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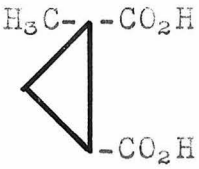

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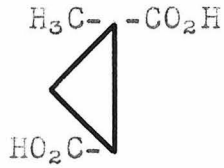


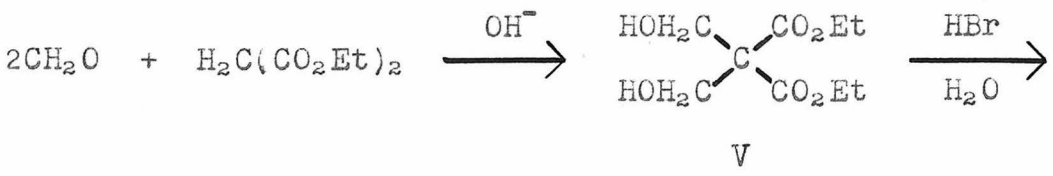
IV

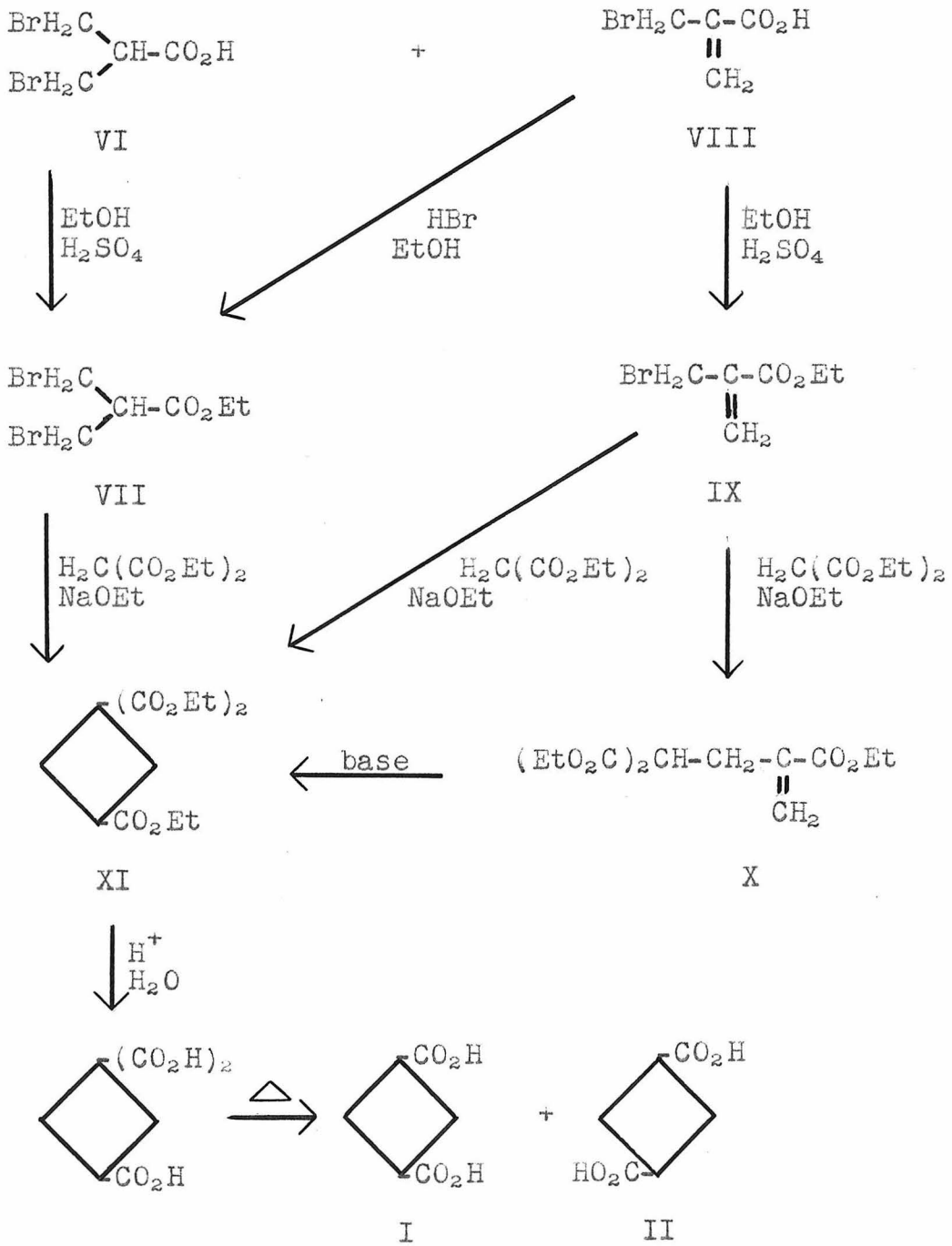
number of probable routes to (I) and (II) were extensively investigated while other less promising routes were only superficially studied. A highly satisfactory synthesis of (I) and (II) was eventually developed.

An obvious paper synthesis of ethyl 1,1,3-cyclobutanetricarboxylate (XI) involves the condensation of ethyl β,β'-dibromoisobutyrate (VII) with sodium malonic ester. Hydrolysis and decarboxylation of (XI) would give (I) and (II).

Since ethyl β,β'-dibromoisobutyrate (VII) has not been reported in the literature, it was prepared as outlined in Table 1. β,β'-Diiodoisobutyric acid had been synthesized by Glattfeld and Schneider (1), but their method was not adaptable to the preparation of β,β'-dibromoisobutyric acid (VI). Welch (2) prepared bis(hydroxymethyl)-malonic ester (V) and

Table 1

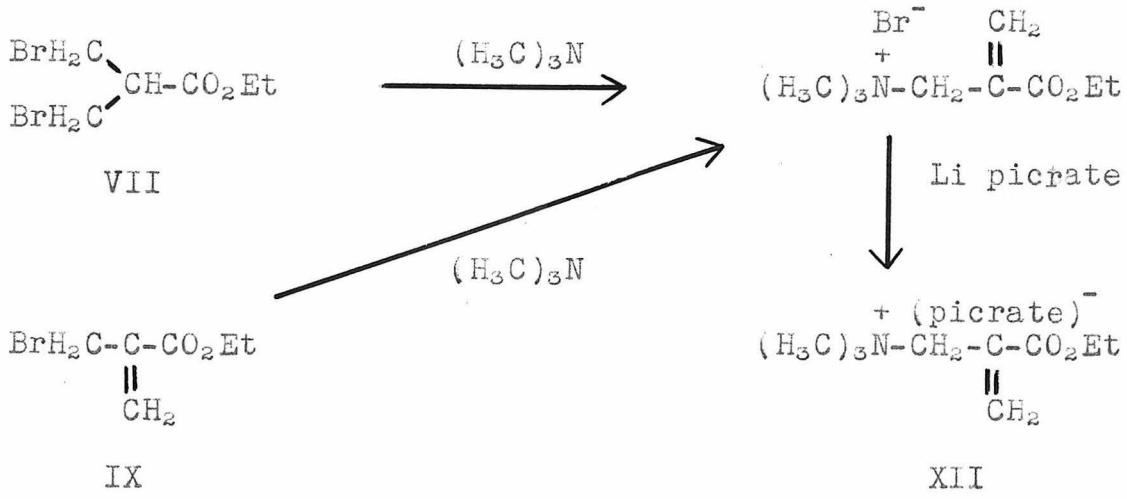




Attempted Syntheses of 1,3-Cyclobutanedicarboxylic Acid

reported that heating (V) with hydriodic acid gave α-(iodomethyl)-acrylic acid— the iodo analog of (VIII). The synthesis of large quantities of bis(hydroxymethyl)-malonic ester (V) was achieved by improving the procedure of Gault and Roesch (3). Treatment of (V) with hydrobromic acid yielded a mixture of β,β'-dibromoisobutyric acid (VI) and α-(bromomethyl)-acrylic acid (VIII). Upon esterification with ethyl alcohol and sulfuric acid, (VI) and (VIII) gave the corresponding esters (VII) and (IX). When the esterification of (VIII) was carried out with alcoholic hydrogen bromide, hydrogen bromide added to the double bond and the ester (VII) was produced.

Both (VII) and (IX) might be expected to yield ethyl 1,1,3-cyclobutanetricarboxylate (XI) when treated with sodium malonic ester, the former by a Perkin reaction (4), the latter by a malonic ester condensation followed by an internal Michael condensation. Numerous cases of internal Michael condensations leading to cyclobutane compounds are discussed at length by Ingold and co-workers (5). When (VII) was treated with sodium malonic ester, it presumably underwent dehydrohalogenation giving (IX) as the first step in the reaction. This was borne out by the fact that both (VII) and (IX) gave the same quaternary picrate when treated with trimethylamine followed by lithium picrate.



An analogous case of dehydrobromination was noted by Perkin, jun. and Simonsen (6):

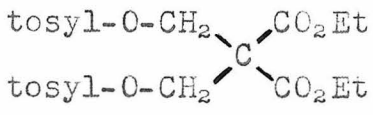
$$BrH_2C\text{-}CHBr\text{-}CH_2Br + H_2C(CO_2Et)_2 \xrightarrow{NaOEt} H_2C{=}CBr\text{-}CH_2\text{-}CH(CO_2Et)_2$$

From both (VII) and (IX) with sodium malonic ester only traces of distillable material could be obtained. The ester (X) presumably underwent a series of inter-molecular Michael condensations leading to non-volatile polymers.

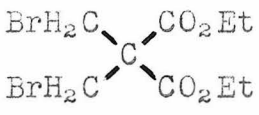
In the hope that milder conditions would give the desired cyclobutane ester (XI), magnesium malonic ester was employed in place of sodium malonic ester. Both (VII) and (IX) gave the same product ethyl α-carbethoxy-γ-methyleneglutarate (X). All attempts to induce cyclization of (X) to (XI) by the action of magnesium ethoxide, sodium ethoxide, or piperidine failed. The structure of (X) was verified by hydrolysis and decarboxylation to α-methyleneglutaric acid and by hydrogenation, hydrolysis, and decarboxylation of (X) to α-methylglutaric acid.

Although the addition of hydrogen bromide to (X) would yield ethyl α-(bromomethyl)-γ-carbethoxyglutarate, which upon elimination of hydrogen bromide might give ethyl 1,1,3-cyclobutanetricarboxylate (XI), the fact that Michael condensations are reversible led the author to believe that (XI) would not be stable in basic media. It is thought that the ring would open giving (X) followed by inter-molecular Michael condensations leading to polymers.

Starting from bis(hydroxymethyl)-malonic ester (V), other routes to 1,3-cyclobutanedicarboxylic acid were open which eliminated the difficulties noted above. With this in mind the tosylate of (V), (XIII), was prepared in the usual manner and subjected to a malonic ester condensation. The only identified product that could be isolated was a small amount of α-methyleneglutaric acid. Attempts to prepare ethyl bis(bromomethyl)-malonate (XIV) from the tosylate (XIII) by an exchange reaction gave tars and unreacted starting material. By refluxing (XIII) with sodium iodide for six days at 100°, only one tosylate group could be replaced by iodine.

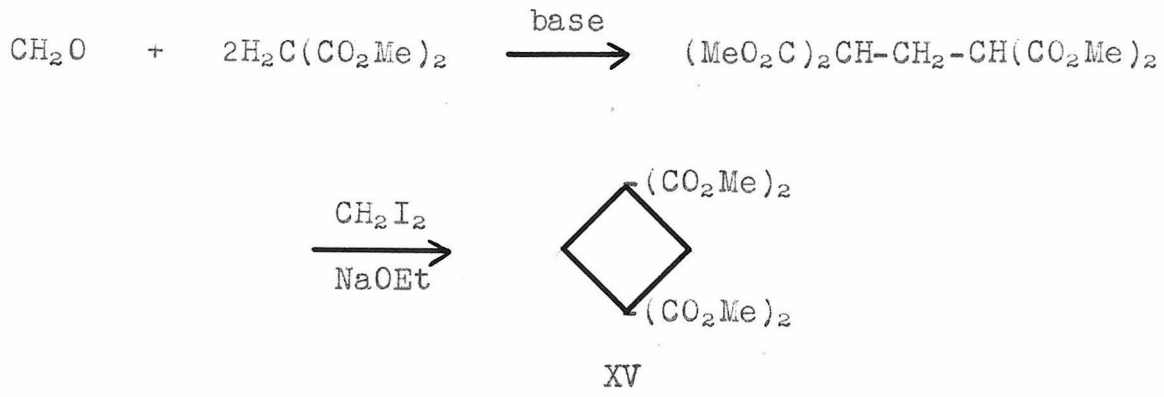


XIII



XIV

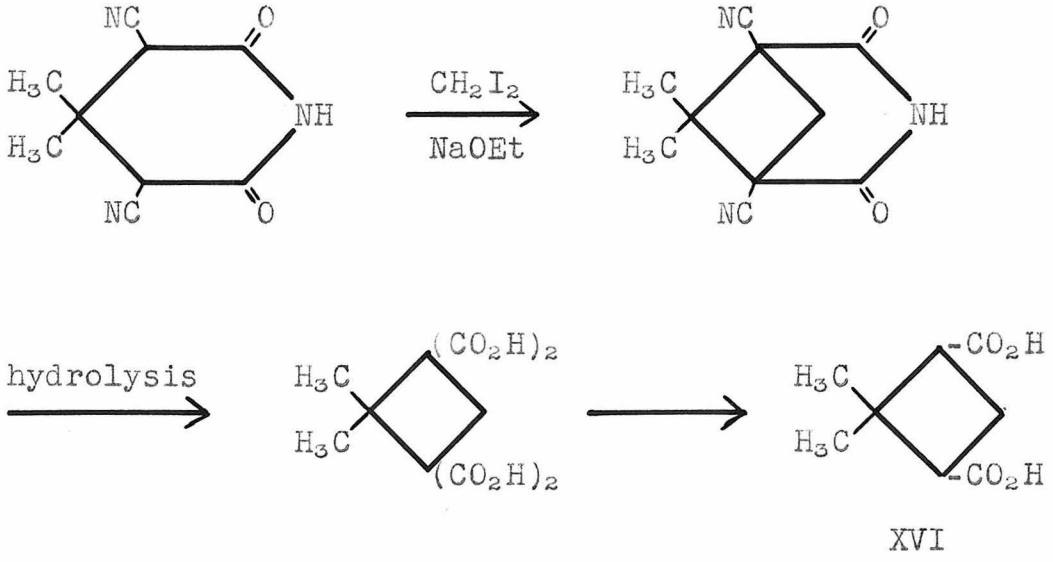
Gutzeit and Dressel (7) had reported the synthesis of methyl 1,1,3,3-cyclobutanetetracarboxylate (XV) by the following steps:



XV

Although the ester (XV) gave proper analytical results, attempts by Gutzeit and Dressel to convert it to 1,3-cyclobutanedicarboxylic acid did not give a pure product. Repetition of this work by Schlatter (8) and by this author were unsuccessful. No pure (XV) could be obtained.

Although a modification of the Kerr (9) synthesis of norpinic acid (2,2-dimethyl-1,3-cyclobutanedicarboxylic acid) (XVI) would be expected to yield 1,3-cyclobutanedicarboxylic



XVI

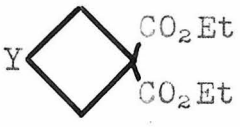
acid, such a synthesis did not prove feasible. Attempts to

repeat Higson and Thorpe's (10) synthesis of ethyl α,γ-dicyanoglutarate (XVII) were uniformly unsuccessful. (XVII) polymer-

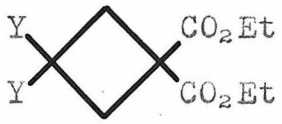
$$EtO_2C\text{-}CH(CN)\text{-}CH_2\text{-}CH(CN)\text{-}CO_2Et \qquad XVII$$

ized in the column and condenser during distillation (cf.11).

Since it was not possible to prepare 1,3-cyclobutanedicarboxylic acid by direct methods, the writer's attention turned to methods of preparing compounds of the type (XVIII) and (XIX) where Y is a methylene or hydroxymethyl group which



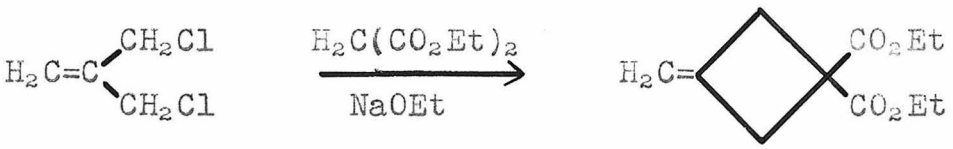
XVIII



XIX

could be oxidized to a carboxylic acid after the cyclobutane ring was formed.

β-(Chloromethyl)-allyl chloride (XX) would theoretically give ethyl 3-methylene-1,1-cyclobutanedicarboxylate (XXI) which could be converted to 1,3-cyclobutanedicarboxylic acid.



XX XXI

(XX) was prepared by the method of Mooradian and Cloke (12) starting from pentaerythritol. Treatment of (XX) with sodium malonic ester did not give any detectable amount of (XXI).

Presumably the methylene group in (XX) increased the bond angles (109° to 120°) sufficiently to prevent ring closure.

A somewhat similar alternate route to 1,3-cyclobutanedicarboxylic acid would start from $YCH_2\text{-}CH(CH_2Br)_2$ (XXII) which might be prepared as follows:

$$HC(CO_2Et)_3 \xrightarrow{LiAlH_4} \underset{\text{XXIII}}{HC(CH_2OH)_3} \xrightarrow{HBr} \underset{\text{XXII}}{YCH_2\text{-}C(CH_2Br)_2}$$

In this case the proposed method failed when the tris(hydroxymethyl)-methane (XXIII), although it presumably formed, could not be isolated from the inorganic salts[+].

The eventual synthesis of <u>cis</u>- and <u>trans</u>-1,3-cyclobutanedicarboxylic acids (I) and (II) was achieved as outlined in table 2 [++]. 2,2-Bis(bromomethyl)-1,3-propandiol (XXIV) was prepared by the method of Beyaert and Hansens (14), Zelinsky and Krawetz's (15) synthesis being unsuitable for large-scale preparative purposes. Following the meager directions given in Chemical Abstracts, the author obtained a 25-35% yield of (XXIV) in contrast to the reported 80% of Beyaert and Hansens (14). After this work was completed a copy of the original

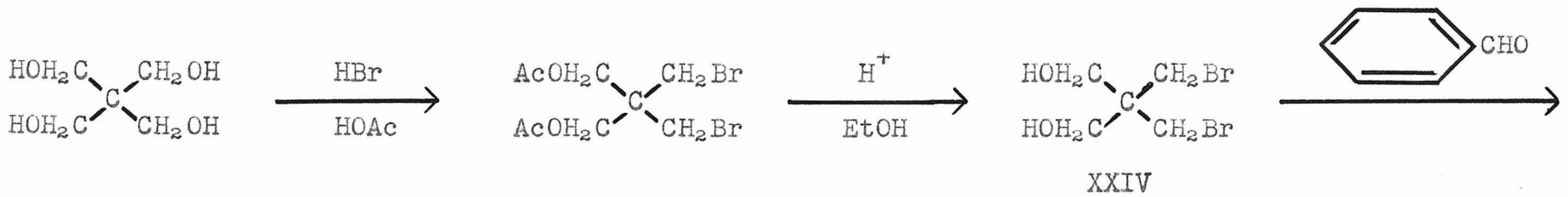
[+]After this work was discontinued an alternate route to (XXIII) appeared in the literature (13) starting from formaldehyde and acetaldehyde:

$$2CH_2O + H_3C\text{-}CHO \xrightarrow{OH^-} (HOH_2C)_2CH\text{-}CHO \xrightarrow{H_2} \underset{\text{XXIII}}{(HOH_2C)_2CH}$$

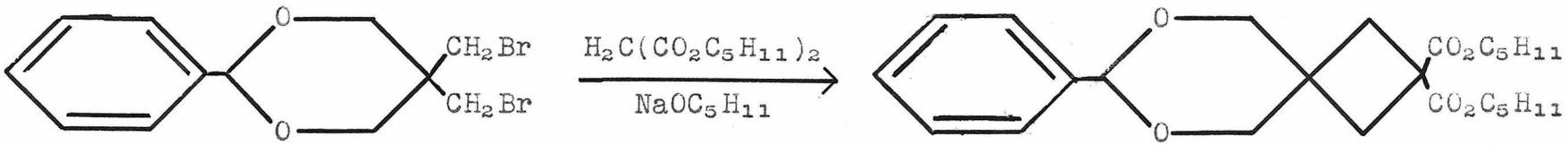
[++]A somewhat analogous scheme was suggested to the writer by Dr. James Conley. Cf. Conley, Ph. D. Thesis (Propositions), Cal. Inst. of Tech., 1950.

Table 2

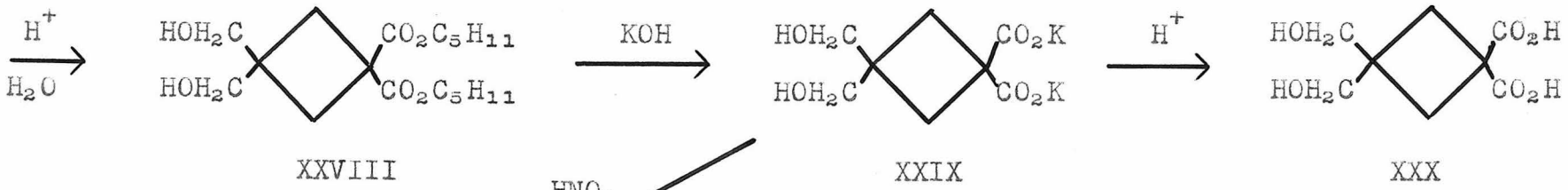
The Successful Synthesis of 1,3-Cyclobutanedicarboxylic Acid



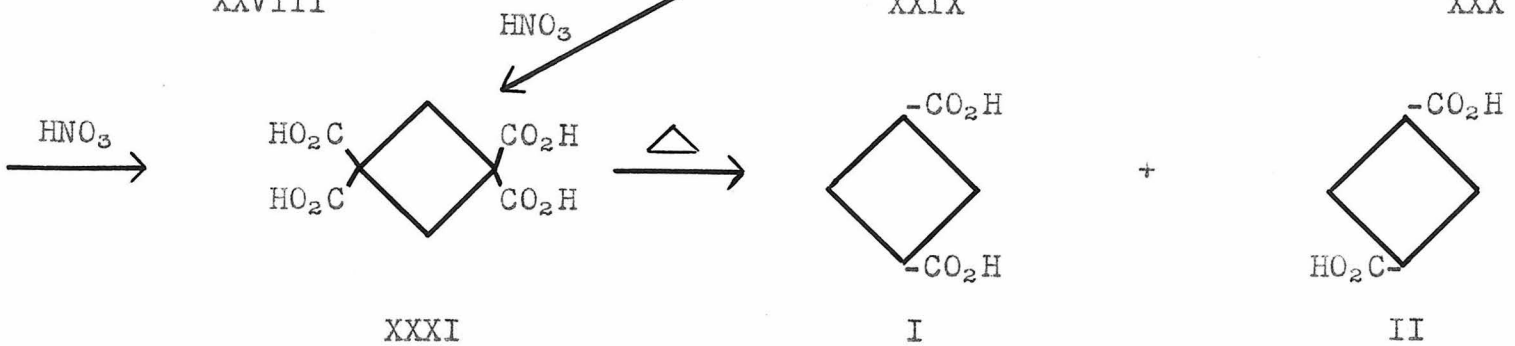
XXIV



XXVI XXVII



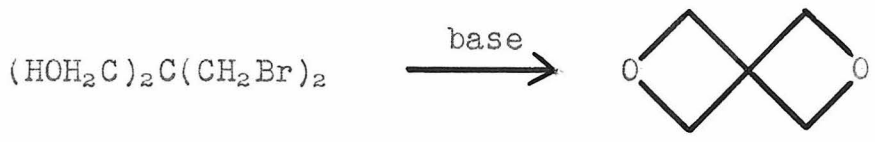
XXVIII XXIX XXX



XXXI I II

article was obtained. Since this journal, Natuurwetenschappelijk Tijdschrift , is quite obscure and the article is written in Flemish, Beyaert and Hansens' procedure is given in detail in the experimental section. Because (XXIV) could not be used directly in the malonic ester condensation,[+] the free hydroxyl groups were protected by preparing the benzylidene derivative (XXVI). (XXVI), when subjected to a malonic ester condensation, gave isoamyl benzylidene-1,1-bis(hydroxymethyl)-3,3-cyclobutanedicarboxylate (XXVII). Acid hydrolysis liberated isoamyl 1,1-bis(hydroxymethyl)-3,3-cyclobutanedicarboxylate (XXVIII). Basic saponification produced potassium 1,1-bis-(hydroxymethyl)-3,3-cyclobutanedicarboxylate (XXIX) which was oxidized directly with nitric acid to 1,1,3,3-cyclobutanetetracarboxylic acid (XXXI). Alternatively, the free 1,1-bis(hydroxymethyl)-3,3-cyclobutanedicarboxylic acid (XXX) was liberated from its potassium salt (XXIX) and then oxidized to the tetra acid (XXXI). The latter method has the advantage that no salts are present to interfere with the isolation of the product (XXXI). Decarboxylation of (XXXI) gave a mixture of cis- and trans-1,3-cyclobutanedicarboxylic acids (I) and (II). The pure cis acid (I) was prepared via its anhydride from the mixed cis and trans acids (I) and (II). By fractional crystalli-

[+]2,6-Dioxaspiro(3,3)heptane (XXV) is formed under these conditions. Cf. Backer and Keuning (16).



XXIV XXV

zation of the mixed *cis* and *trans* acids from benzene-dioxane and acetone the pure *trans* acid (II) was isolated.

EXPERIMENTAL

Ethyl bis(hydroxymethyl)-malonate (V).

In a 5-l. round-bottom flask, provided with a powerful Hershberg stirrer, were placed 250 g. of sodium carbonate, 2 l. of water, and 1 kg. of ice. After the temperature had fallen to 0°, 570 ml. (6.3 moles) of 37% aqueous formaldehyde was added all at once, and then 480 g. (3.0 moles) of ethyl malonate was slowly run in (thirty to forty-five minutes). The mixture was maintained at 0-5° by the occasional addition of ice and vigorously stirred during the addition and for one hour thereafter. Technical grade ammonium sulfate was added until the solution was saturated— two liquid phases formed. One liter of ether was added, and the lighter organic phase was separated. The ether was stripped off under a water aspirator at room temperature for eighteen hours and then at 50-60° for thirty minutes. Upon cooling to 0°, the entire residue solidified, weight 544 g. Crystallization from 1 l. of carbon tetrachloride gave 315 g. (48%) of nearly pure ethyl bis(hydroxymethyl)-malonate (V), m.p. 49° (Welch (2) reported m.p. 52°). A second crop of less pure product separated upon standing, 63 g. (9%).

The tosylate of ethyl bis(hydroxymethyl)-malonate (XIII) was prepared by the method of Sekera and Marvel (17). A solution of 71 g. (0.37 mole) of the diol (V) in 350 ml. of pyridine was cooled to 0° and 155 g. (0.8 mole) of tosyl chloride (Eastman Kodak Co., white label) was added portion-

wise during one hour with occasional stirring. After standing over night, the reaction mixture was poured into 1 l. of 20% sulfuric acid. An oil separated which quickly solidified. The air dried product crystallized slowly from methyl alcohol as splendid rhombohedral prisms; yield, nearly quantitative. After two recrystallizations from methyl alcohol the tosylate melted sharply at 98°

Anal. Calcd. for $C_{23}H_{18}S_2O_{10}$: C, 52.14; H, 5.34. Found: C, 52.31; H, 5.40.

β,β'-Dibromoisobutyric acid (VI) and α-(bromomethyl)-acrylic acid.(VII).

To 1 l. of 48% hydrobromic acid in a 2-l. round-bottom flask was added 220 g. (1.0 mole) of ethyl bis(hydroxymethyl)-malonate (V). The solution was refluxed for exactly one hour under a total reflux partial take-off condenser; during this time 100 ml. of distillate was collected (mostly ethyl bromide). The light yellow residue was transferred to a beaker and cooled to -12°. A crystalline precipitate separated which was filtered off on a sintered glass funnel and then dissolved in hot petroleum ether (b.p. 100-130°). The aqueous phase which remained was combined with the original filtrate, refluxed for an additional hour, cooled to room temperature, and extracted twice with 100-ml. portions of benzene. These extracts were combined with the above petroleum ether solution, solvents were stripped off, and the residue was distilled. Two main fractions were collected. Fraction A, 57 g. (32%), b.p. 108° at 3 mm., was crystallized from petroleum ether (b.p.100-

130°); m.p. 73.5°. Fraction B, 24 g. (9%), b.p. 140-142° at 3-4 mm., was crystallized twice from water; m.p. 99.2-99.7°. The analyses agreed with the formulation of A as α-(bromomethyl)-acrylic acid and B as β,β′-dibromoisobutyric acid.

Anal. (A) Calcd. for $C_4H_5O_2Br$: C, 29.12; H, 3.06. Found: C, 29.20; H, 3.14.

Anal. (B) Calcd. for $C_4H_6O_2Br_2$: C, 19.53; H, 2.46. Found: C, 19.68; H, 2.52.

Ethyl α-(bromomethyl)-acrylate (IX).

A mixture of 57 g. (0.345 mole) of α-(bromomethyl)-acrylic acid (VIII), 50 ml. of absolute alcohol, 150 ml. of carbon tetrachloride and 1 ml. of sulfuric acid was refluxed for four hours during which time the water that formed was removed by means of an automatic liquid separator. The carbon tetrachloride solution was washed with aqueous sodium bicarbonate and dried over magnesium sulfate. Distillation of the carbon tetrachloride solution gave 47.8 g. of the crude ester, b.p. 80° at 10 mm. Redistillation through an 18-inch column gave 33.4 g. (66.5%) of pure ethyl α-(bromomethyl)-acrylate (IX), b.p. 80° at 10 mm., n_D^{25} 1.4734, d_4^{26} 1.361.

Anal. Calcd. for $C_6H_9O_2Br$: C, 37.33; H, 4.70. Found: C, 37.45; H, 4.79.

Ethyl β,β′-dibromoisobutyrate (VII).

Crude α-(bromomethyl)-acrylic acid, 24 g. (0.145 mole), was dissolved in 100 ml. of absolute alcohol, and the solution was saturated with gaseous hydrogen bromide at 0°. After standing overnight at 4° the solution was poured into 1 l. of water whereupon a brown oil separated. The aqueous phase was extracted with 100 ml. of chloroform, and the extract was combined with the bulk of the ester. After being washed with water, aqueous sodium bicarbonate, and again with water, the chloroform solution was dried over magnesium sulfate. Distillation of the chloroform solution gave 17.6 g. (44%) of the dibromo-ester (VII), b.p. 120-121° at 10 mm., n_D^{25} 1.4938, d_4^{23}1.711; MR_D calcd., 47.07, found, 46.95.

Anal. Calcd. for $C_6H_{10}O_2Br_2$: C, 25.70; H, 3.68. Found: C, 26.05; H, 3.78.

This ester (VII) was also prepared from β,β′-dibromoisobutyric acid (VI) by direct esterification as in the case of ethyl α-(bromomethyl)-acrylate (IX).

α-(Chloromethyl)-acrylic acid.

A mixture of 55 g. (0.25 mole) of ethyl bis(hydroxymethyl)-malonate (V) and 200 ml. of 12N hydrochloric acid was refluxed for one hour. Upon being cooled to -10°, 12 g. (40%) of α-(chloromethyl)-acrylic acid crystallized out as large blades. After three recrystallizations from petroleum ether (b.p. 100-130°), the acid melted at 60.0-61.2°.

Anal. Calcd. for $C_4H_5O_2Cl$: C, 39.85; H, 4.18. Found: C, 39.94; H, 4.27.

Ethyl α-(chloromethyl)-acrylate.

A solution of 37.6 g. (0.313 mole) of α-(chloromethyl)-acrylic acid, 0.5 ml. of sulfuric acid, 100 ml. of absolute alcohol, and 100 ml. of carbon tetrachloride was refluxed for five hours. The water that formed during the esterification was removed from the system by means of an automatic liquid separator. After being cooled the solution was poured into water; the organic phase was separated, washed with aqueous sodium bicarbonate, dried over magnesium sulfate, and the solvent was distilled off. Distillation of the residue gave 26.8 g. (56.5%) of ethyl α-(chloromethyl)-acrylate, b.p. 70-75° at 16 mm., n_D^{25} 1.446, d_4^{26} 1.0874.

The attempted preparation of ethyl 1,1,3-cyclobutanetricarboxylate (XI). Method A.

To a solution of 6.6 g. (0.286 mole) of sodium in 200 ml. of absolute alcohol was added 23 g. (0.143 mole) of dry ethyl malonate. Upon the slow addition of 39.4 g. (0.143 mole) of ethyl β,β'-dibromoisobutyrate (VII) to the above hot solution, a vigorous reaction took place and sodium bromide precipitated. After the mixture was refluxed for two hours, the precipitate was filtered off and washed with absolute alcohol, and the combined filtrates were reduced to a small volume on a steam cone under reduced pressure. The residue was washed twice with water, dried over magnesium sulfate, and distilled in vacuo. The following fractions were collected:

below 150° at 10 mm.	2.5 g.
to 150° at 1-2 mm.	4.7 g.
to 220° at 1-2 mm.	8.6 g.
residue, estimated	25 g.

None of the fractions was homogeneous. The estimated boiling point of (XI) was 125-135° at 3 mm. This experiment was repeated three times with essentially the same results— tars and high boiling products.

Method B.

To a solution of 5.0 g. (0.205 mole) of sodium in 200 ml. of absolute alcohol was added 26.3 g. (0.164 mole) of dry ethyl malonate. After the solution was cooled to 0°, 31.7 g. (0.164 mole) of ethyl α-(bromomethyl)-acrylate (IX) was added over a five minute period. This gave rise to a vigorous reaction; heat was evolved, and sodium bromide precipitated. The reaction mixture was then heated to reflux for two hours, cooled to room temperature, and poured into dilute hydrochloric acid. After the organic phase was separated, the aqueous phase was extracted twice with ether. The combined ether extract and organic product were dried over magnesium sulfate, and the ether was stripped off under a water pump. Distillation of the residue gave only small amounts of high boiling materials and non-distillable tars.

Ethyl α-methylene-γ-carbethoxyglutarate (X).

Magnesium turnings, 12.5 g. (0.5 mole), were refluxed with 300 ml. of absolute alcohol, a crystal of iodine, and 40 g. (0.25 mole) of dry ethyl malonate. After the reaction subsided, 200 ml. of purified isopropyl ether was added; the mixture was refluxed for twenty hours after which all of the magnesium turnings had dissolved, and a large white precipitate had formed. The mixture was cooled to room temperature, and 71 g. (0.25 mole) of ethyl β,β′-dibromoisobutyrate (VII) was added all at once with stirring. A vigorous reaction ensued which was moderated with a water bath. When the reaction had subsided, the mixture was refluxed for ninety minutes, and then the bulk of the alcohol and ether were distilled off. The residue was poured into water, and treated with hydrochloric acid until all of the solid salts had dissolved. The organic materials were then taken up in isopropyl ether. After the aqueous solution was extracted with isopropyl ether, the combined isopropyl ether solutions were washed with aqueous ferrous sulfate and dried over magnesium sulfate. The isopropyl ether was removed on a steam cone under reduced pressure. Upon fractionation through a ten-inch column the residue yielded 36 g. (53%) of ethyl α-methylene-γ-carbethoxyglutarate (X), b.p. 130° at 3 mm., n_D^{25} 1.4408.

Anal. Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40.
Found: C, 57.40; H, 7.43.

Ethyl α-methylene-γ-carbethoxyglutarate (X) was also prepared from ethyl α-(bromomethyl)-acrylate (IX) in a similar manner.

A solution of 2.99 g. of ethyl α-methylene-γ-carbethoxyglutarate (X) in 35 ml. of absolute alcohol was prepared, and 20 mg. of Adams' catalyst was added. On hydrogenation until no further amount of hydrogen was absorbed, 323.5 ml. (102%) of hydrogen was taken up. The hydrogenated product was hydrolyzed with 100% excess of alcoholic potassium hydroxide. The alcohol was removed in vacuo, and the residue was acidified with hydrochloric acid. After the solution was evaporated to dryness, the residue was decarboxylated by heating to 220° for twenty minutes. The product was extracted three times with ether; the ether was evaporated off from the extract, and the material which remained was dissolved in a little hot water. When this solution was cooled to 0°, α-methylglutaric acid crystallized out, m.p. 76.0-76.5° (literature values: (18), 77-78°; (19), 77.5°).

Three grams of ethyl α-methylene-γ-carbethoxyglutarate (X) was refluxed overnight with 50 ml. of 6N hydrochloric acid. After the solution was evaporated down to dryness, the residue, α-methyleneglutaric acid, was recrystallized twice from water (Norite); m.p. 130.0-130.5°. A mixed melting point of this material with an authentic sample of α-methyleneglutaric acid showed no depression.

(β-Carbethoxyallyl)trimethylammonium picrate (XII).

Approximately 0.3 g. of ethyl α-(chloromethyl)-acrylate was treated with an excess of trimethylamine in benzene. The precipitate which formed immediately was centrifuged, washed with a little benzene, and dried in vacuo. After the salt was dissolved in a little water, an excess of saturated aqueous

lithium picrate was added; there resulted the immediate crystallization of the yellow-orange picrate (A). (A) was recrystallized twice from water; m.p. 130.0-130.2°.

Anal. Calcd. for $C_{15}H_{20}O_9N_4$: C, 45.00; H, 5.04. Found: C, 44.97; H, 5.04.

A picrate (B), m.p. 130.0°, was obtained from ethyl α-(bromomethyl)-acrylate by the above procedure. The mixed melting point of (A) and (B) was 130.0-130.2°.

A picrate (C), m.p. 129.5-130.5°, was obtained from ethyl β,β′-dibromoisobutyrate by the above procedure. The mixed melting point of (A) and (C) was 130.0-130.5°.

Ethyl (iodomethyl)-(tosyloxymethyl)-malonate.

A solution of 52.8 g. (0.10 mole) of ethyl bis (tosyloxymethyl)-malonate (XIII) and 60 g. (0.4 mole) of sodium iodide in 500 ml. of butanone was refluxed for six days; during this time sodium tosylate precipitated out, and the solution turned black (free iodine). After the precipitate was filtered off, the butanone was stripped off, and the residue was poured into water. The product was taken up in benzene, washed with aqueous sodium bisulfite, and dried over magnesium sulfate, and the benzene was stripped off. Recrystallization of the residue three times from absolute alcohol gave pure ethyl (iodomethyl)-(tosyloxymethyl)-malonate, m.p. 58.5-59.0°.

Anal. Calcd. for $C_{16}H_{21}O_7SI$: C, 39.69; H, 4.37. Found: C, 39.77; H, 4.51.

2,2-Bis(bromomethyl)-1,3-propandiol (XXIV).

A solution of 246 g. (3.0 moles) of gaseous hydrogen bromide, 1530 g. (9.0 moles) of 48% hydrobromic acid, and 408 g. (3.0 moles) of pentaerythritol in 1440 g. of glacial acetic acid was refluxed for forty hours. After being cooled to room temperature, the solution was diluted with water to 10 l., whereupon the diacetate of (XXIV) separated as a brown oil. Further small amounts of this ester were obtained from the aqueous solution by ether extraction after the free acid was neutralized. The crude diacetate of (XXIV) was refluxed with 500 ml. of absolute alcohol under a partial take-off total reflux condenser. After all of the ethyl acetate had distilled out and the boiling point of 77° had been reached (six hours), the excess ethyl alcohol was removed on a steam cone under reduced pressure. Repeated extraction of the oily residue with hot water gave 265 g. of the crude crystalline diol (XXIV). The air dried product was recrystallized from benzene; yield, 225 g. (32%), m.p. 102-104° (Beyaert and Hansens (14) reported m.p. 111°). An additional 55 g. (8%) of less pure product was obtained by further extraction.

The procedure of Beyaert and Hansens (14) for the preparation of (XXIV). Glacial acetic acid, 120 ml., 20 g. of pentaerythritol, and 1 ml. of 66% hydrobromic acid were placed in a 500-ml. two-necked flask which was provided with a reflux condenser and a dropping funnel. The mixture was refluxed until the solid dissolved; 41 ml. of 66% hydrobromic acid was then added slowly, and the solution was refluxed

for an additional twenty hours. The reaction mixture was reduced to dryness with moderate heating in vacuo. The residue, 50 ml. of absolute alcohol, and 3 ml. of 66% hydrobromic acid were heated in a distilling flask which was provided with a two-meter fractionating column. Ethyl acetate (25 ml.) distilled over slowly at 71°. During the distillation of the next 10 ml., the temperature rose slowly to 78°. An additional 50 ml. of absolute alcohol was added to the pot and slowly distilled out. The residue was concentrated in vacuo, evaporated down with 50 ml. of toluene, heated to 115° in vacuo, and again evaporated down with 50 ml. of toluene. After the residue was boiled with 100 ml. of benzene, the benzene solution was poured into a clean beaker. As the solution cooled the bromide (XXIV) crystallized out. The solution and precipitate were set in an ice box for one hour, and the product was then filtered off and washed with a little benzene; weight 31 g., m.p. 103-105°. One recrystallization from water yielded 29.6 g. of (XXIV), m.p. 111°.

Benzylidene-2,2-bis(bromomethyl)-1,3-propandiol (XXVI).

A mixture of 225 g. (0.86 mole) of 2,2-bis(bromomethyl)-1,3-propandiol (XXIV), 100 g. (0.95 mole) of benzaldehyde, and 3 g. of p-toluenesulfonic acid was refluxed with 1 l. of benzene. In the course of three hours 19 ml. of water distilled out and was collected in an automatic liquid separator. The residue was washed with aqueous sodium carbonate, dried over anhydrous potassium carbonate, and stripped of benzene. Crystallization of the residue from methyl alcohol

yielded 217 g. (72%) of the benzylidene derivative (XXVI); m.p. 67.6-68.3°. Recrystallization from methyl alcohol gave colorless clusters of prisms; m.p. 68.0-68.3°.

Anal. Calcd. for $C_{12}H_{14}O_2Br_2$: C, 41.17; H, 4.03. Found: C, 41.59; H, 3.99.

Isoamyl benzylidene-1,1-bis(hydroxymethyl)-3,3-cyclobutane-dicarboxylate (XXVII).

A 2-l. standard-tapered, three-necked flask was provided with a "tru-bore" stirrer, a partial take-off total reflux condenser, a tube for the addition of solids, and a 500 ml. graduated dropping funnel-the stem of which extended to the bottom of the flask. Isoamyl alcohol, 1200 ml., was put in the flask,and a small forerun distilled off. After 22.1 g. (0.916 mole) of sodium was dissolved in the alcohol, the solution was cooled somewhat,and 500 ml. of this solution was forced up into the graduated dropping funnel by a stream of nitrogen. Dry ethyl malonate, 88.5 g. (0.547 mole), was added to the reaction flask. The solution was heated to reflux and 160 g. (0.458 mole) of benzylidene-2,2-bis(bromomethyl)-1,3-propandiol (XXVI) and the 500 ml. of sodium isoamylate solution contained in the dropping funnel were added in portions as follows: Each of the above addenda was divided into eight equal parts,and at thirty minute intervals one part of each was added to the reaction flask. During the addition,200 ml. of ethyl and isoamyl alcohols were distilled out from the reaction flask,and the distilling temperature

reached 123°. Refluxing was continued for sixteen hours. After the bulk of the isoamyl alcohol was distilled off, the mixture was cooled to room temperature and washed with 200 ml. of 2N hydrochloric acid. Ether extraction of the aqueous washing gave further small amounts of product. This residue containing the isoamyl benzylidene-1,1-bis(hydroxymethyl)-3,3-cyclobutanedicarboxylate (XXVII) was used directly in the following reaction.

1,1-Bis(hydroxymethyl)-3,3-cyclobutanedicarboxylic acid (XXX).

The crude condensation product (XXVII) was hydrolyzed by refluxing with 350 ml. of water and 20 ml. of 12N hydrochloric acid. Water, benzaldehyde, and isoamyl alcohol were distilled off until the distillate was clear. To the residue (two phases) was added 112 g. of potassium hydroxide (100% excess) dissolved in 400 ml. of ethyl alcohol. A vigorous reaction ensued and a large white precipitate formed. After the mixture was heated on a steam bath for one hour, the bulk of the alcohol and water were removed under reduced pressure. The residual pasty mass was repeatedly shaken with absolute alcohol until the supernatant liquid was colorless. The precipitate was filtered, washed with ether, and air dried. To this potassium salt 100 ml. of 12N hydrochloric acid was added, and the resultant precipitate of potassium chloride was filtered off and washed with acetone. Combination of the hydrochloric acid solution and the acetone washings gave an additional precipitate of potassium chloride. The total weight of potassium chloride

was 82 g. After the acetone was removed by distillation, the pH of the solution was adjusted to the acid side of Congo red. This solution was then extracted with ether using a special emulsification stirrer[+] and a down-draft condenser. The ether extract yielded 7 g. of dark oily residue upon evaporation of the solvent. The aqueous solution was further acidified with 90 ml. of 12N hydrochloric acid and again extracted for twenty hours. The ether flask contained two phases, (1,1-bis(hydroxymethyl)-3,3-cyclobutanedicarboxylic acid (XXX) is very hygroscopic and nearly insoluble in ether). Distillation of the ether left 20 g. of light brown oily material. Upon further extraction for three days an additional 40 g. of similar material was obtained, presumably a concentrated aqueous solution of the hydroxy-acid (XXX).

1,1,3,3-Cyclobutanetetracarboxylic acid (XXXI).

One portion, 20 g., of the crude aqueous solution of 1,1-bis(hydroxymethyl)-3,3-cyclobutanedicarboxylic acid (XXX) was mixed with 0.2 g. of ammonium vanadate in a 1-l. flask provided with a reflux condenser. In one portion, 200 ml. of 70% nitric acid was added. A vigorous reaction started after a few minutes; nitrogen oxides were copiously evolved, and the solution refluxed. After the reaction had subsided (ten minutes), the mixture was refluxed for another ten minutes, and then placed in an ice bath for thirty minutes. The nicely crystalline precipitate which separated was filtered off and

[+] A special stirrer was employed which consisted of a glass tube, sealed at the center and at both ends, and having two holes three inches from one end and also three short curved glass tubes sealed perpendicular to the shaft at this same end. In operation the ether was sucked in through the holes and sprayed out in the lower aqueous phase. This greatly increased the efficiency of the extraction.

dissolved in water. The bulk of the water and nitric acid was removed on a steam bath under reduced pressure, and the residue was dried at 60° in vacuo. Crystallization of the product from acetone-benzene gave 11.8 g. of the tetra-acid (XXXI). By distilling off the nitric acid from the mother liquor, an additional 5.7 g. of less pure tetra-acid was obtained. The estimated overall yield for the malonic ester condensation, acidic and basic hydrolyses, and the nitric acid oxidation was 50%. A portion of the tetra-acid (XXXI) was recrystallized from ether-benzene; m.p. 205° (dec.).

Anal. Calcd. for $C_8H_8O_8$: C, 41.38; H, 3.47.
Found: C, 41.35; H, 3.51.

cis-1,3-Cyclobutanedicarboxylic acid(I).

1,1,3,3-Cyclobutanetetracarboxylic acid (XXXI) was decarboxylated to a mixture of cis- and trans-1,3-cyclobutanedicarboxylic acids (I) and (II) by heating to 210-220° for thirty minutes. The resultant mixture was refluxed with ten times its weight of acetyl chloride for two and one-half hours. After the excess acetyl chloride and acetic anhydride were distilled off, the anhydride of cis-1,3-cyclobutanedicarboxylic acid was sublimed at 2-3 mm. (bath temperature 125-130°). The anhydride crystallized from benzene as long needles; m.p. 131-132°.

Anal. Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80.
Found: C, 57.14; H, 4.76.

Hydrolysis of the cis-anhydride by refluxing with dilute

hydrochloric acid gave the free cis-1,3-cyclobutanedicarboxylic acid (I). After the solution was evaporated to dryness, the cis-acid was crystallized from acetone-benzene; m.p. 131-132°.

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.60. Found: C, 49.79; H, 5.79.

Methyl cis-1,3-cyclobutanedicarboxylate was prepared by the method of Clinton and Laskowshi (20). A mixture of 5.0 g. (0.034 mole) of cis-acid (I), 6.7 g. (0.14 mole) of methyl alcohol, 20 ml. of ethylene dichloride, and 0.2 ml. of sulfuric acid was refluxed overnight. The resulting liquid was washed with water, aqueous sodium bicarbonate, and again with water. After the solvent was stripped off, the residue was distilled giving 3.22 g. (54%) of pure methyl ester, b.p. 132.5° at 30 mm. and 0.90 g. (15%) of less pure ester, b.p. 125.5-132.5° at 30 mm.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.50; H, 7.23

trans-1,3-Cyclobutanedicarboxylic acid (II).

The mixed cis- and trans-1,3-cyclobutanedicarboxylic acids (I) and (II) (see above) were fractionally crystallized twice from acetone at-25° and then twice from dioxane-benzene. By this means pure trans-acid (II) was isolated in approximately 20% yield; m.p. 189.8-190.3°.

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.60. Found: C, 50.43; H, 5.73.

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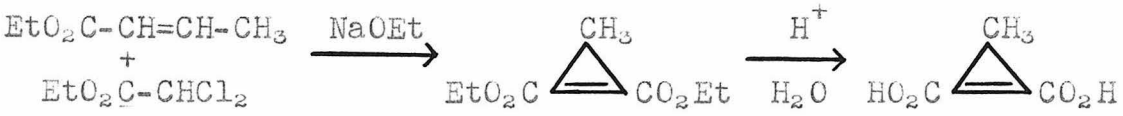
PROPOSITIONS

1. The synthesis of a wide variety of cyclopropane compounds could be easily achieved by the basic condensation of an unsaturated compound, suitably activated ($-CO_2Et$, $-CN$, $-NO_2$, etc.), with an αhalo compound similarly activated.

Cf. part II of this thesis.

2. An acid which was assigned the structure 3-methyl-1,2-cyclopropenedicarboxylic acid (I) was reported by Feist. I propose that (I) could be prepared by the following sequence:



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3. d and l trans-1,2-Cyclopropanedicarboxylic acids could be degraded to the optically active d and l trans-1,2-dibromocyclopropanes by the Hunsdiecker reaction. The latter compounds are of particular interest since Kirkwood's Theory of Optical Rotatory Power permits the exact calculation of both the magnitude and sign of their optical rotation. The correspondence between an optically active compound and its

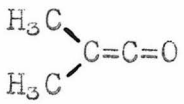
physical model would then be unambiguously established for the first time.

J. G. Kirkwood, J. Chem. Physics, 5, 479 (1937).

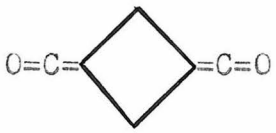
4. The ring cleavage of d and l trans-1,2-dibromo-cyclopropane (by such agents as hydrogen or hydrogen bromide) could each lead to only one optically active product, and the configuration of the remaining optically active carbon atom in each case would be retained. By relating these open chain products to d and l lactic acids the validity of Fisher's convention could be confirmed or refuted.

5.(a) I propose that the suffix carbone be adopted as the designation of the =C=O group in ketenes.

Examples:



propan-2-carbone



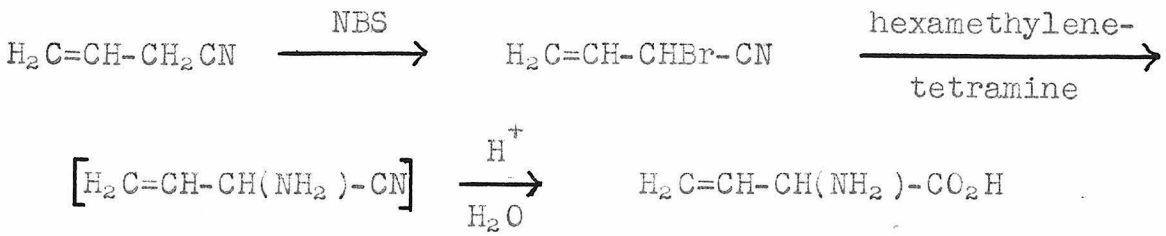
cyclobutan-1,3-dicarbone

(b) The preparation of poly-spiro-cyclobutane hydrocarbons could be effectively achieved through the cross polymerization of cyclobutancarbone with cyclobutan-1,3-dicarbone or spiro(3,3)nonan-2,6-dicarbone followed by a Wolff-Kishner or mercaptol reduction.

6. I propose that the absolute configuration of an optically active compound such as α-ethyl-α-aminostearic acid (I) acid could be experimentally determined by the following method. Saturate a mixture of water and benzene with (I). The mono-layer of (I) which is formed at the interface will be orientated so that the polar ends of the molecules will be in the aqueous phase. Apply an electrostatic field parallel to the interface thus aligning the dipoles of (I) in the direction of the field. The interfacial boundries at the junction of the liquid interface with the walls of the container in the two regions perpendicular to the direction of the field will be different due to the fixed orientation of the asymmetric molecules (I). By correlating the interfacial tension of various surface active agents in a water-benzene system with the meniscus distortion described above, the absolute configuration of (I) could be ascertained.

7. One of the major problems of bio-chemistry is the elucidation of enzymatic specificity. I propose that cyclopropane and cyclobutane derivatives are ideally suited for the study of enzyme reactions because these compounds possess rigid molecules of known or calculable dimensions.

8. Vinylglycine, which has been postulated as a metabolic intermediate, could be synthesized by the following series of reactions:



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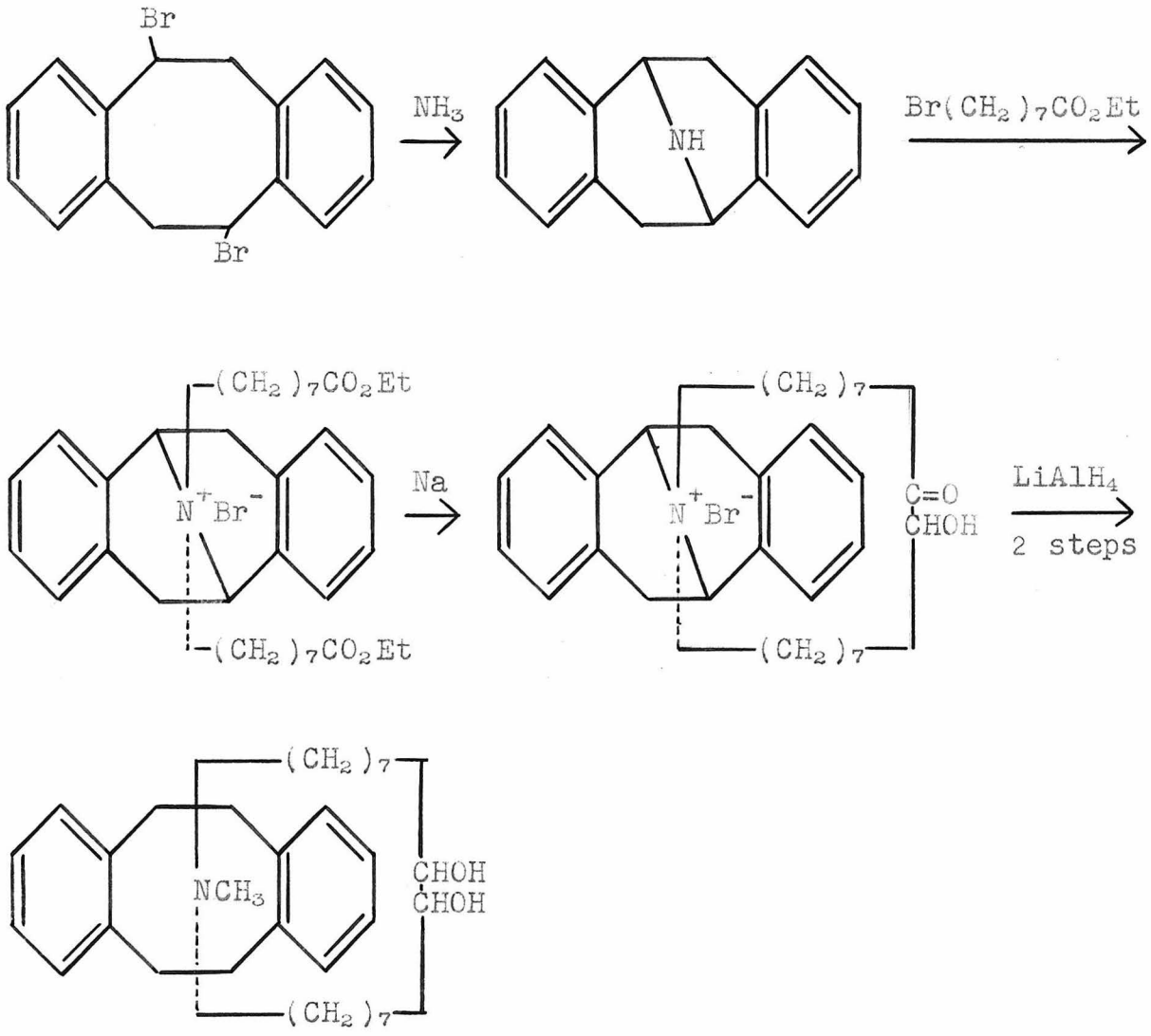
9. I propose that chemistry journals be printed on less expensive paper for current use and micro-card copies be issued for permanent files. This would be more economical for all parties concerned and eliminate the enormous storage problem facing libraries and individuals today.

10. I propose that the Chemistry Department offer a year course in the mechanism of organic reactions. The basis for such a course might be E. R. Alexander's book Principles of Ionic Organic Reactions, John Wiley and Sons, New York (1950).

11. I propose that a <u>chain compound</u> could be prepared by the following series of reactions:



Cope and Fenton, Abstract of papers presented at the Division of Organic Chemistry, American Chemical Society Meeting, Chicago, Sept., 1950.

12. It has not been possible to determine the angle of contact of water on solids such as asphalt because the angle of contact depends upon whether the liquid is contracting or expanding. I propose that this angle of contact could be determined indirectly as follows: A series of liquids of varying surface tension (preferably pure liquids) which are insoluble in both water and asphalt are tested on the asphalt surface in the order of decreasing surface tension. From the known surface tension of the liquid sample which spreads out completely on the surface and the liquid of slightly higher surface tension which does not spread out completely on the surface, the angle of contact between water and asphalt could be calculated by Dupre's Equation.