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CHLORINATION OF SODIUM-ENDO-3-PHENYL-(2.2.1)-BICYCLOHEPT-5-ENE-EXO-2-CARBOXYLATE IN AQUEOUS SOLUTION

by

Richard Joseph Zielinski

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the
University of Michigan
1961

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In Nomine Patris
et Filii
et Spiritus Sancti

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r.j.z.

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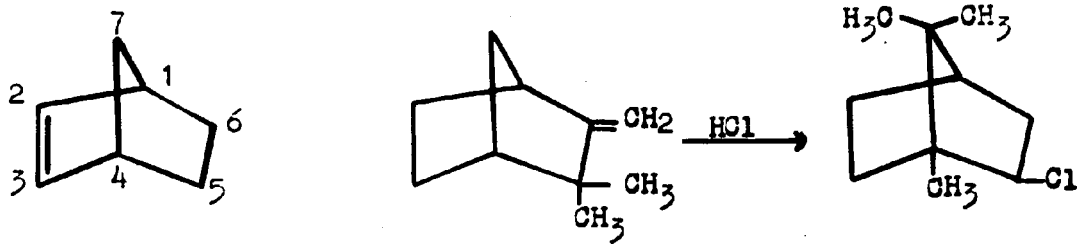
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HISTORICAL BACKGROUND

ADDITIONS TO THE DOUBLE BOND OF (2.2.1)-BICYCLOHEPTENE (NORBORNENE) DERIVATIVES

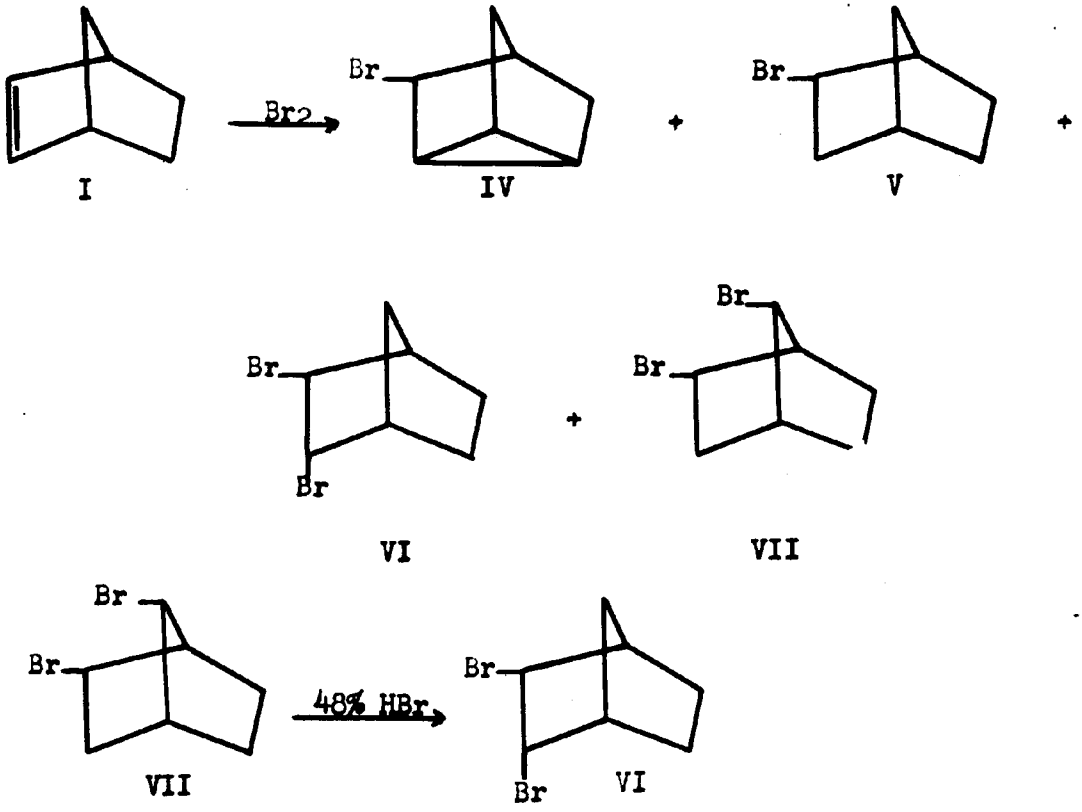
In reactions at the double bond of a great number of norbornene (I) derivatives the normal or expected product resulting from trans-addition does not occur or is accompanied by rearranged products. Similar observations have also been noted in the terpene series. For example, the formation of isobornyl chloride (III) from camphene (II) (1).



I II III

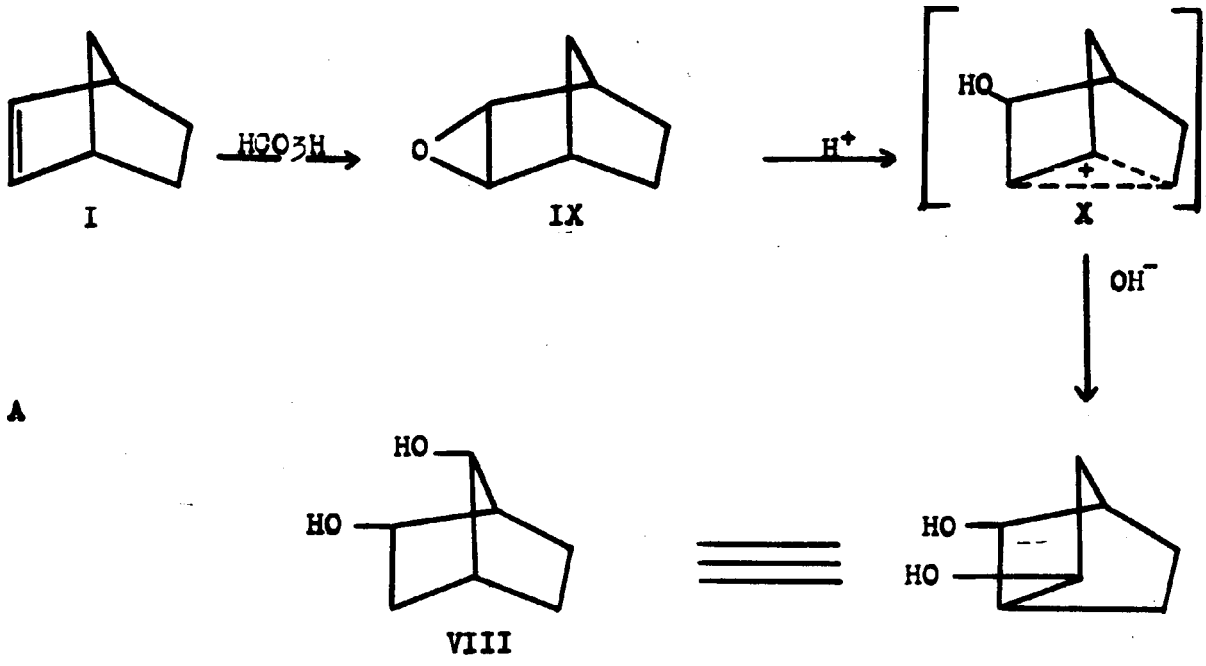
Roberts, Trumbull, Bennett, and Armstrong (2) have demonstrated that bromination of norbornene (I) with N-bromosuccimide or with bromine in carbon tetrachloride gives 3-bromonortricyclene (IV), exo-norbornyl bromide(V), and unidentified dibromo products. When one equivalent of pyridine was included in the reaction, the exo-norbornyl bromide (V) was not formed, whereas the proportion of IV, which was the major product of the reaction, was increased. Kwart and Kaplan (3) have determined the structures of the dibromides formed in the bromination of norbornene with bromine in carbon tetrachloride. They

have isolated two products: a trans-2,3-dibromide (VI) and a rearranged 2,7-dibromide (VII). The ratio of the 2,7-dibromide (VII) to the 2,3-dibromide (VI) was 1.8 to 1.0. The same dibromides were formed on bromination in the presence of one equivalent of pyridine; however, the ratio of VII to VI was raised to 3.6 to 1.0. Kwart and Kaplan (3) have also observed that the 2,7-dibromide (VII) may be transformed into the 2,3-dibromide (VI) by acidic catalysts. It is believed, however, that both VI and VII are primary reaction products (3).



Another addition to norbornene, the hydroxylation or addition of the elements of hydrogen peroxide, has resulted in a rearranged product. The peracid oxidation of olefins is known to give trans-1,2-glycols (4).

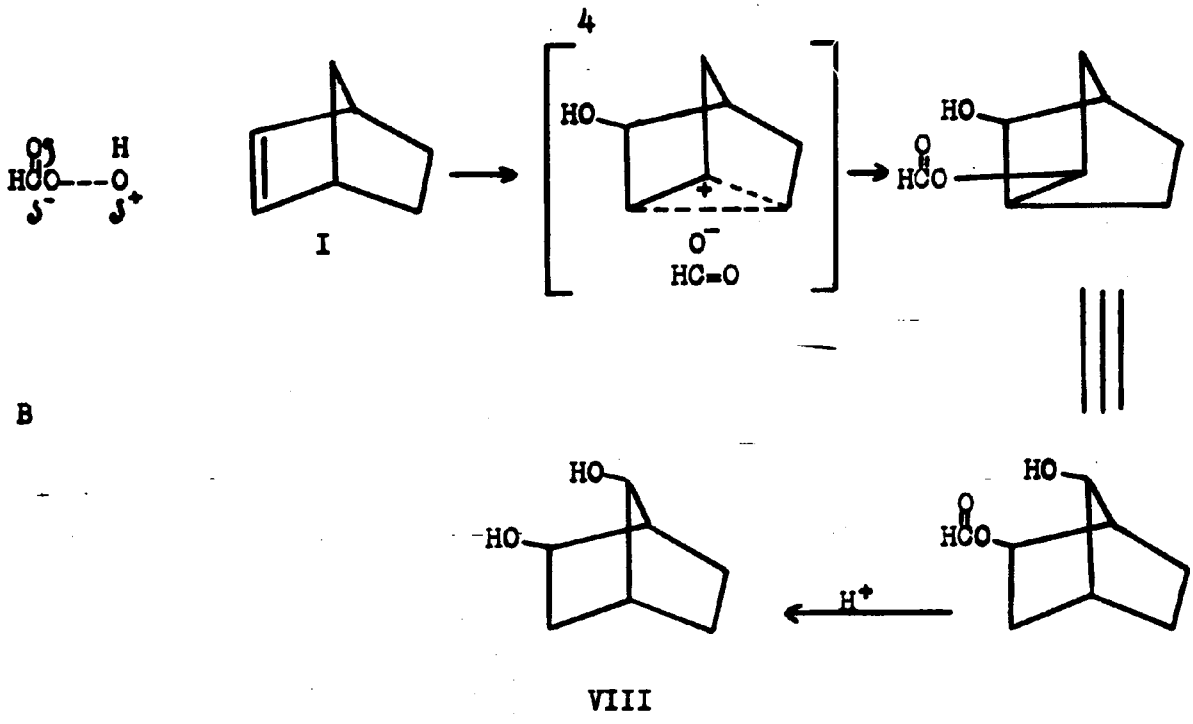
However, Walborsky and Loncrini (5) and Kwart and Vosburgh (6) have shown that the product of the hydroxylation of norbornene (I) with performic acid is a rearranged 2,7-diol (VIII). An ionic mechanism is assumed to be operative in this reaction and two mechanisms have been proposed. Walborsky and Loncrini (5) picture the reaction as first involving an epoxide (IX) which is opened by the acid present to form a bridged ion (X) which then reacts with the solvent to form the diol (VIII) (Mechanism A). Kwart and Vosburgh (6), however, propose mechanism B as shown below.



I IX X

A

VIII

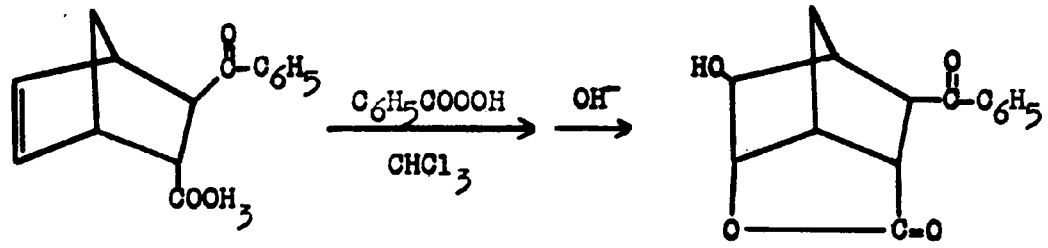


VIII

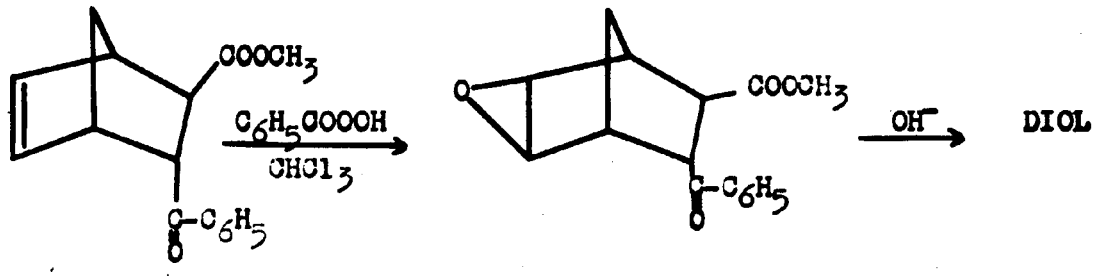
Walborsky and Loncrini (5) prepared epoxide (IX) by careful oxidation of norbornene with peracetic acid. Subsequent hydrolysis of IX with formic acid or sulfuric acid yielded the diol (VIII). Kwart and Vosburgh (6) also prepared the epoxide (IX) using monoperphthalic acid. Hydrolysis of IX with perchloric acid gave the diol (VIII) (6). On the basis of these observations it would appear that Mechanism A correctly represents the path of the hydroxylation reaction.

Winternitz, Mousseron, and Rouzier (7) report that reaction of methyl <u>exo</u>-3-benzoyl-(2.2.1)-bicyclohept-5-ene-<u>endo</u>-2-carboxylate (XI) with perbenzoic acid in chloroform followed by basic hydrolysis produces the hydroxylactone (XII). The same authors (7) report that similar treatment of methyl <u>endo</u>-3-benzoyl-(2.2.1)-bicyclohept-5-ene-<u>exo</u>-2-carboxylate (XIII) yields initially the epoxide (XIV) and subsequently a diol. In this case, however, neither the epoxide or the diol was

isolated.



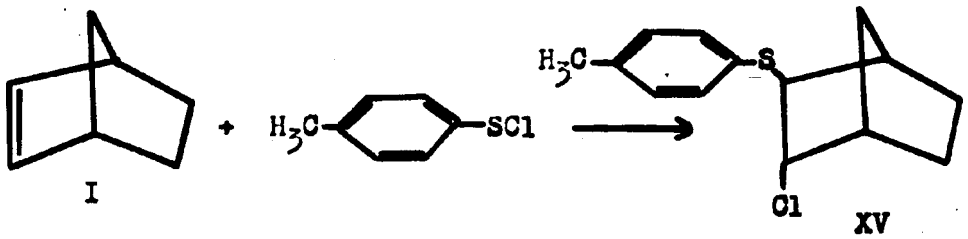
XI XII

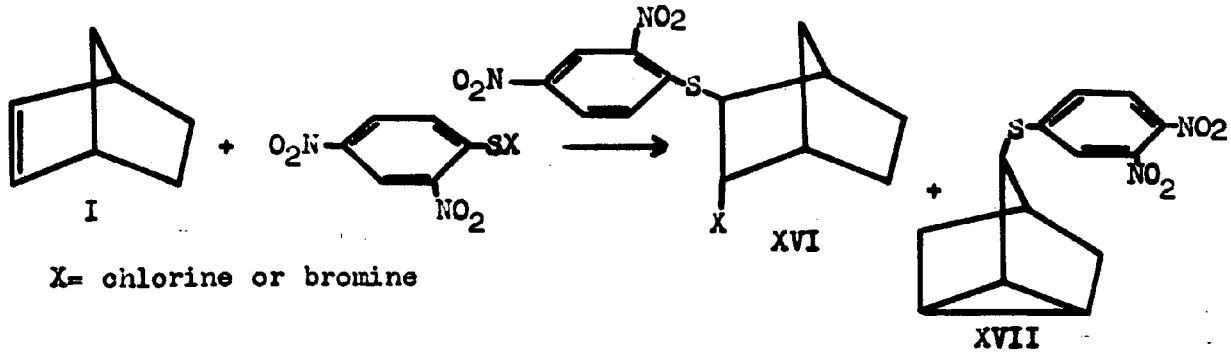


XIII XIV

Roberts, Johnson, and Carboni (8) have identified rearrangement products from the addition of chlorine and hypochlorous acid to norbornene (I). These reactions appear to parallel the bromination and hydroxylation reactions. This work also clarified the results of the chlorination of norbornene observed by Schmerling (9).

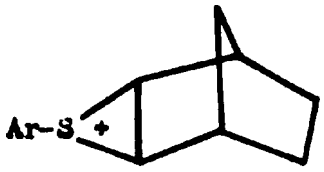
In contrast to the addition reactions noted, Kwart and Miller (10) and Cristol, Arganbright, Brindell, and Heitz (11) have shown that the addition of arylsulfenylhalides to norbornene does not give a 2,7-rearranged product. p-Toluenesulfenyl chloride gives only endo-3-chloro-exo-2-norbornyl-p-tolyl thioether (XV) (10, 11). The addition of 2,4-dinitrobenzenesulfenylhalides to norbornene (I) gives in addition to the normal product XVI a small amount of the nortricyclyl sulfide (XVII) (10).



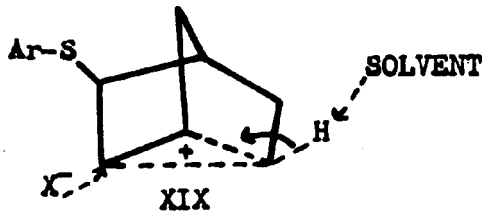


X= chlorine or bromine

Kwart and Miller (10) attribute the lack of the formation of the 2,7-rearranged product to the fact that the aryl group shields C_3 and C_4 in the bridged intermediate (XIX). As a consequence of the shielding, halide ion cannot attack C_4 in ion XIX; since ion XVIII has no electron deficiency at C_4, no route is open for formation of the 2,7-rearranged product. The normal product is obtained by endo attack of halide at C_3 in the ion (XVIII) and the nortricyclene derivatives by proton loss to the solvent at C_5 in the bridged ion (XIX) as indicated.



XVIII

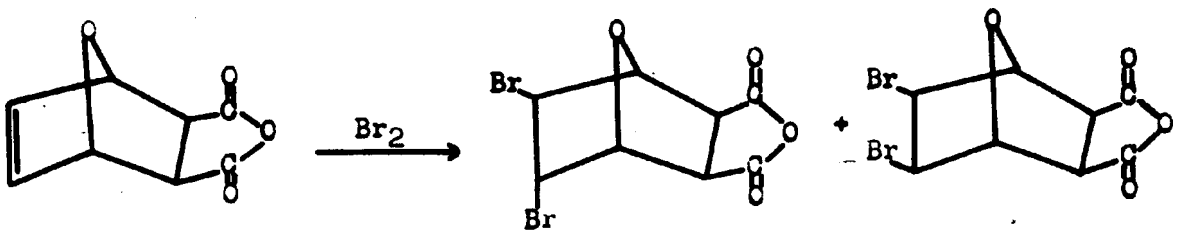


XIX

Cristol and coworkers (11) state that the results indicate that, when Ar is p-tolyl, XVIII is a lower energy intermediate than XIX and XIX does not compete for the halide ion. When Ar is 2,4-dinitrophenyl, however, XIX may be competitive with XVIII because of the

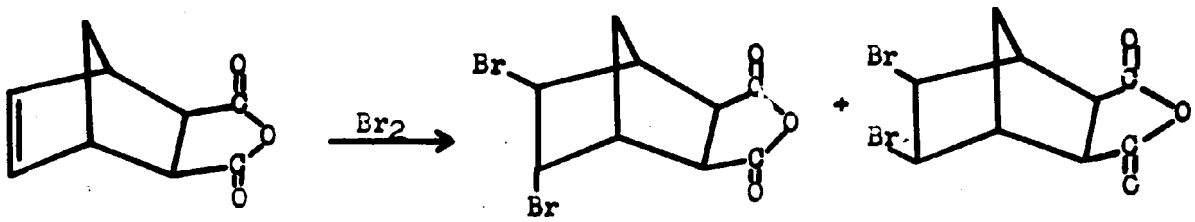
strong attracting power of the nitro group.

An apparent cis-addition to certain norbornene (I) derivatives has been examined by Berson and Swidler (12) and Kwart and Kaplan (13). Bromination of exo-cis-3,6-endoxo-Δ^4-tetrahydrophthalic anhydride (XX) in methylene chloride gave trans-(XXI) and cis-(XXII) dibromides in a ratio of about 2 to 1 (12). Formation of the cis-dibromide (XXII) was favored by non-polar solvents and illumination which suggests a radical mechanism.



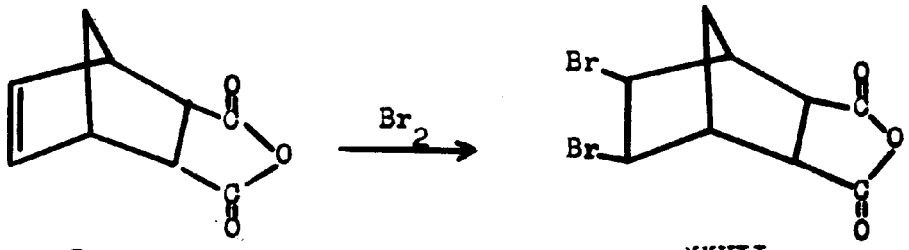
XX XXI XXII

Berson (14) has also demonstrated that (2.2.1)-bicyclohept-5-ene-exo-cis-2,3-dicarboxylic acid anhydride (XXIII) gives both trans-(XXIV) and cis-(XXV) dibromides if bromination is carried out in carbon tetrachloride and in the presence of light. However, only the trans-dibromide (XXIV) was isolated when ethyl acetate was the solvent.



XXIII XXIV XXV

The bromination of (2.2.1)-bicyclohept-5-ene-endo-cis-2,3-dicarboxylic acid anhydride (XXVI) in a non-polar solvent yields only the cis-dibromide (XXVII) as was carefully proven by Berson and Swidler (12), Berson (15), and Kwart and Kaplan (13). Bromination in ethyl acetate also gave the cis-dibromide (XXVII) as well as a glassy mixture of bromination products.

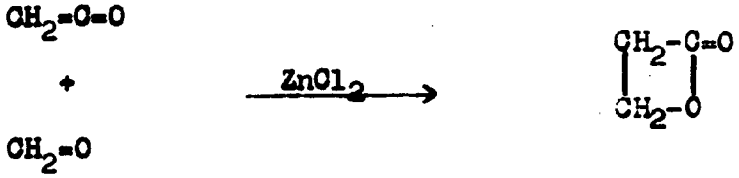


XXVI XXVII

LACTONIZATION

The formation of an internal cyclic ester, or lactonization, has been used extensively as an important aid in the structure proof of certain acidic norbornene derivatives. More recently lactonization techniques have been employed in the estimation of endo/exo isomer ratio in Diels-Alder reaction products (7,17,18,19) (vide infra).

The simplest lactone is β-propiolactone (XXVIII) which is formed from ketene and formaldehyde in the presence of suitable condensation catalysts such as mercuric or zinc chlorides (19).

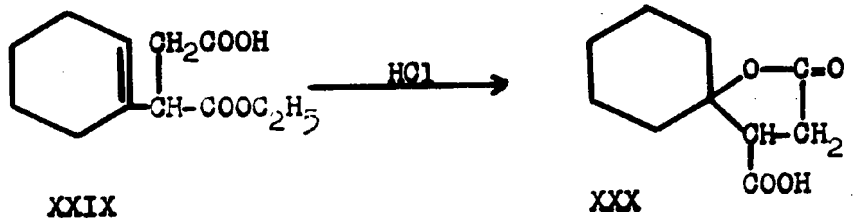


XXVIII

β -Hydroxy acids do not yield β -lactones due to the strain in closing the four membered ring. However, γ -and δ -hydroxy acids spontaneously undergo internal esterification to form stable γ - and δ -lactones.

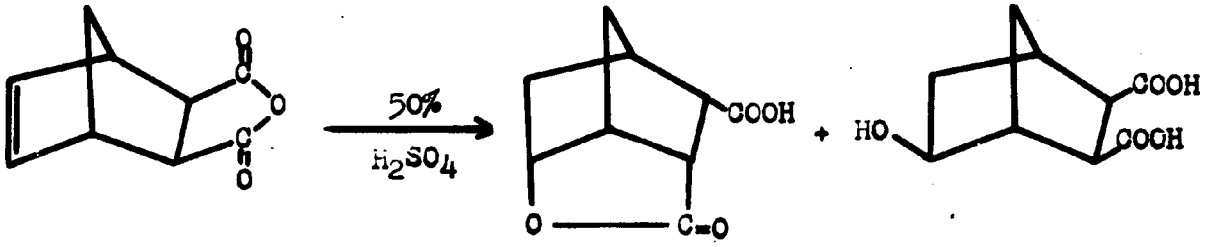
One of the important routes to lactones is through certain unsaturated acids. Several conditions for bringing about lactonization are known, methods in which β - γ and γ-δ -unsaturated acids form γ -lactones and δ- ε -unsaturated acids give δ -lactones.

Fittig (20) and Stobbe (21) made extensive use of concentrated mineral acids to bring about lactonization of unsaturated acids. Johnson, Davis, Hunt, and Stork (22) heated β -carbethoxy- β -cyclohexenylpropionic acid (XXIX) with concentrated hydrochloric acid for fifteen minutes and obtained γ - γ -pentamethyleneparaconic acid (XXX) in 98% yield.

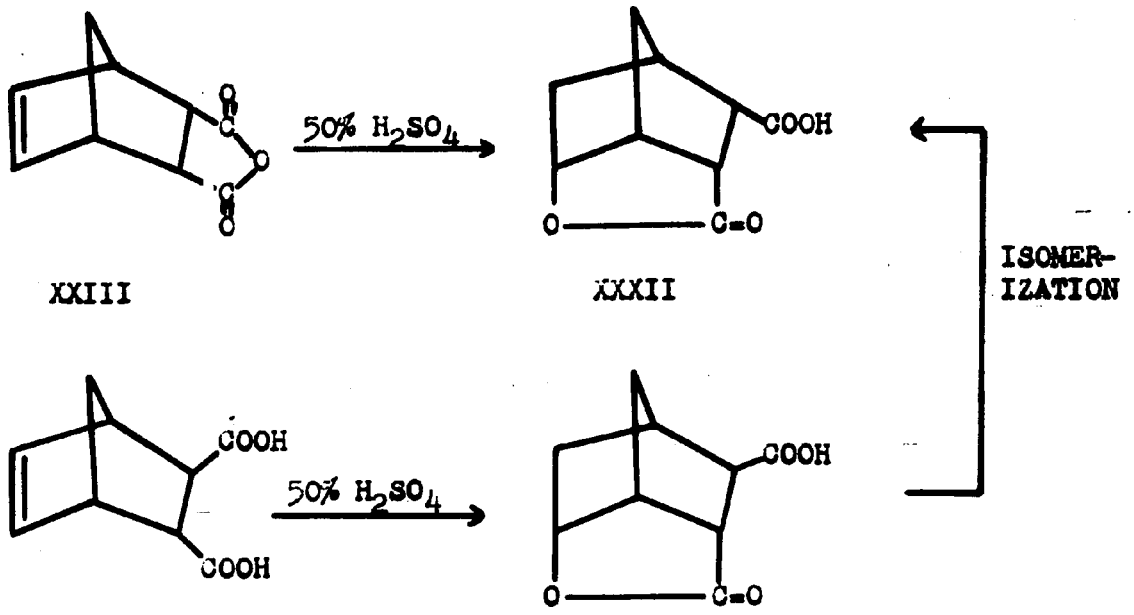


XXIX XXX

Alder, Stein, and coworkers (23) used an acid catalyzed lactonization as a structure proof of the Diels-Alder adducts XXIII, XXVI, and XXXI. A summary of these reactions is given below.



XXVI XXXII XXXIV



XXIII XXXII

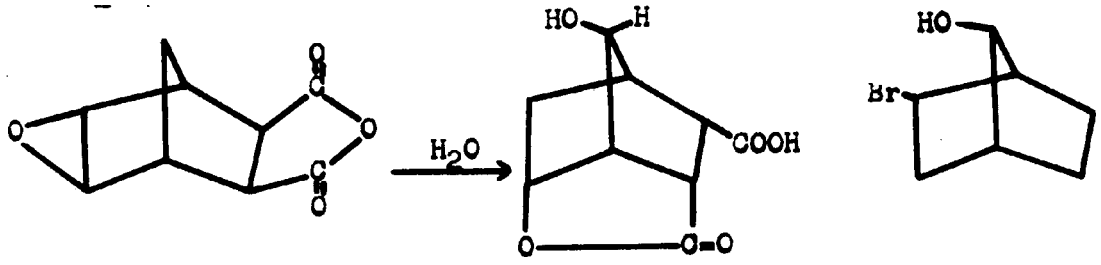
XXXI XXXIII

The lactonic acids XXXII and XXXIII apparently are formed in good yield and are identical with the hydrogenolysis products of the corresponding bromolactonic acids XLI and XLIII. (See page 13). The hydroxy acid (XXXIV) was isolated in about 45% yield. From this same reaction a 5 to 10% yield of XXXII was also isolated. Alder, Stein, and coworkers (23) proposed that a Wagner-Meerwein rearrangement would explain this product.

Alder, Stein, and coworkers (23) presented no sound evidence for the structure of the hydroxy acid (XXXIV). Berson and Suzuki (24), however, have provided a complete proof of the structure of the hydroxy acid (XXXIV) and have shown that the original assignment (23) was correct.

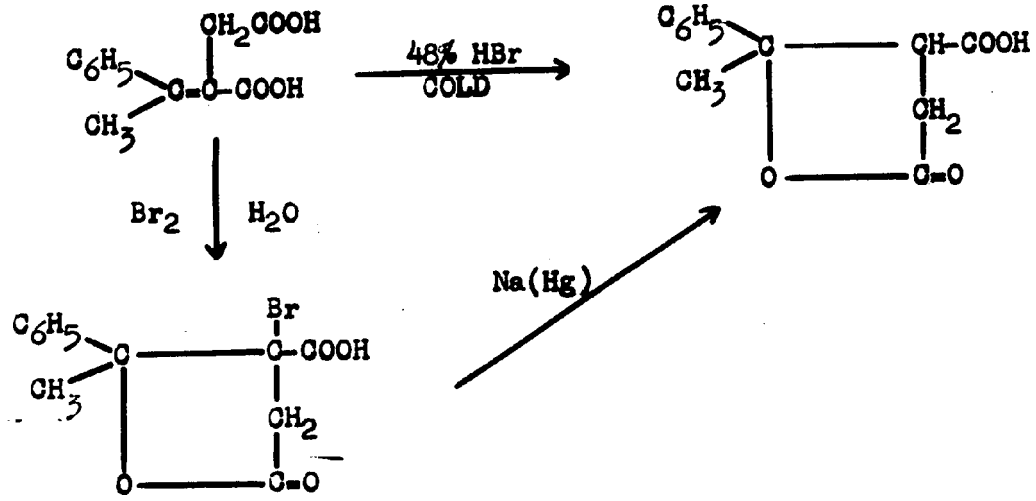
During the course of their investigations Berson and Suzuki (24) suggested that anti-7-hydroxy-endo-6-hydroxy-(2.2.1)-bicyclohep-

tane-endo-3-carboxy-endo-2-carboxylic acid lactone (XXXVI) was formed during the hydration of exo-5,6-epoxy-(2.2.1)-bicycloheptane-exo-cis-2,3-dicarboxylic acid anhydride (XXXV). The suggestion is not unreasonable in view of the observations of Walborsky and Loncrini (5) and Kwart and Vosburgh (6) on the hydration of norbornene epoxide (IX). Further support is provided by the observations of Walborsky and Loncrini (25) and Winstein and Stafford (26) that addition of hydrogen bromide to norbornene epoxide (IX) gives the 2,7-bromohydrin (XXXVII).



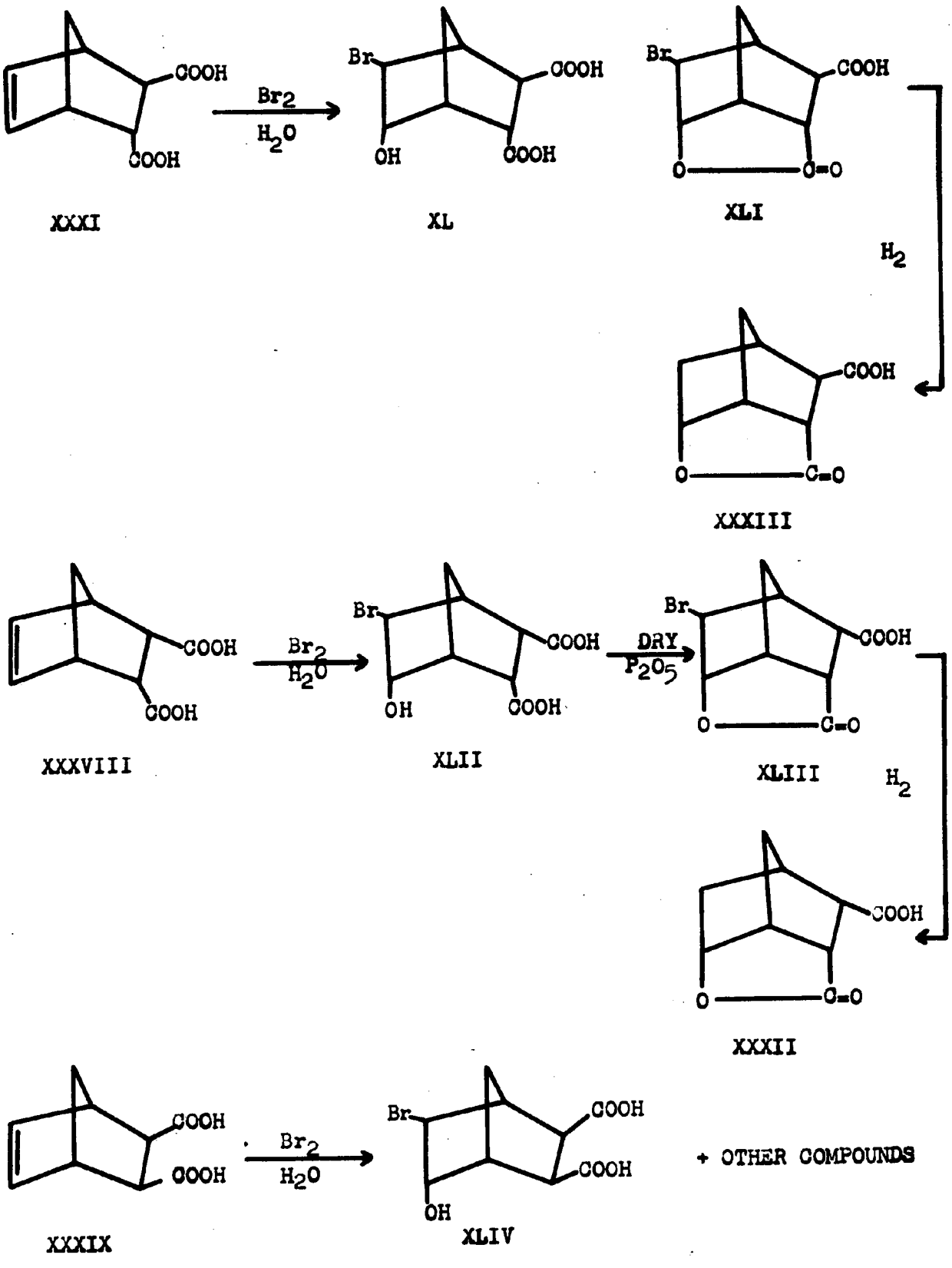
XXXV XXXVI XXXVII

Bromination of certain unsaturated acids gives bromolactones in excellent yields. This reaction has been used extensively by Fittig (20) and Stobbe (21) and more recently by others. Stobbe brominated the unsaturated acids in water solution and in chloroform. An example of reactions carried out by Stobbe is shown below.



Iodolactonization was first reported by Bougault (27) who prepared iodolactones from β- γ and γ-δ-unsaturated acids and used the method to separate these acids from α - β-unsaturated acids which do not react. Two iodination conditions were offered: 1) iodide-moist ether and mercuric oxide; and 2) iodine-potassium iodide solution added to a sodium bicarbonate solution of the acid. van Tamelen and Shamma (20), using the second procedure, have demonstrated that γ - δ-unsaturated acids form δ-iodo- γ-lactones while β - γ-unsaturated acids give β-iodo-γ-lactones. They emphasize that δ - ϵ-acids and acids having the unsaturation further removed afford poorly characterized iodohydrins.

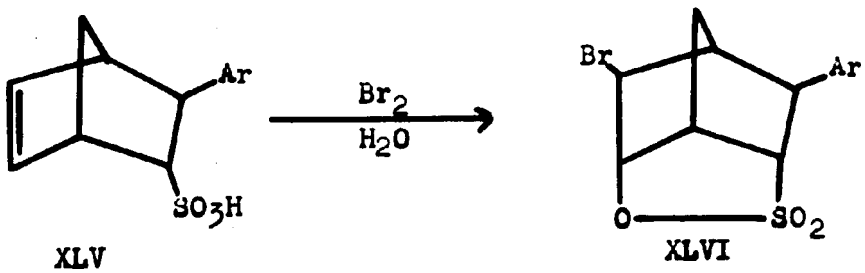
Bromolactonization of unsaturated Diels-Alder products was first reported by Diels and Alder (29). In a later paper Alder, Stein, and coworkers (30) used the reaction in an attempt to prove the structure of the isomeric (2.2.1)-bicyclohept-5-ene-2,3-dicarboxylic acids (XXXI, XXXVIII, and XXXIX). The bromohydrin (XL) was not isolated but by recrystallization of the crude bromination product the bromolactonic acid (XLI), m.p. 187°, was isolated. However, the autho·s report that the bromohydrin (XLII), m.p. 116°, can be isolated and then dried over phosphorous pentoxide at reduced pressure to give the bromolactonic acid (XLIII), m.p. 157°. Although no experimental details were given, Alder, Stein, and coworkers (30) mention briefly that the bromination of the <u>exo-cis</u>-acid (XXXIX) is a "complex process" and evaluation of the products for determination of the configuration


COOH
COOH
Br2
H2O
Br
OH
COOH
COOH
Br
COOH
O
C=O
H2
COOH
O
C=O
XXXI
XL
XLI
XXXIII
COOH
COOH
Br2
H2O
Br
OH
COOH
COOH
DRY
P2O5
Br
COOH
O
C=O
H2
COOH
O
C=O
XXXVIII
XLII
XLIII
XXXII
COOH
COOH
Br2
H2O
Br
OH
COOH
COOH
+ OTHER COMPOUNDS
XXXIX
XLIV

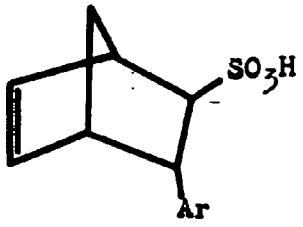
of the carboxyl groups is not worthwhile.

It is doubtful that lactone formation proceeds through a bromohydrin intermediate as assumed by Alder, Stein, and coworkers (30) and also by Bougault (27) for the iodolactonization reaction in sodium bicarbonate solution. Linstead and May (31) comment on the iodolactonization mechanism and point out that sodium salts of γ-hydroxy acids show no tendency to lactonize and, by analogy, iodohydrin acids in basic solution should not lactonize. As to the bromohydrin (XLII) reported by Alder, Stein, and coworkers (30), Berson and Swidler (12) and Kwart and Kaplan (13) have isolated a crystalline hydrate, m.p. 116°, of the bromolactonic acid (XLIII). The infrared spectrum of this compound is reported by Berson (32) to have a strong lactone absorption. Thus it is reasonable to say that Alder, Stein, and coworkers (30) had actually isolated the hydrate of the bromolactonic acid (XLIII) rather than the bromohydrin (XLII).

Rondestvedt and Wygant (16) used a bromolactonization technique to determine the endo/exo isomer ratio of the Diels-Alder adducts of cyclopentadiene and trans- α-β-unsaturated arylsulfonic acids and their derivatives. The endo-isomer (XLV) yields the bromosultone (XLVI), whereas the exo-isomer (XLVII) yields only unidentified acidic bromination products.



XLV XLVI

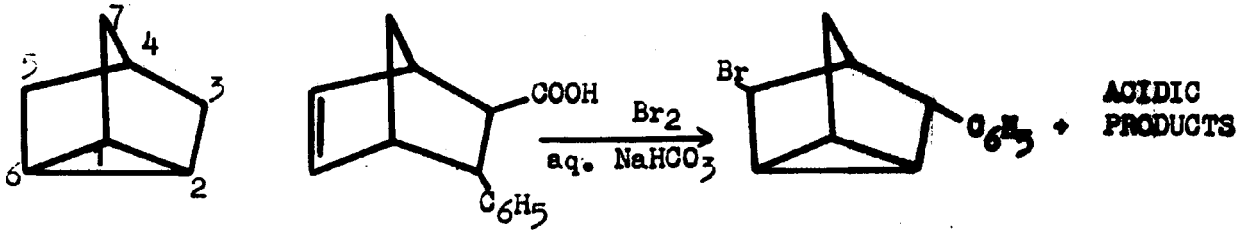


$\xrightarrow[H_2O]{Br_2}$ ACIDIC BROMINATION PRODUCTS

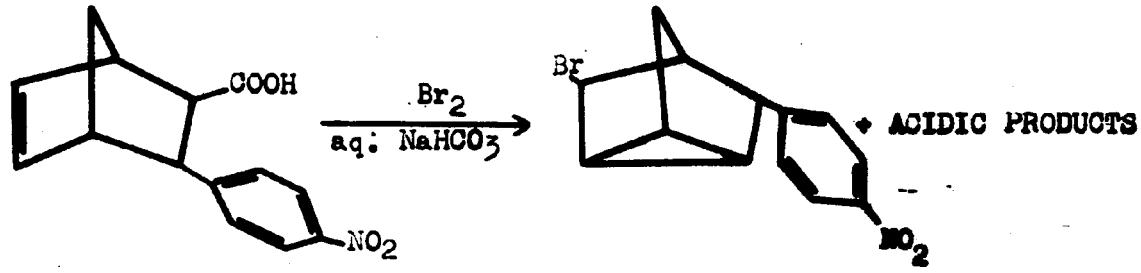
XLVII

Ver Nooy and Rondestvedt (17,33) attempted to use the same technique in the determination of the endo/exo isomer ratio of the Diels-Alder adducts of trans-cinnamic acid derivatives and cyclopentadiene. In this case, however, the bromolactonization procedure failed as mixtures of base insoluble products were obtained. Ver Nooy and Rondestvedt (17) conducted an investigation of the failure of the method and found that (2.2.1.$0^{2.6}$)-tricycloheptane (nortricyclene, XLVIII) derivatives were produced, in addition to uncharacterized acidic bromination products, from compounds containing an exo-carboxyl group. The corresponding compounds containing an endo-carboxyl group yielded only the expected bromolactones.

Bromination of endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic acid (XLIX) and the corresponding p-nitrophenyl compound (L) in sodium bicarbonate solution gave 3-bromo-5-phenyl-nortricyclene (LI) and 3-bromo-5-(p-nitrophenyl) nortricyclene (LII) respectively in about 65% yield (17).

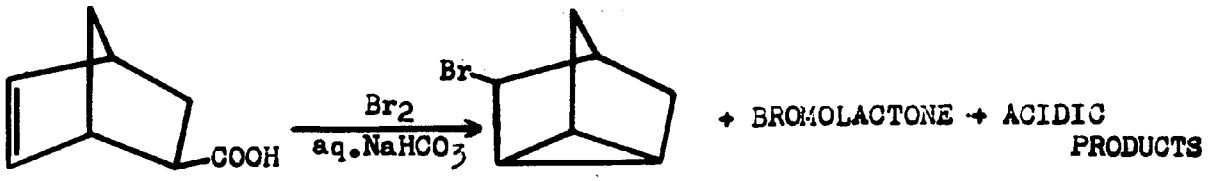


XLVIII XLIX

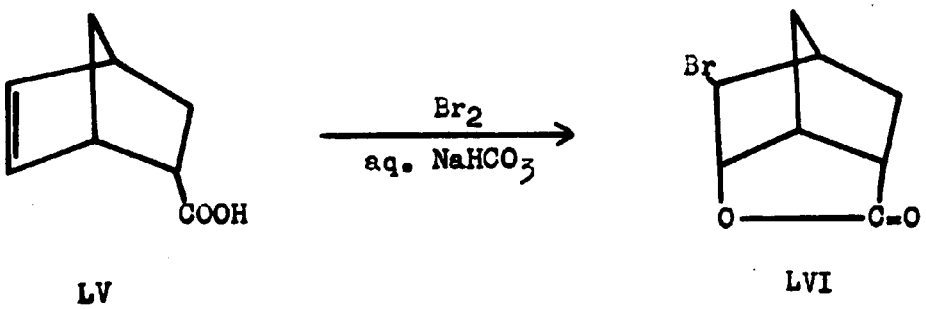


L LII

Bromination of (2.2.1)-bicyclohept-5-ene-exo-2-carboxylic acid (LIII) in sodium bicarbonate solution gave 3-bromonortricyclene (IV) (6-8%), a bromolactone (LIV) (1%), which depressed the melting point of the bromolactone (LVI) obtained from the bromination of the endo-acid (LV), and uncharacterized acidic products (17).



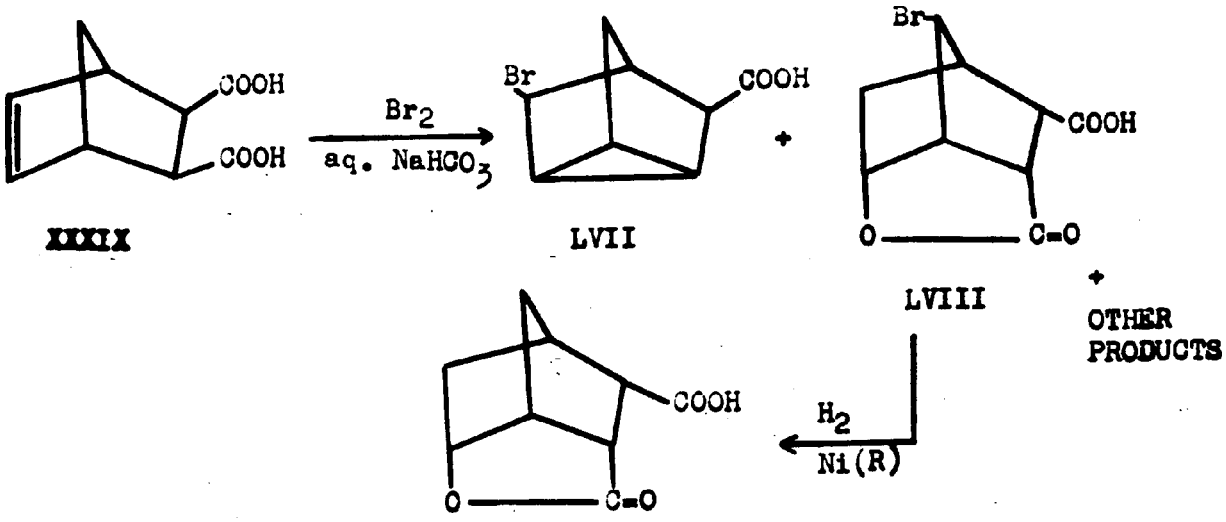
LIII IV LIV



LV LVI

The bromination of (2.2.1)-bicyclohept-5-ene-exo-cis-2,3-dicarboxylic acid (XXXIX) was reported previously by Alder, Stein, and co-

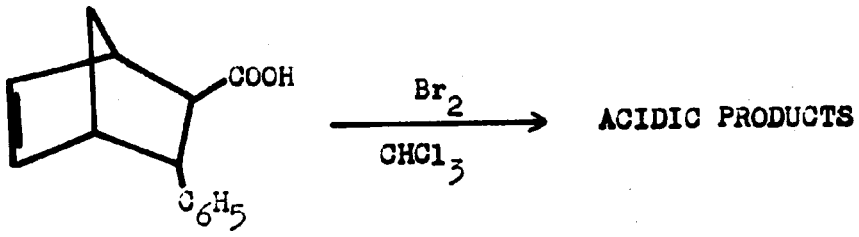
workers (30) to be a "complex reaction". (See page 12). Ver Nooy and Rondestvedt (17) repeated this bromination and found among the products 5-bromonortricyclene-3-carboxylic acid (LVII) and a bromolactonic acid (LVIII). Reductive debromination of the bromolactonic acid (LVIII) gave the known lactonic acid (XXXII).



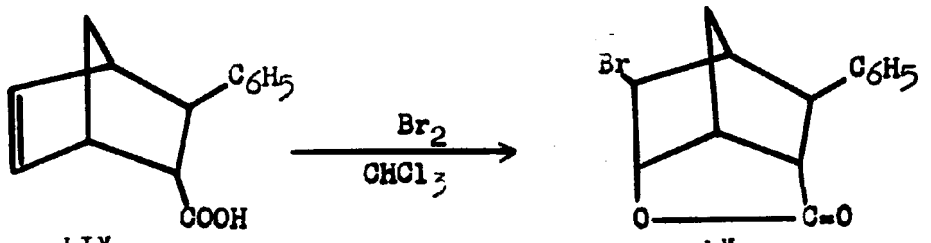
XXXIX LVII LVIII + OTHER PRODUCTS

XXXII

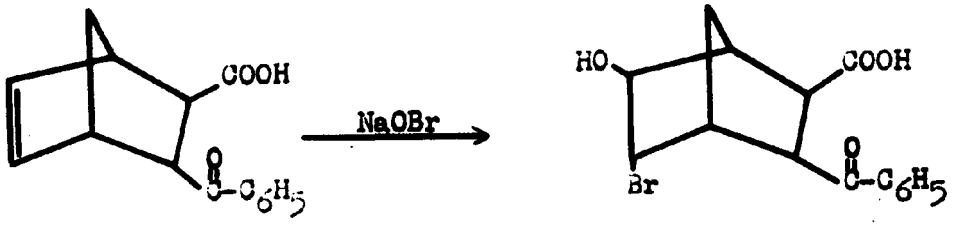
Winternitz, Mousseron, and Rouzier (7) have used bromination in chloroform as a method of estimating the endo/exo isomer ratio in various Diels-Alder reaction products; for example, the trans-cinnamic acid-cyclopentadiene adducts (XLIX) and (LIX). The exo isomer (XLIX) is reported to give only acidic bromination products and the endo isomer (LIX) to give the bromolactone (LX).



XLIX



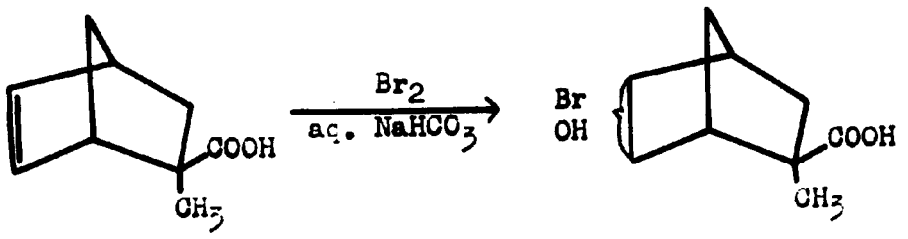
LIX LX



LXI LXII

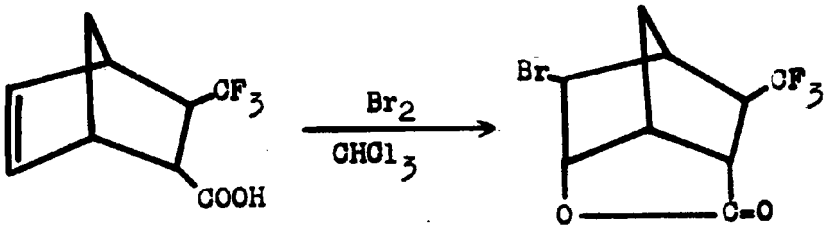
Winternitz, Mousseron, and Rouzier (7) also report that the reaction of endo-3-benzoyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic acid (LXI) with sodium hypobromite yields only the bromohydrin acid (LXII). This result is unexpected for the results of Ver Nooy and Rondestvedt (17) indicate that the formation of nortricyclene derivatives, during bromination in sodium bicarbonate solution, of (2.2.1)-bicyclohept-5-ene derivatives containing an exo-carboxyl group and an α-hydrogen atom is quite general.

Meek and Trapp (34) report that the bromination, in sodium bicarbonate solution, of endo-2-methyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic acid (LXIII) gives only a bromohydrin acid (LXIV).

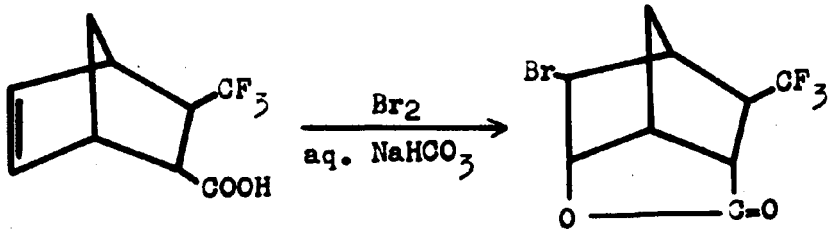


LXIII LXIV

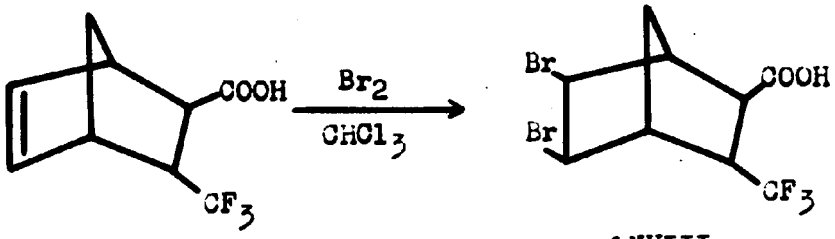
McBee, Hsu, and Roberts (18) used bromination in chloroform as a means of determining the endo/exo isomer ratio of the Diels-Alder adducts from trans-4,4,4-trifluorocrotonic acid and cyclopentadiene. The endo isomer (LXV) gives only the bromolactone (LXVII), while the exo isom r (LXVI) gives only a dibromoacid (LXVIII).



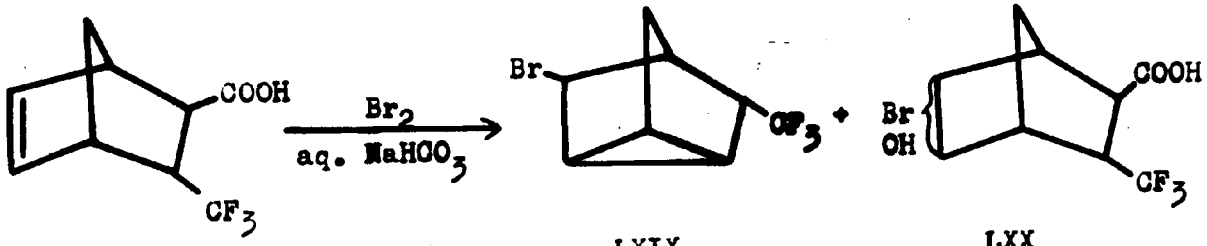
LXV LXVII



LXV LXVII



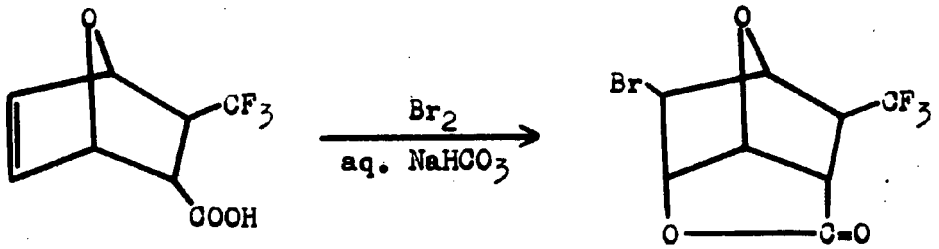
LXVI LXVIII



LXVI LXIX LXX

McBee, Hsu, and Roberts (18) also brominated the mixed adducts (LXV and LXVI) in sodium bicarbonate solution. Similar results to those reported by Ver Nooy and Rondestvedt (17) were obtained. The endo isomer (LXV) gave the bromolactone (LXVII) and the exo isomer gave a nortricyclene derivative (LXIX). In addition a bromohydrin acid (LXX) was isolated from the acidic bromination products. No rearranged bromolactone from the exo-acid (LXVI) was found. However, since the pure exo-acid (LXVI) was not brominated, if a small amount of a rearranged bromolactone was formed, it may have been lost during the purification of the bromolactone (LXVII). No basis is given for the assignment of the structure of the bromohydrin acid (LXX).

McBee, Hsu, and Roberts (18) also report that bromination in sodium bicarbonate solution of 7-oxa-exo-3-trifluoromethyl-(2.2.1)-bicyclohept-5-ene-endo-2-carboxylic acid (LXXI) gives the bromolactone (LXXII) in 95% yield. The corresponding exo-acid (LXXIII) was not isolated and therefore not brominated.

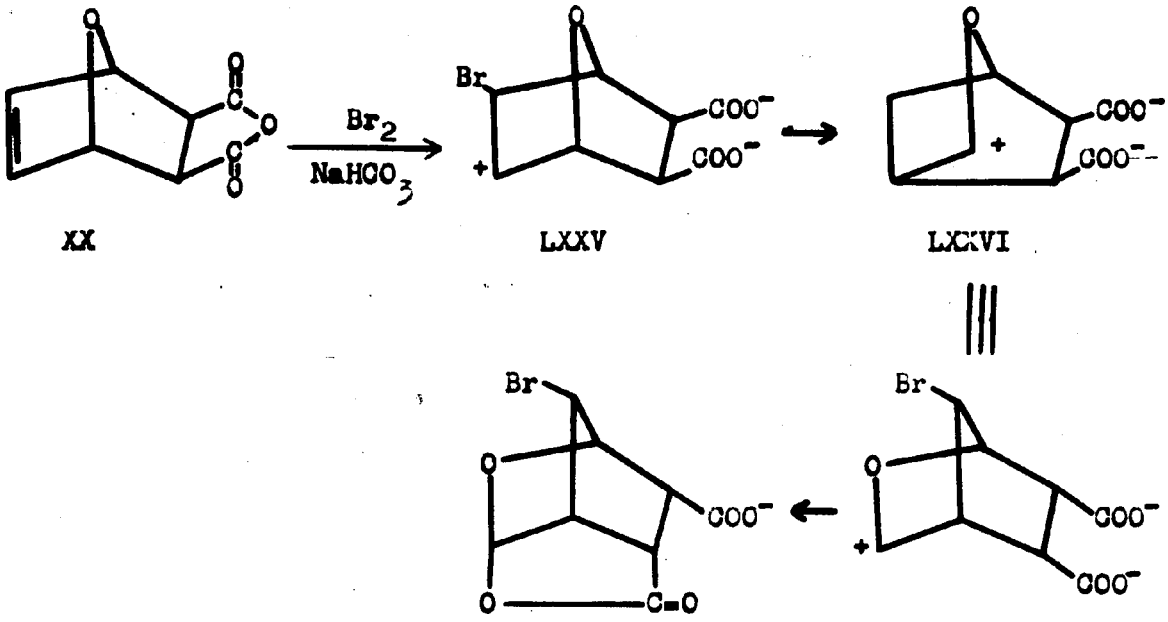


LXXI LXXII

Woodward and Baer (35) and Berson and Swidler (36) have reported that the bromination, in sodium bicarbonate solution, of 7-oxa-(2.2.1)-bicyclohept-5-ene-exo-cis-2,3-dicarboxylic acid anhydride (XX) gives the rearranged bromolactonic acid (LXXIV) together with unidentified

dibromide products. Woodward and Baer (35) have studied the structure of the bromolactonic acid (LXXIV) and there is little doubt that it is correct.

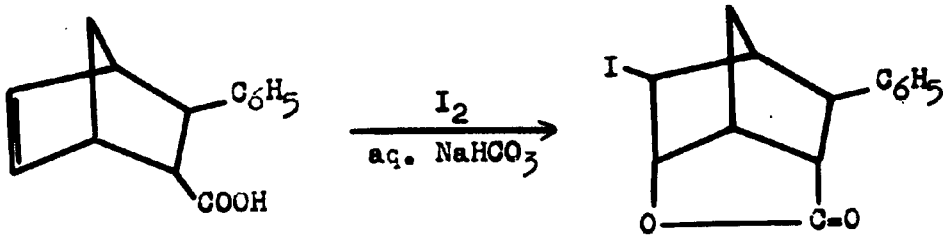
Woodward and Baer (35) proposed that this product was the result of lactonization subsequent to a Wagner-Meerwein rearrangement. They pictured the mechanism as first giving the ion (LXXV), or its equivalent, by positive bromine attack. This could not spontaneously lactonize as would a corresponding ion having the carboxyl group in the endo-position but after a Wagner-Meerwein rearrangement the new ion (LXXVI) now having the carboxyl group in a favorable steric position would lactonize to give the bromolactonic acid (LXXIV).



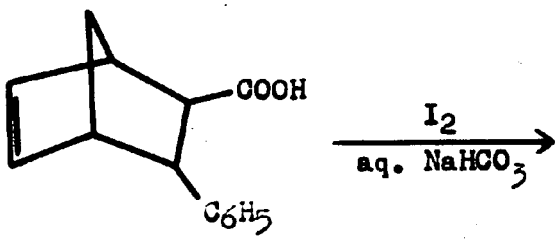
XX LXXV LXXVI LXXIV

After the failure of bromination in sodium bicarbonate solution to furnish a quantitative estimation of the endo/exo isomer ratio of trans-cinnamic acids and cyclopentadiene adducts. Ver Nooy and Rondestvedt (17,33) found that iodolactonization (27,28) gave the desired

results. The endo isomer (LIX) gave the iodolactone (LXXVII) while the exo isomer (XLIX) did not react.



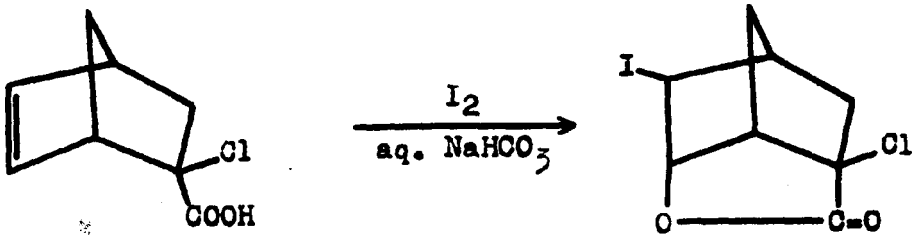
LIX LXXVII



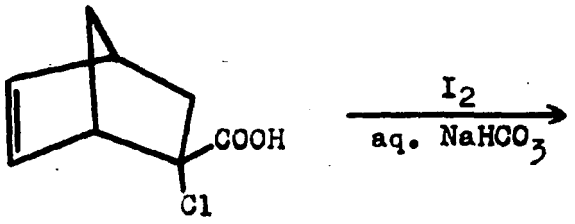
NO REACTION

XLIX

Iodolactonization has been found to be a general reaction for the separation and estimation of the endo and exo isomers of (2.2.1)-bicyclohept-5-ene-2-carboxylic acid derivatives (34,37,38). For example, Alder, Hartmann, and Roth (37) used iodolactonization to separate the isomers (LXXVIII and LXXIX) formed in the Diels-Alder reaction of α-chloroacrylic acid and cyclopentadiene. The endo/exo isomer ratio was estimated from the results of the same reaction. The endo isomer (LXXVIII) gave the iodolactone (LXXX), while the exo isomer (LXXIX) is reported to be recovered unchanged.



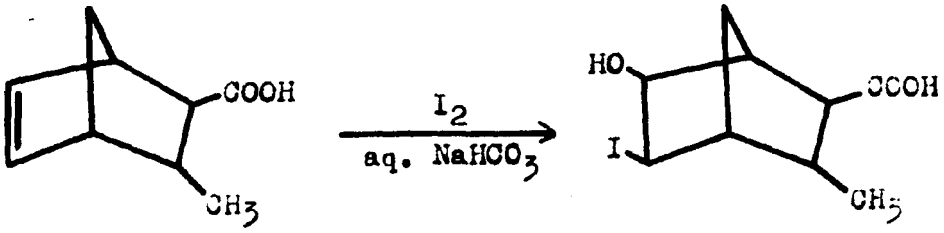
LXXVIII LXXX



NO REACTION

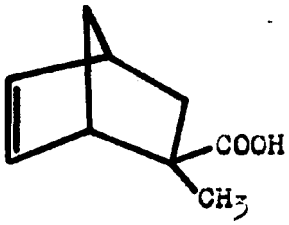
LXXIX

Beckmann and Mezger (38) report the formation of an iodohydrin (LXXXII) in 95 per cent yield on iodination, in sodium bicarbonate solution, of endo-3-methyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic acid (LXXXI). No basis is given for the assignment of the structure of LXXXII.



LXXXI LXXXII

Meek and Trapp (34) and Boehme and coworkers (39), however, disagree on the results of the iodination in sodium bicarbonate solution of endo-2-methyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic acid (LXIII). Meek and Trapp (34) report LXIII is unreactive to the iodine reagent, while Boehme and coworkers (39) report the isolation of an iodohydrin in 68% yield from the same reaction.



$\xrightarrow[\text{aq. } NaHCO_3]{I_2}$

NO REACTION
or
IODOHYDRIN ACID

LXIII

PURPOSE OF THE INVESTIGATION

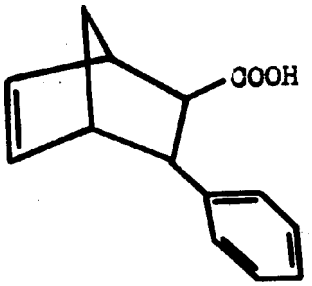
It was previously known that the addition of bromine to endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic acid (exo-acid) in aqueous sodium bicarbonate solution gave rise to unexpected products, whereas iodine did not react. The study of the addition of chlorine to the exo-acid was undertaken to learn further what effect the electrophilicity of the reagent has on the proportions of the products products produced. It was further intended to study the effect of the experimental environment; e.g., pH and solvent, on the proportions produced.

After a cursory investigation of the structure of the products of the chlorination reaction indicated the reaction was more complex than was predicted, the first objective of the research was discontinued.

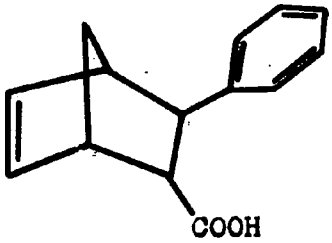
Full attention was diverted to the determination of the structure of three of the products isolated for it was felt that more information about the structure of the products was needed before the information to be gained from the objective first outlined could be properly applied.

RESULTS AND DISCUSSION

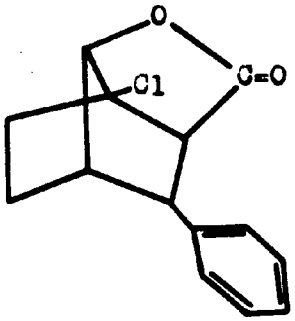
Abbreviations of nomenclature used in this section:



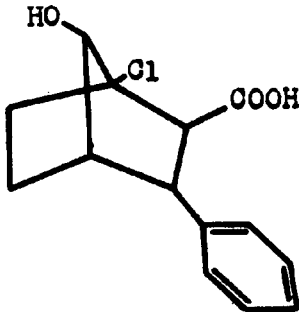
Compound number XLIX
Systematic name:
Endo-3-phenyl-(2.2.1)-bicyclo-hept-5-ene-exo-2-carboxylic acid
Abbreviation: exo-acid



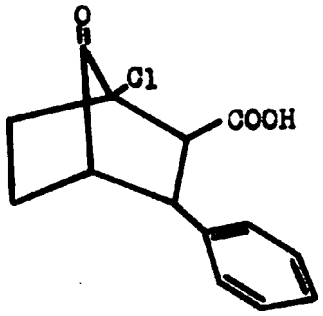
Compound number LIX
Systematic name:
Exo-3-phenyl-(2.2.1)-bicyclo-hept-5-ene-endo-2-carboxylic acid
Abbreviation: endo-acid



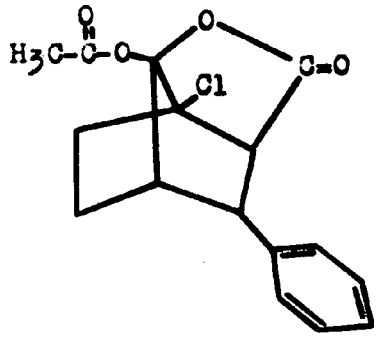
Compound number XCI
Systematic name:
1-chloro-endo-3-phenyl-syn-7-hydroxy-(2.2.1)-bicycloheptane-exo-2-carboxylic acid lactone
Abbreviation: rearranged chloro-lactone



Compound number XCII
Systematic name:
1-chloro-endo-3-phenyl-anti-7-hydroxy-(2.2.1)-bicycloheptane-exo-2-carboxylic acid
Abbreviation: chlorohydrin acid

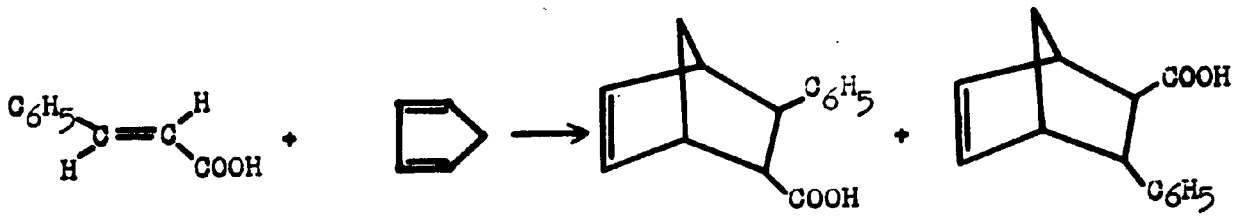


Compound number CVII
Systematic name:
1-chloro-endo-3-phenyl-7-keto-(2.2.1)-bicycloheptane-exo-2-carboxylic acid
Abbreviation: chloroketo acid



Compound number CVIII
Systematic name:
1-chloro-endo-3-phenyl-anti-7-acetoxy-syn-7-hydroxy-(2.2.1)-bicycloheptane-exo-2-carboxylic acid lactone
Abbreviation: acetate lactol

The exo-acid (XLIX) was prepared by means of the Diels-Alder reaction of trans-cinnamic acid and cyclopentadiene. The reaction is not quantitative and a mixture of isomeric products was obtained (33). The endo-acid (LIX) was separated by means of iodolactonization (17,33).

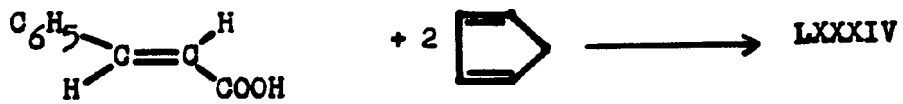


LIX XLIX

Acidification of the sodium bicarbonate solution gives a mixture of the exo-acid (XLIX) and unreacted trans-cinnamic acid.

The method of Rondestvedt and Ver Nooy (33) for the separation of the exo-acid (XLIX) and trans-cinnamic acid was found to be impractical when dealing with large quantities of material. While it is true that trans-cinnamic acid is almost insoluble in cyclohexane and 30-40° petroleum ether (33), it was found that the exo-acid is likewise almost insoluble in these solvents. Two methods were found to be satisfactory for the separation of large amounts of the exo-acid from trans-cinnamic acid: 1) partial neutralization of the sodium salts of the mixture of acids and 2) fractional crystallization of the sodium salts of the mixture of acids. Method 1 makes use of the observation that the exo-acid is a weaker acid than trans-cinnamic acid and almost pure exo-acid can be obtained by the careful addition of acid to the mixture of sodium salts. The second method is based on the observation that the sodium salt of the exo-acid is less soluble in water than the sodium salt of trans-cinnamic acid. Neither method, however, provides a complete separation of the two acids.

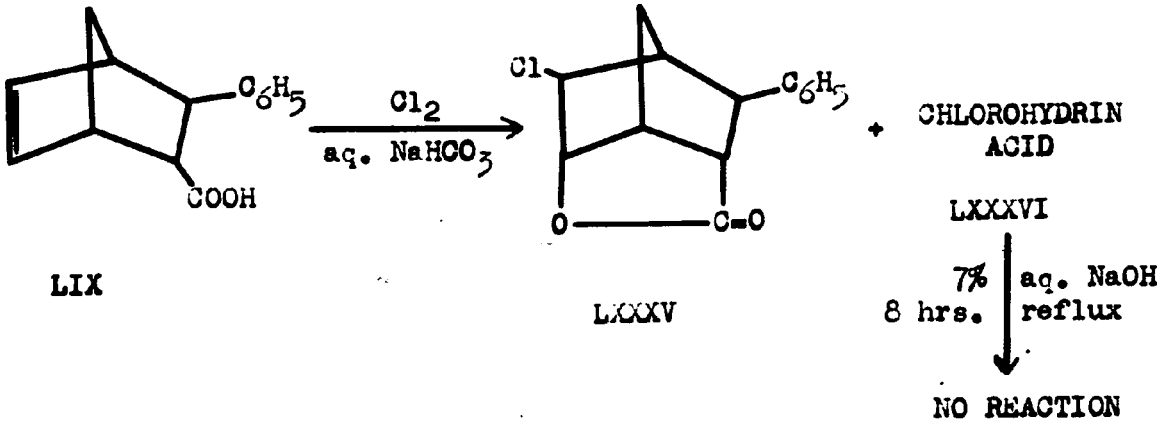
During work on the synthesis of the exo-acid (XLIX), it was found that the use of a large excess of cyclopentadiene and a long reaction time led to the production of a compound (LXXXIV), the analysis of which showed it to be composed of two molecules of cyclopentadiene and one molecule of trans-cinnamic acid. The structure of the compound (LXXXIV) was not investigated.



LXXXIV

The <u>endo</u>-acid (LIX) was brominated in sodium bicarbonate solution using the procedure of Rondestvedt and Ver Nooy (17,33). A 90% yield of the bromolactone (LX) was obtained, however, a small quantity of acidic bromination products was also found to be present. No pure acidic products were isolated.

Chlorination of the <u>endo</u>-acid (LIX) in sodium bicarbonate solution gave the expected chlorolactone (LXXXV) but it was not obtained in the nearly quantitative yield as were the corresponding iodo and bromo lactones (LX and LXXVII) (17,33). From the acidic products there was isolated a chlorohydrin acid (LXXXVI) in 22% yield. The structure of the chlorohydrin acid (LXXXVI) was not investigated beyond the observation that it was recovered unchanged after it had been refluxed with 7% aqueous sodium hydroxide for eight hours.

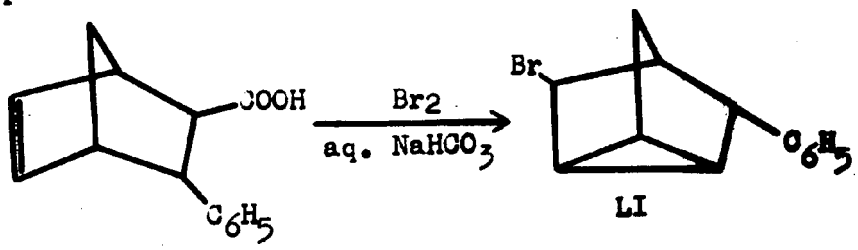


LIX

LXXXV

The bromination in sodium bicarbonate solution of the <u>exo</u>-acid (XLIX) reported by Rondestvedt and Ver Nooy (17,33) was repeated. While the 3-bromo-5-phenylnortricyclene (LI) was isolated in comparable yield, closer investigation of the non-acidic product indicated that trace amounts of a bromolactone were formed during the reaction. Examination of the acidic bromination products resulted in the isolation of three

products: two bromohydrin acids (LXXXVII and LXXXVIII), m.p. 173-174° and m.p. 143-144° respectively, and a monobromo acid (LXXXIX), m.p. 233-234°. Because the analogous compounds appear to have been isolated from the chlorination of the exo-acid (vida infra) no attempts at a structure proof were made on LXXXVII, LXXXVIII, and LXXXIX.



XLIX

LI

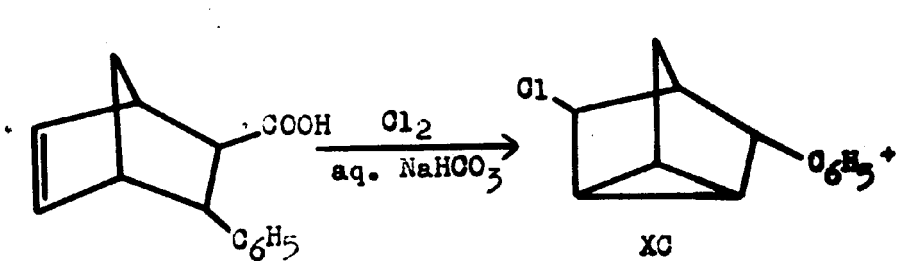
+ BROMOLACTONE (?)

+ BROMOHYDRIN ACID LXXXVII

+ BROMOHYDRIN ACID LXXXVIII

+ MONOBROMO ACID LXXXIX

The chlorination in sodium bicarbonate solution of the exo-acid (XLIX) was more thoroughly investigated. From the non-acidic products there were isolated the expected 5-chloro-3-phenylnortricyclene (XC) and a rearranged chlorolactone (XCI). Investigation of the acidic chlorination products resulted in the isolation of three compounds: two chlorohydrin acids (XCII and XCIII), m.p. 172.5-173.5° and 146-147° respectively, and a monochloro acid (XCIV), m.p. 236-237.5°.



XLIX

XC

XCI

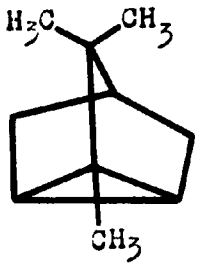
+ CHLOROHYDRIN ACID XCII

+ CHLOROHYDRIN ACID XCIII

+ MONOCHLORO ACID XCIV

The major chlorination products were the nortricyclene derivatives (XC), the chlorolactone (XCI), and the chlorohydrin acid (XCII). It was found that the same products were obtained when chlorine gas was passed into a sodium bicarbonate solution of the exo-acid and when an aqueous solution of chlorine was added to a sodium bicarbonate solution of the exo-acid. The same products were also obtained when chlorine water was added to the exo-acid dissolved in a standard Clark and Lubs buffer of pH 7.2 (40). No attempt was made to isolate the minor products XCIII and XCIV from all of these reactions.

The nortricyclene structure of XC is assigned on the basis of analysis and infrared spectrum. XC exhibits strong absorption bands at 800 and 820 cm^{-1} and weaker absorption bands at 1940, 1860, and 1800 cm^{-1}. Roberts and coworkers (2), Winston and Wilder (41), and many others have found an absorption at 12.4-12.5 microns (800-810 cm^{-1}) to be characteristic of nortricyclene and its derivatives. It was also previously known (42) that the tricyclene (XCV) in the terpene series has a strong absorption at 12.3 microns (815 cm^{-1}).



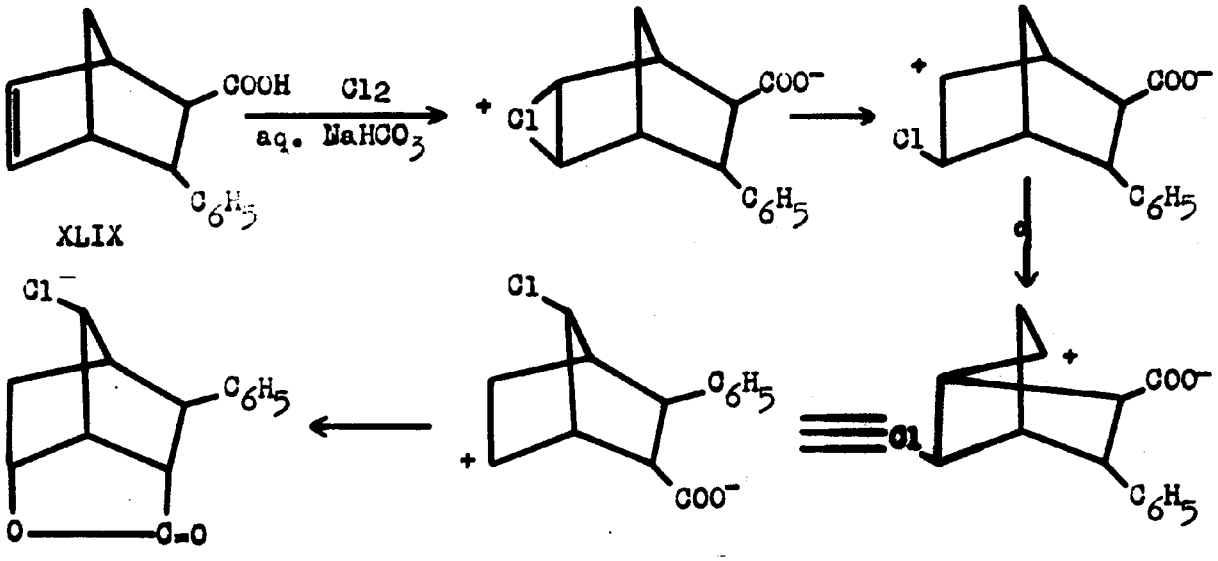
XCV

The Raman and infrared spectra of nortricyclene (XVII) and 3-bromonortricyclene (IV) was studied in great detail by Lippincott (43).

The absorptions of XC observed at 1940, 1860, and 1800 cm^{-1} are in close agreement with the absorptions reported by Lippincott (43) for IV and XLVIII.

The position of the chlorine atom in XC was assigned on the basis of its fairly rapid reaction with alcoholic silver nitrate. The position of the phenyl group is assigned on the assumption that the tricyclic system was formed simultaneously with loss of carbon dioxide.

An investigation of the chlorolactone (XCI) was started in order to confirm its structure. A compound of the assigned structure would result from lactonization subsequent to a Wagner-Meerwein rearrangement in a manner analogous to the work of Ver Nooy and Rondestvedt (17) and Woodward and Baer (35). (See pages 17 and 21).

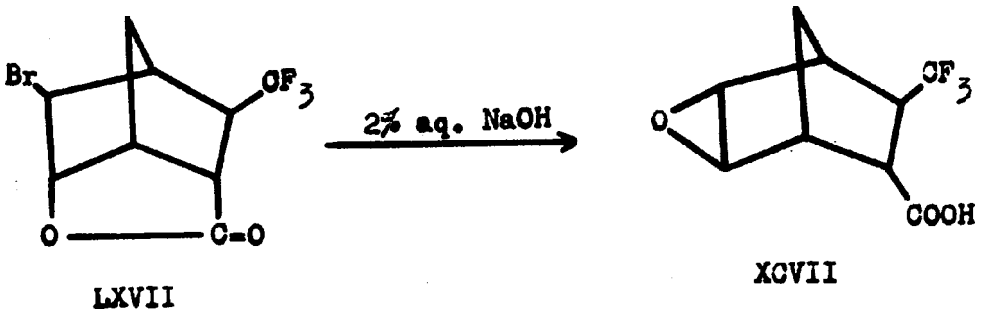


Saponification of the chlorolactone (XCI) with aqueous sodium hydroxide, followed by acidification gave only the chlorolactone (XCI). No chloride ion could be detected with silver nitrate. In one case, a small amount of a compound (XCVI), m.p. 172-184°, was isolated. This

compound showed a hydroxyl band in the infrared spectrum. The compound XCVI could not be purified further and it relactonized on standing to the chlorolactone (XCI). XCVI was probably the chlorohydrin acid of the chlorolactone.

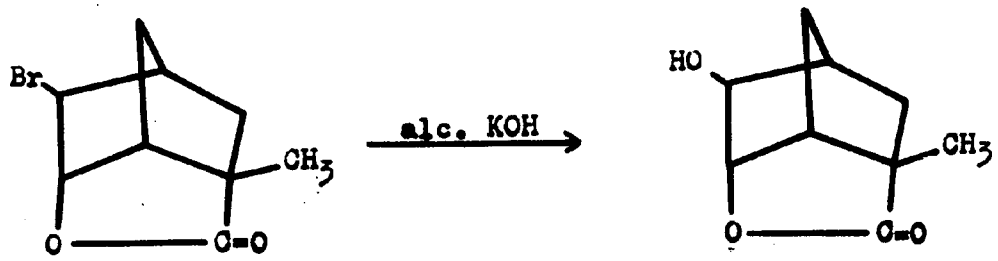
Concurrently with the investigation of the structure of the chlorolactone (XCI), an investigation of the structure of the chlorohydrin acid (XCII), m.p. 172-173°, was conducted. The chlorohydrin acid (XCII) was recovered unchanged after it was refluxed with 20% aqueous sodium hydroxide for forty hours. XCII was also recovered unchanged after it was refluxed with 20 per cent ethanolic potassium hydroxide for twenty-two hours. In all cases no precipitate of silver chloride was obtained with silver nitrate.

The results of these reactions may be compared to the observations of McBee, Hsu, and Roberts (18), Meek and Trapp (34), and Roberts and coworkers (8). McBee, Hsu, and Roberts (18) report that the bromolactone (LXVII) on refluxing with 2% aqueous sodium hydroxide gives the exo-5,6-epoxy acid (XCVII). Meek and Trapp (34) on heating the bromolactone (XCVIII) with ethanolic potassium hydroxide on a steam bath for thirty minutes obtained the corresponding vicinal hydroxylactone (XCIX). Roberts and coworkers (8), under conditions comparable to those used with XCII, obtained 2-chloro-2-norbornene (CII) in small yields from the endo-cis- and trans-2,3-dichloronorbornanes (C and CI).



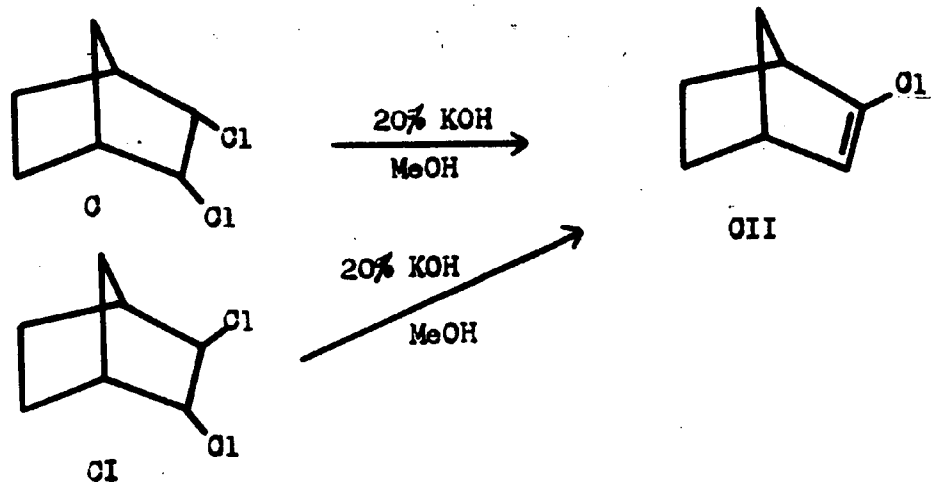
LXVII

XCVII



XCVIII

XCIX



CII

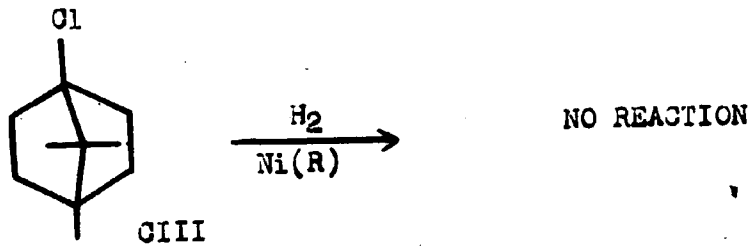
CI

The results obtained with XCI and XCII thus indicate that the chlorine and hydroxyl (or potential hydroxyl) group are not in a 1,2-position. They also indicate that the chlorine atom is not situated in the 5 or 6 positions.

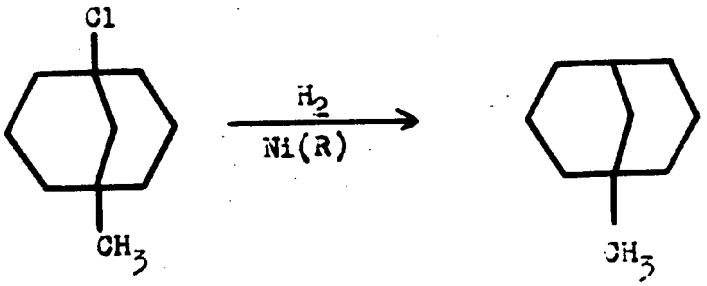
The chlorolactone (XCI) was recovered unchanged when it was stirred under hydrogen for six days with palladium on carbon as a catalyst. The chlorohydrin acid was likewise recovered unchanged when it

was stirred under hydrogen for four days with palladium on carbon as catalyst and when it was stirred under hydrogen for two days with Raney nickel (W-4) as catalyst.

No examples of the reductive dehalogenation of a chlorine atom on a methylene bridge were found in the literature, however, Ver Nooy and Rondestvedt (17) report the successful reductive debromination of the bromolactonic acid (LVIII, page 17) with Raney nickel. It may be noted here, that while various 1-bromo-(2.2.2)-bicyclooctanes have been successfully debrominated with hydrogen and Raney nickel (44, 45, 46, 47), 4-chlorocamphane (CIII) was not dechlorinated by hydrogen and Raney nickel after five days (48). Rabe and coworkers (49) report the successful reductive dechlorination of the bridgehead chlorine atom in 1-chloro-5-methyl-(3.3.0)-bicyclononane (CIV).



CIII

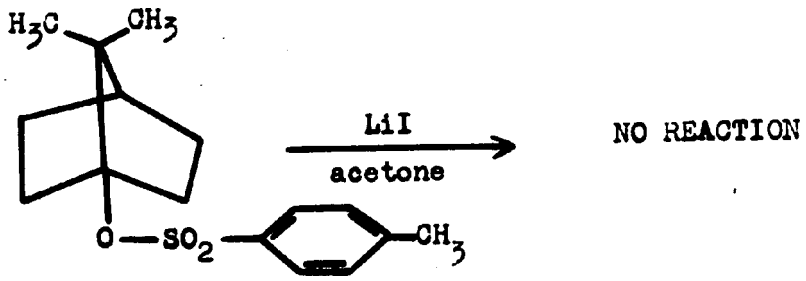


CIV

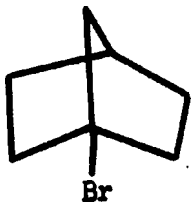
The chlorohydrin acid (XCII) was recovered unchanged after it was refluxed with sodium iodide in acetone for twelve days and no pre-

cipitate of silver chloride was obtained when XCII was refluxed with ethanolic silver nitrate for forty-eight hours.

Methyl-7-oxa-exo-cis-5,6-dibromo-(2.2.1)-bicycloheptane-exo-cis-2,3-carboxylate is reported (50) to be inert toward these reagents. However, it reacts rapidly with base liberating bromide ion. The reaction of XCII with base has been discussed. (See pages 33 and 34). While no reference to the behavior of these reagents toward a chlorine atom on a methylene bridge was found in the literature, the results suggest that the chlorine atom may be at a bridgehead position. It is known (51) that the bridgehead positions in the (2.2.1)-bicycloheptane ring system are very inert toward displacement reactions. For example, 1-apocamphyl-p-toluenesulfonate (CV) has been reported (52) not to react with lithium iodide in acetone when they were refluxed for twenty-two hours. The bridgehead halogen atoms are very inert to silver nitrate (48,51,52,53). 1-Bromo-(2.2.1)-bicycloheptane (CVI) was reported (53) to be recovered unchanged when it was heated with alcoholic silver nitrate at 150° for two days.



CV



$\xrightarrow{\text{alc. } AgNO_3}$ NO REACTION

CVI

Since the non-reactivity of the chlorine atom indicates that it may be at a bridgehead position, the nuclear magnetic resonance (NMR) spectra of XCI, XCII, and other available (2.2.1)-bicyclic derivatives were investigated. Professor W.R. Vaughan kindly consented to run and interpret the NMR spectra. The results of the investigation indicate very strongly that the chlorine atom in XCI, XCII, CVII, and CVIII (vide infra) (see table 1 on page 38) is at a bridgehead position.

Saponification of the chlorolactone (XCI), followed by sodium permanganate oxidation of the sodium salt of the chlorohydroxy acid, gave the chloroketo acid (CVII). Oxidation of the chlorohydrin acid XCII with chromium trioxide in water-acetic acid or Jones' reagent (54, 55) also gave the chloroketo acid (CVII). The chloroketo acid obtained from the chlorolactone (XCI) was found to be identical with the chloroketo acid obtained from the chlorohydrin acid (XCII). The confirmation of the identity of the chloroketo acids was on the basis of admixture melting point, superimposable infrared spectra, and derivatives.

That the relative positions of the hydroxyl group and carboxyl group in the chlorolactone (XCI) had not changed during oxidation was shown by formation of the acetate lactol (CVIII) (56). That the chlorine atom had not migrated was strongly indicated by the NMR spectrum of the chloroketo acid (CVII).

TABLE 1

COMPOUND	SOLVENT	-REFERED TO WATER	ASSIGNMENT	RELATIVE INTENSITY
Chloroketo acid (CVII)	pyridine	-7.2	$CO_2\underline{H}$	1[a]
		+0.7	-C-H (bridgehead)	1[b]
		+1.9	$-\underset{\underset{CO_2H}{|}}{C}-\underline{H}$	1[c]
Acetate lactol (CVIII)	pyridine	+0.98	-C-H (bridgehead)	1[b]
		+2.1	$-\underset{\underline{H}}{\overset{O^-}{C}}-\overset{O^-}{C}=O$	1[c]
		+3.61(No fine structure)	$-O-\overset{O}{\overset{\|}{C}}-CH_3$	3[d]
Rearranged chloro-lactone (XCI)	acetone	+0.9	-C-H (bridgehead)	1[b]
		+1.7	$-\underset{\underline{H}}{\overset{O^-}{C}}-\overset{O^-}{C}=O$ or $(-O-\underset{\underline{H}}{C}-)$	1[c]

Evidence for only one bridgehead hydrogen atom based on relative intensity of lines.

REFERENCES FOR TABLE 1

a.) L. H. Meyer, A. Saika, and H. S. Gutowsky, J. Am. Chem. Soc., 75, 4567 (1953).

b.) Bridgehead protons in Norbornene: δ=+1.2
bicyclo-(2.2.1)-heptadiene: δ= +0.93
dibenzobicyclo-(2.2.1)-octadiene: δ= -0.05 (CCl_4)
dibenzobicyclo-(2.2.1)-heptadiene: δ= +0.45 (CCl_4)
First two examples obtained in this laboratory. The last two examples by Dr. E. B. Baker of Dow Chemical Company.

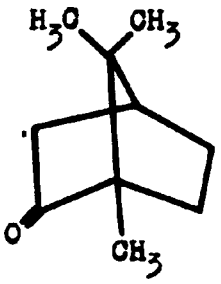
c.) Assigned on the basis of isobutyric acid H: δ = +2.5; diisopropylketone δ= +2.3; This laboratory as pure liquids.

d.) Acetate protons 3.2 to 3.4 in methyl, ethyl, and propyl esters. As pure liquids.

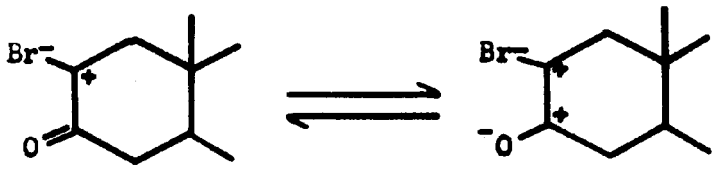
The ketonic carbonyl stretching frequency in the infrared spectrum of the chloroketo acid (CVII) was 1770 cm^{-1}. Allen, Davis, Stewart, and Van Allan (57) have studied the infrared absorptions of carbonyl groups in bridged compounds. As a result of their intensive study, Allen and coworkers (57) have determined that those substances which have a 1,4-(para) carbonyl bridge across a six membered ring have a characteristic carbonyl band at 5.64 microns (1770 cm^{-1}). This suggests that a keto group in the chloroketo acid (CVII) is on the methylene bridge.

The carbonyl stretching frequency in camphor (CIX) was found to be 1740 cm^{-1}. An α-bromo ketone is reported (58) to raise the carbonyl frequency about 20 cm^{-1}, and chlorine substition appears to affect the carbonyl absorption frequency to about the same amount as bromine (58). On this basis the absorption of α-chlorocamphor would have a carbonyl absorption at approximately 1760 cm^{-1}, which is very near the observed value of 1770 cm^{-1}. Since it has been shown (page 33) that the chlorine atom cannot be in the 5-position if the hydroxyl or pseudohydroxyl group of XCII and XCI respectively occupies the 6-position, this possibility for the abnormally high carbonyl absorption frequency of the chloroketo acid (CVII) can be discarded. Other evidence has shown the strong possibility that the chlorine atom occupies a bridgehead position (page 38). Thus the possibility that the bridgehead chlorine atom is responsible for the "abnormal" carbonyl absorption frequency must be considered. The effect of the α-halogen atom, in the increase of the frequency of the carbonyl absorption, appears to be to increase the double

bond character of the carbonyl group (59). In steroids this effect is exerted only if the C-X link is coplanar with the ketonic group so that the proportion of the polar structure (CXI) is increased (60).



CVIX



CX CXI

Thus bromine substituted at an α-equatorial position in a ring with a chair configuration will raise the frequency of an adjacent carbonyl group by 20 cm^{-1}. On the other hand, substitution in an axial position does not result in any alteration in the frequency (60).

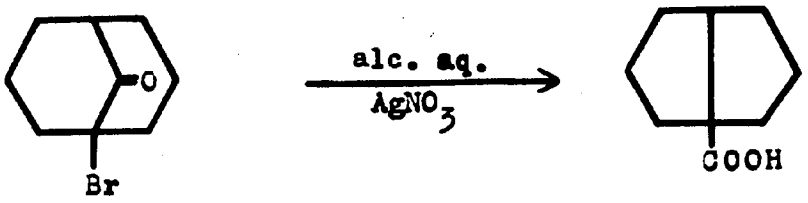
In the chloroketo acid (CVII) it seems unlikely that CXIII would be a contributing structure due to lack of coplanarity of the chlorine atom and carbonyl group, therefore, the carbonyl absorption frequency of the ketone would not be expected to be increased.



CXII CXIII

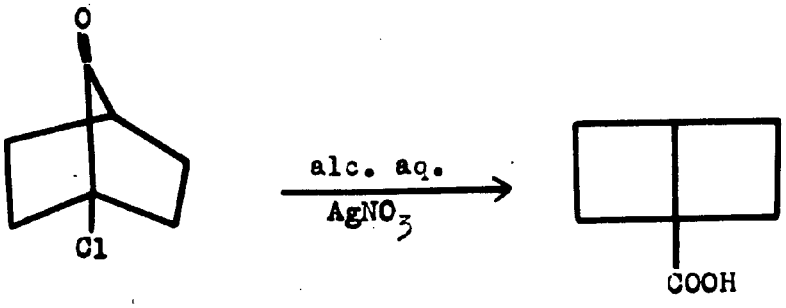
There was no precipitate of silver chloride formed in refluxing the chloroketo acid (CVII) with alcoholic silver nitrate for forty-eight hours. Cope and Graham (61) have reported that 1-bromo-(3.3.1)-bicyclononan-9-one (CXIV) reacts immediately with aqueous

ethanolic silver nitrate to give the carboxylic acid (CXV). Cope and Graham (61) also report that a mixture of α-bromoisobutyrophenone and ethanolic silver nitrate precipitated silver bromide when it was heated.



CXIV CXV

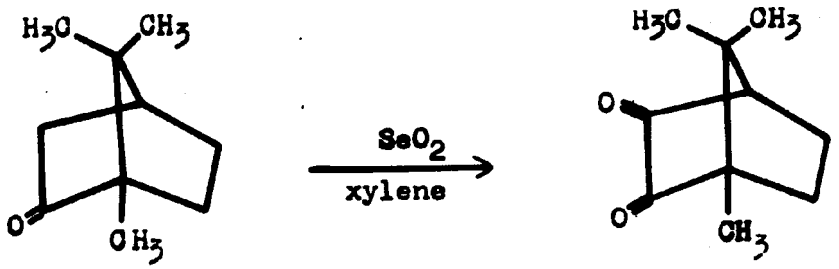
These results supply additional evidence that the chlorohydrin acid (XCII) is not a 1,2-chlorohydrin with the respective groups situated in the 5 and 6 positions. A possibility for the failure of a structure of the type of CXVI to react with silver nitrate could be a slight tendency to form two fused four membered rings (CXVII).



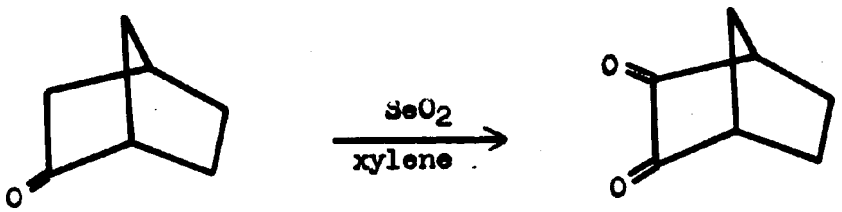
CXVI CXVII

The reaction of the chloroketo acid (CVII) with selenium dioxide in refluxing xylene and pseudocumene resulted only in recovery of the starting chloroketo acid (CVII). These conditions have been used to form camphorquinone (CXVIII) from camphor (CIX) (62) and norcamphorquinone (CXX) from norcamphor (CXIX) (63) in high yield. This result indicates that the keto group is not in the 6-position of the

chloroketo acid (CVII) and, therefore, the hydroxyl group of the chlorohydrin acid (XCII) and the pseudo hydroxyl group of the chlorolactone (XCI) are not in the 6-position.

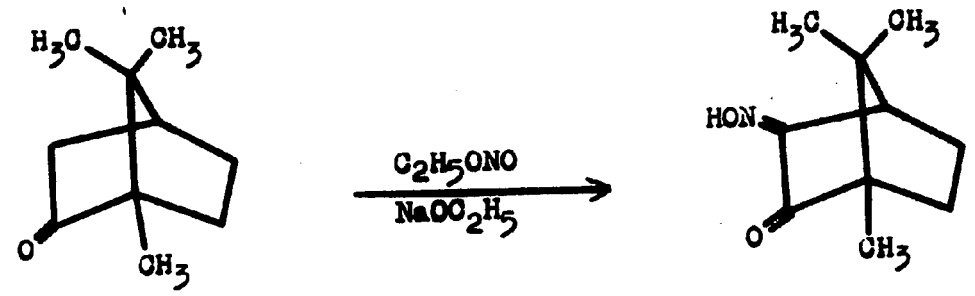


CVIX CXVIII

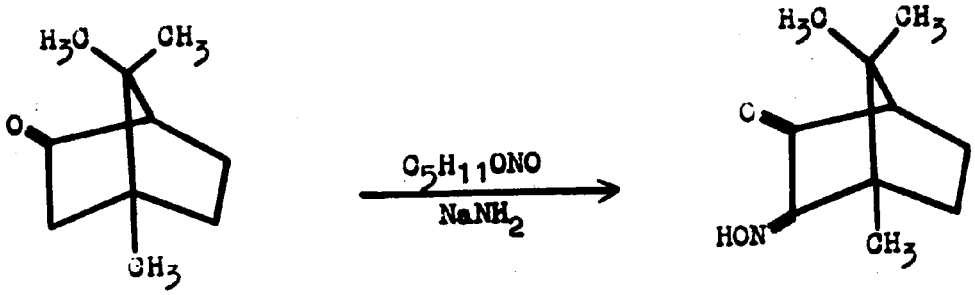


CXIX CXX

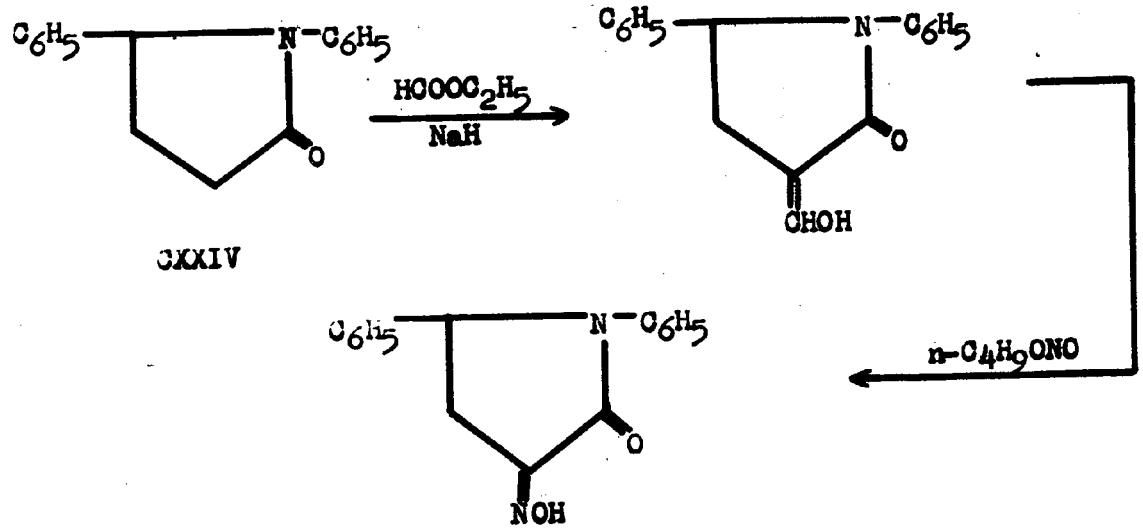
Thr reaction of the chloroketo acid (CVII) with ethyl formate or ethyl formate followed by n-butyl nitrite with sodium hydride as the base also gave negative results; only CVII was isolated. It is known that camphor (CIX) can be converted to the α-oximino ketone (CXXI) by the use of a nitrite and sodium ethoxide (64, 65). Epicamphor (CXXII) is converted to the α-oximino ketone (CXXIII) by the action of amyl nitrite and sodamide (66). Meyer and Vaughan (67) report that the lactam (CXXIV) is converted to the α-oximino compound (CXXV) by the action of ethyl formate, n-butyl nitrite, and sodium hydride.



CVIX CXXI



CXXII CXXIII



CXXIV CXXV

These results may be considered to be additional evidence that the keto group of CVII is in the 7-position and not in the 6-position. With the keto group in the 7-position no reaction would be expected to occur since the α-positions, being bridgehead positions, are very inert (51). A substance with the keto group in the 6-position would

be expected to react at the adjacent (5-position) carbon atom with results similar to those obtained with camphor and epicamphor. However, it may be that the carboxylate anion of CVII in some manner prevents the formation of the α-oximino compound.

The methyl ester (CVIIa) of the chloroketo acid (CVII) was prepared by chromium trioxide oxidation of the methyl ester (XCIIa) of the chlorohydrin acid (XCII). The reaction of CVIIa with isopropenyl acetate, with either sulfuric acid or p-toluenesulfonic acid as catalyst, gave only the starting methyl ester (CVIIa).

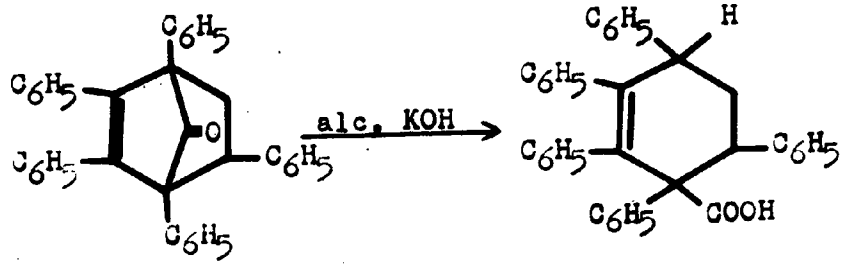
Hagemeyer and Hull (68) report that isopropenyl acetate reacts with all enolizable carbonyl compounds; i.e., any carbonyl compound containing at least one available hydrogen atom adjacent to the carbonyl group. This negative reaction, therefore, provides strong evidence for the position of the keto group in CVII and CVIIa. For while the 7-position has at least one hydrogen adjacent to it, an enol cannot be formed because this would constitute a violation of Bredt's Rule (69,70). The 6-position also has hydrogen atoms adjacent to it but, in this case, there is no geometrical restriction to the formation of an enol and a reaction would take place.

When the chloroketo acid (CVII) or its methyl ester (CVIIa) was refluxed with 10% aqueous sodium hydroxide, there was obtained a mixture of diacids (CXXVI and CXXVII). This mixture gave a negative Beilstein test and reacted rapidly with neutral aqueous potassium permanganate. There was no indication that either of the diacids (CXXVI and CXXVII) contained a keto group.

The evidence for the absence of a keto group consisted of

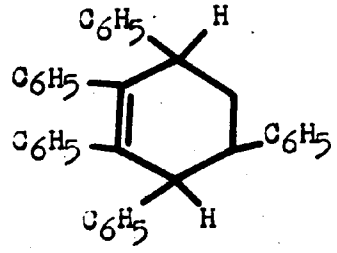
infrared spectra and a negative 2,4-dinitrophenylhydrazine test. Thus it seems that the keto group was converted to a carboxyl group and the elements of hydrogen chloride were lost. The neutralization equivalent of 125 and the elemental analysis of the di-p-bromophenacyl ester prepared from one of the acids confirms this analysis of the reaction results.

Allen, Jones, and Van Allan (71,72) have reported similar observations when carbonyl bridged compounds are treated with alcoholic potassium hydroxide. For example, the pentaphenyl bicyclic ketone (CXXVIII) gave a mixture of two acids (CXXIX and CXXX) when refluxed with ethanolic potassium hydroxide. When CXXVIII was refluxed with methanolic potassium hydroxide the corresponding methyl esters (CXXIXa) and CXXXa) were obtained.(71).



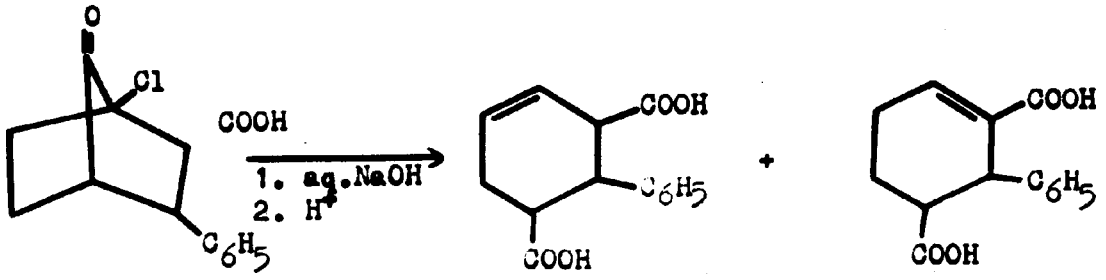
CXXVIII

CXXIX +



CXXX

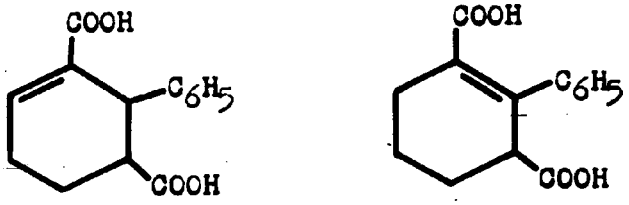
CHART I.



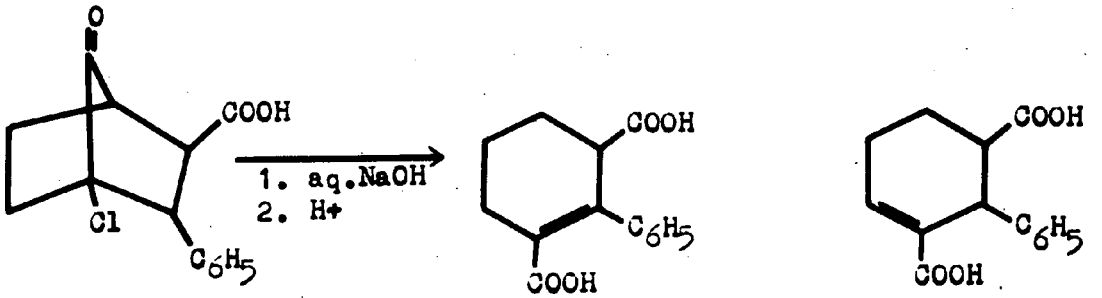
A B

CXXVI

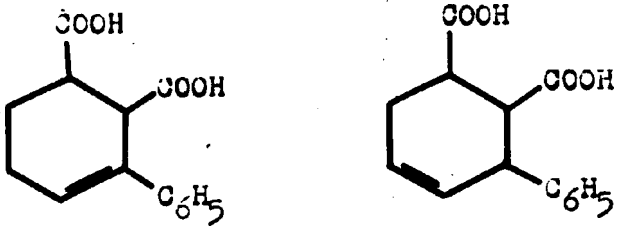
CXXVII= B, C, or D



C D

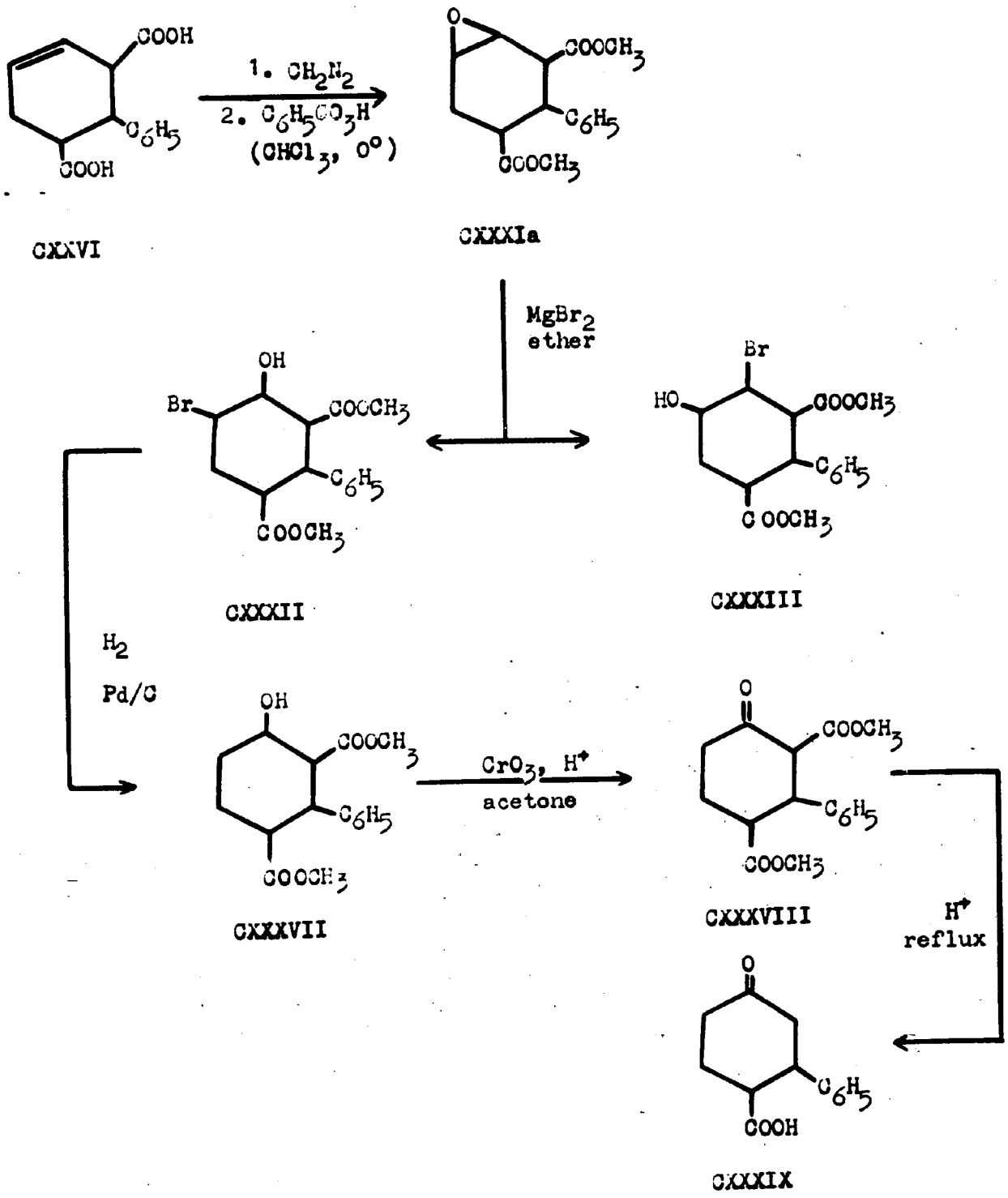


E F



G H

CHART II.



CXXVI

CXXXIa

CXXXII

CXXXIII

CXXXVII

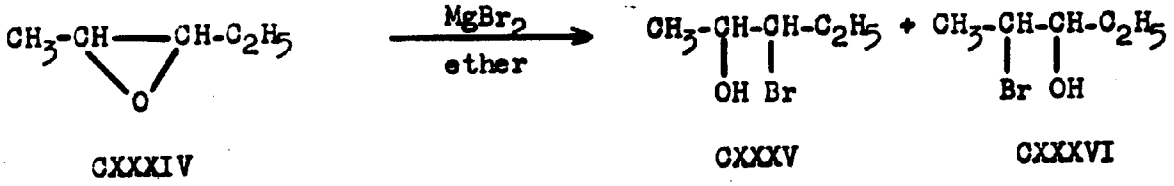
CXXXVIII

CXXXIX

Oxidation of the mixture of diacids (CXXVI and CXXVII) with perbenzoic acid in chloroform at 0° is believed to have given an epoxy diacid (CXXXI). It is also believed that one of the diacids (CXXVII) was isolated from the same reaction. The elemental analysis of these compounds was low in carbon while the hydrogen value was within experimental error.

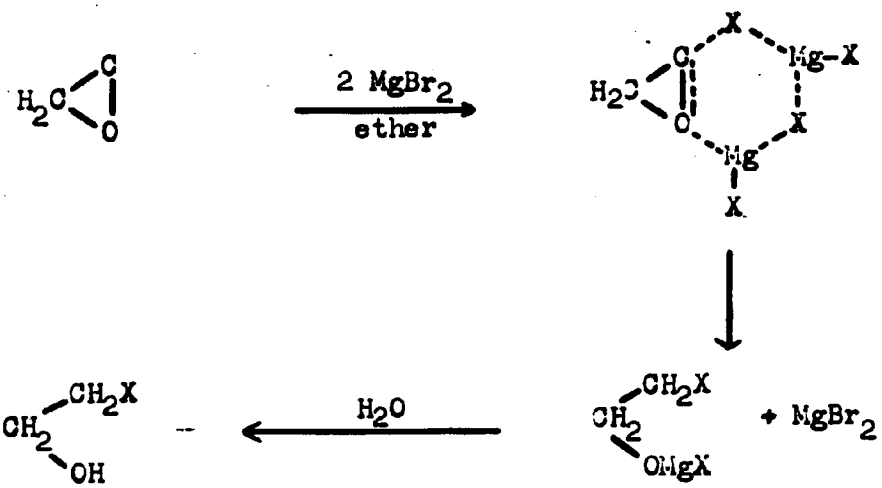
Esterification of the mixture of diacids (CXXVI and CXXVII) with diazomethane gave the corresponding methyl esters (CXXVIa and CXXVIIa). Again, it is believed that one of the dimethyl esters was isolated, however, as above, the carbon analysis is high while the hydrogen analysis is very close to the calculated value. Treatment of the mixture of dimethyl esters with perbenzoic acid in chloroform at 0° gave a small yield of an epoxy diester (CXXXIa). The elemental analysis of CXXXIa agrees very closely with the calculated values. The residue (after removal of CXXXIa) was an uncrystallizable oil.

Treatment of the epoxide CXXXIa with magnesium bromide etherate gave a mixture of bromohydrins (CXXXII and CXXXIII) with CXXXII as the predominant product. In most cases, the reaction of an epoxide and magnesium bromide etherate results in the formation of an aldehyde or ketone (73,74,75) but the formation of bromohydrins has been reported in a few cases (73,75). For example Tiffeneau and Tchoubar (76) report that treatment of 2,3-epoxypentane (CXXXIV) in the cold with magnesium bromide etherate gave the bromohydrins (CXXXV and CXXXVI) with CXXXV the predominate product.



CXXXIV CXXXV CXXXVI

Kharasch and Reinmuth (75) propose that a quasi six membered ring is involved in the action of magnesium bromide etherate on epoxides to yield bromohydrins. This is illustrated below using ethylene oxide as an example.



Reductive debromination of the bromohydrin, (CXXXII) with hydrogen and palladium in carbon as catalyst, gave the alcohol (CXXXVII).

Oxidation of the alcohol with Jones' Reagent (55,56) gave the ketone (CXXXVIII) indicating that CXXXVII was a secondary alcohol. The ketone (CXXXVIII) gave a positive ferric chloride test indicating that CXXXVIII was a β -keto ester.

The experimental observations which have been previously presented have given strong indications that the chlorine atom was situated at a bridgehead position but it was not possible to state at

which bridgehead position the chlorine atom was situated. The formation of the β -keto ester (CXXXVIII) now makes this assignment possible. Assuming a reaction similar to that observed by Allen and coworkers (71, 72) to have taken place when the diacid or diester mixture was refluxed with aqueous sodium hydroxide (page 46) seven of the eight possible products (Chart I) may now be eliminated. Structures B, C, D, E, and F may be eliminated on the basis of epoxide formation. The conditions of the epoxidation reaction were chosen in such a manner that α, β -unsaturated carboxylic acids or their esters would not react with perbenzoic acid (4). Compounds G and H may be eliminated on the basis of β -keto ester formation. Both G and H may be epoxidized under the conditions used (4) but none of the bromohydrins formed are capable of yielding a β -keto ester after reductive bromination and oxidation of the resulting alcohol to a ketone. Compound A is the only product which is consistent with the observed reactions (Chart II). Compound A is then CXXXVI with the dimethyl ester being CXXXVIa. CXXXVII is probably B, C, or D.

The β -keto ester (CXXXVIII) was refluxed with 0.1 N hydrochloric acid for 52 hours. This resulted in the hydrolysis of both carbomethoxy groups and the loss of carbon dioxide (as evidenced by formation of barium carbonate in a barium hydroxide trap) to give the keto acid (CXXXIX).

Structures of the chlorolactone (XCI) and the chlorohydrin acid (XCII) consistent with the experimental observations presented and a summary of the reactions involved are presented in Charts II, III, and IV.

CHART III.

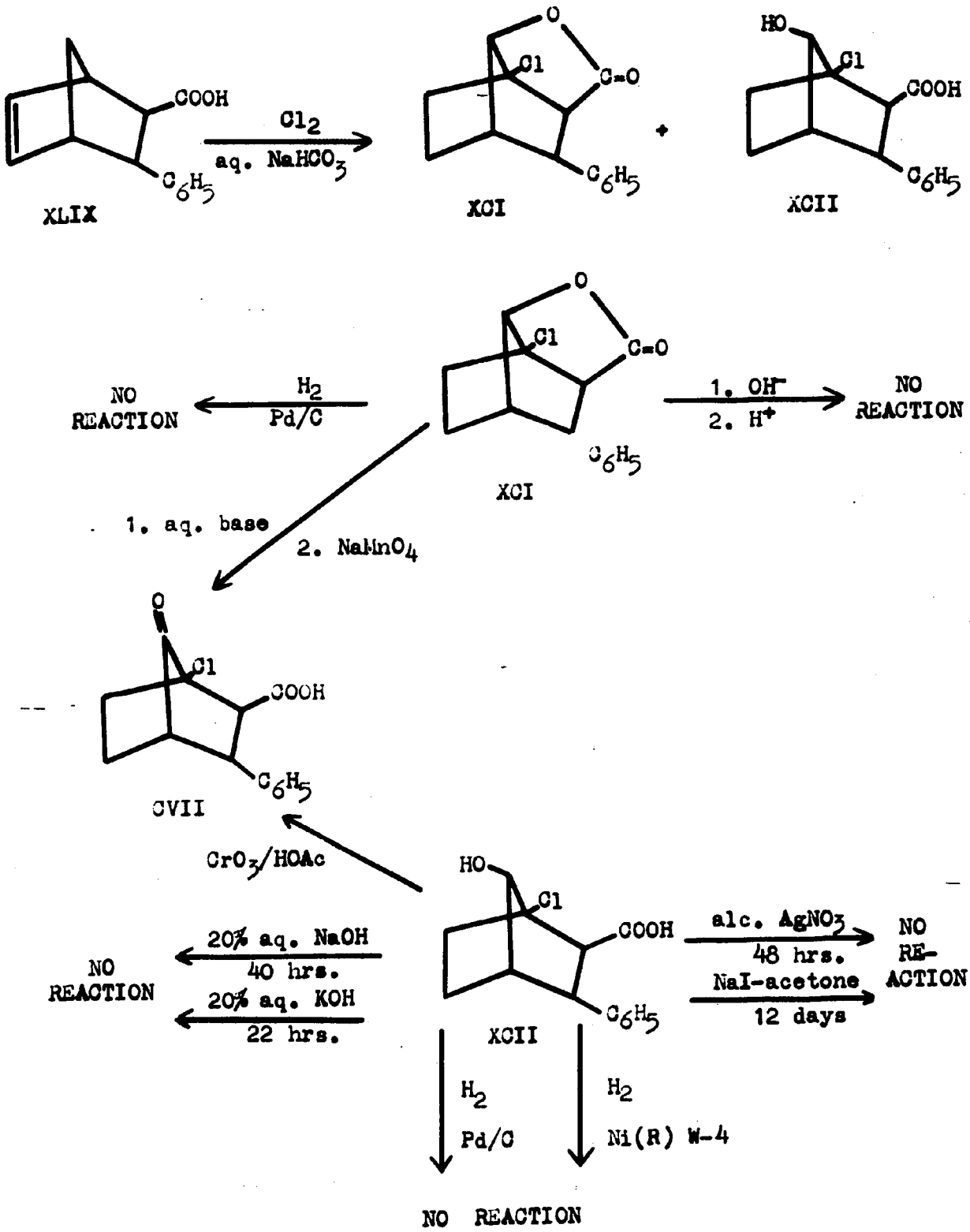
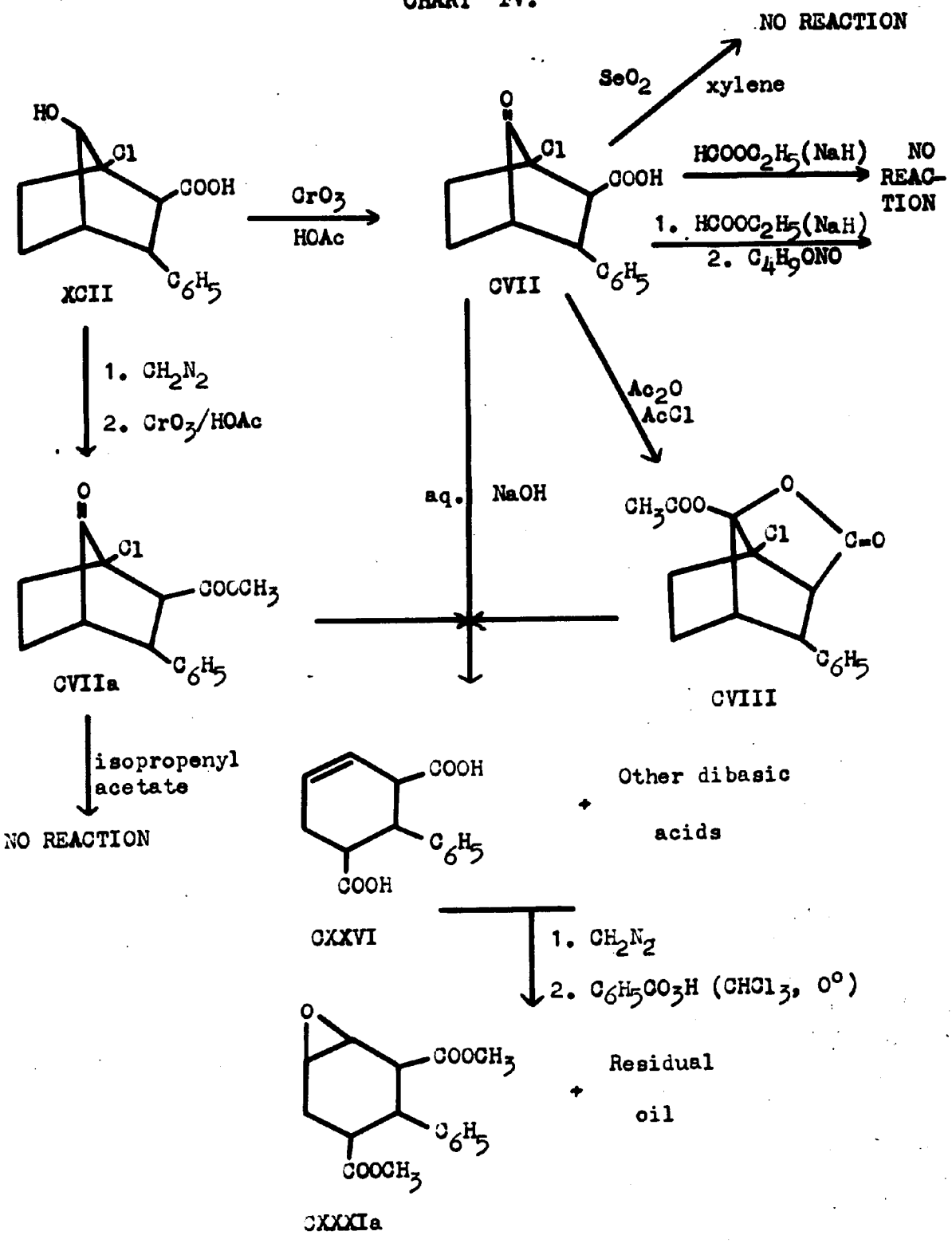
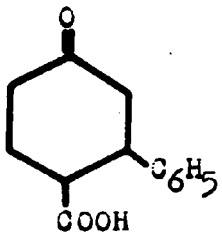

XLIX
Cl_2
aq. $NaHCO_3$
XCI
XCII
NO REACTION
H_2
Pd/C
1. OH^-
2. H^+
NO REACTION
1. aq. base
2. $NaMnO_4$
CVII
CrO_3/HOAc
20% aq. NaOH
40 hrs.
20% aq. KOH
22 hrs.
NO REACTION
alc. $AgNO_3$
48 hrs.
NaI-acetone
12 days
NO RE-ACTION
H_2
Pd/C
H_2
Ni(R) W-4
NO REACTION

CHART IV.

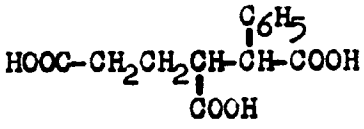

NO REACTION
SeO2
xylene
HO
Cl
COOH
C6H5
XCII
CrO3
HOAc
O
Cl
COOH
C6H5
CVII
HCOOC2H5(NaH)
NO REAC-TION
1. HCOOC2H5(NaH)
2. C4H9ONO
1. CH2N2
2. CrO3/HOAc
Ac2O
AcCl
aq. NaOH
O
Cl
COOCH3
C6H5
CVIIa
CH3COO
O
Cl
C=O
C6H5
CVIII
isopropenyl acetate
NO REACTION
COOH
C6H5
COOH
CXXVI
Other dibasic
+
acids
1. CH2N2
2. C6H5CO3H (CHCl3, 0°)
O
COOCH3
C6H5
COOCH3
CXXXIa
Residual
+
oil

A literature search revealed that the compound (CXXXIX) to which the structure of the phenylketo acid was assigned was unknown. The assumed oxidation products of CXXXIX (CXL and CXLI) were also found to be unknown. It was decided, therefore, to synthesize 2-phenyl-4-keto-cyclohexanecarboxylic acid.



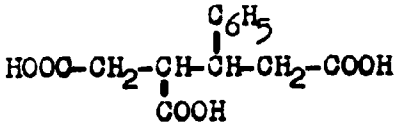
CXXXIX

$\xrightarrow{(O)^-}$



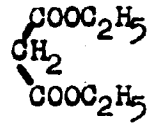
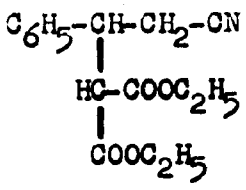
CXL

and/or

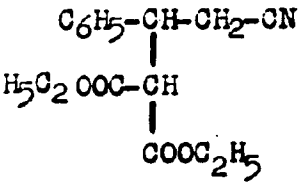
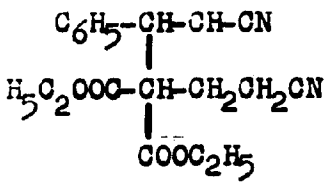


CXLI

The initial plan for the synthesis of CXXXIX is outlined below.

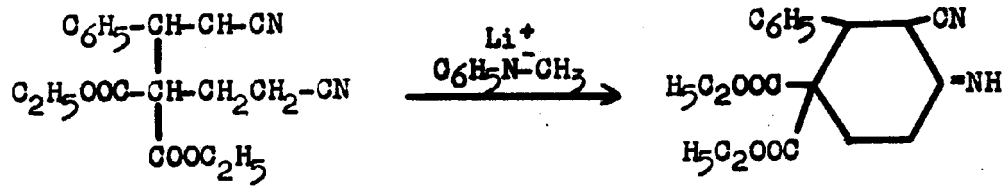
1. $C_6H_5-CH=CH-CN$ +  $\xrightarrow{NaOC_2H_5}$ 

CXLII

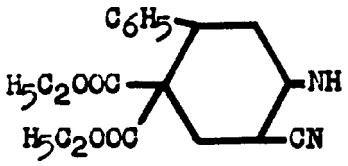
2.  $\xrightarrow[\text{Triton B}]{CH_2=CHCN}$ 

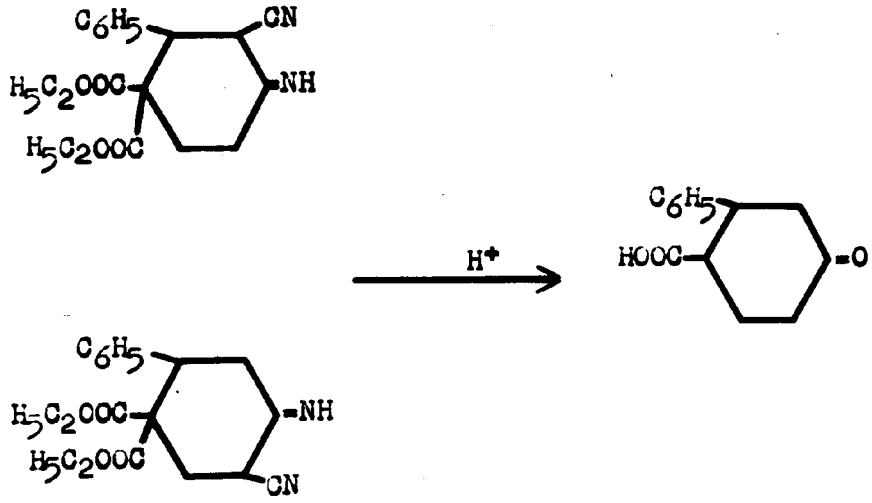
CXLII

CXLIII

3. 

and/or

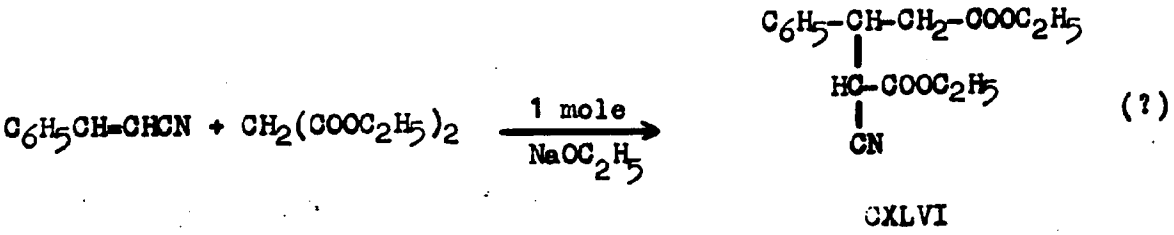


4. 

CXLII was reported (77) to be formed in good yield by the Michael reaction of cinnamonitrile and ethyl malonate. CXLIII is an unknown compound, however, reaction 2 is a simple cyanoethylation and similar reactions were reported in high yields (78). Reaction 3 is a Thorpe cyclization which has been used successfully in the preparation of cycloalkanones (79,80). Reaction 4 is the acid hydrolysis and

decarboxylation of the possible imines obtained from reaction 3.

Some difficulties were encountered initially in the synthesis of CXLII. The physical properties; i.e., boiling point and melting point of the product obtained, did not agree with those reported by Koelsch (77). Since one mole of sodium ethoxide per mole of ethyl malonate was used, the possibility that an "abnormal" Michael reaction (81,82) had occured to give CXLVI was investigated.



$$C_6H_5CH{=}CHCN + CH_2(COOC_2H_5)_2 \xrightarrow[NaOC_2H_5]{1\ \text{mole}} \begin{matrix} C_6H_5{-}CH{-}CH_2{-}COOC_2H_5 \\ | \\ HC{-}COOC_2H_5 \\ | \\ CN \end{matrix} \qquad (?)$$

CXLVI

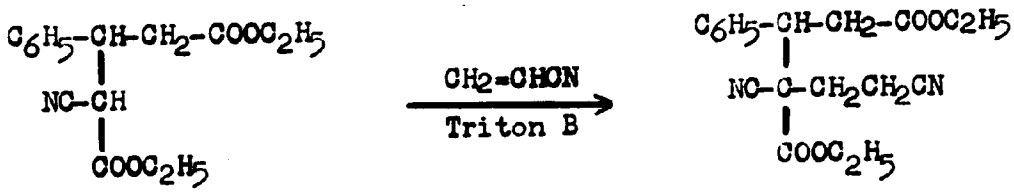
Koelsch (77) and Desai (83) report that the Michael reaction of ethyl cinnamate and ethyl cyanoacetate gives CXLVI. The boiling point of CXLVI reported (77) was very close to the observed in the preparation of CXLII. However, since a one to one molar ratio of sodium ethoxide to ethyl cyanoacetate was also used in the reported preparation of CXLVI, there remained a possibility that CXLVI was in reality CXLII.

An investigation of the synthesis of CXLII and CXLVI was conducted in order to confirm the structures assigned by Koelsch (77). The reaction of cinnamonitrile and ethyl malonate yielded the same product when one mole and one sixth mole of sodium ethoxide per mole of ethyl malonate was used as the base. The boiling point of the product was much lower than that reported by Koelsch (77). The product using one sixth mole of sodium ethoxide solidified after distillation and the

product obtained by the use of one mole of sodium ethoxide (with the product obtained using one sixth mole) also solidified. After crystallization the melting point was the same as reported by Koelsch (77).

The reaction of ethyl cinnamate and ethyl cyanoacetate gave the same product (CXVI) when one mole and one sixth mole of sodium ethoxide per mole of ethyl cyanoacetate was used as the base. The boiling point and index of refraction were very close to those observed for CXLII. Attempts to solidify the product (CXLVI), by cooling or seeding with CXLII, were unsuccessful. The infrared spectra of CXLII and CXLVI were very similar.

The reaction of CXLII and CXLVI with acrylonitrile gave CXLIII (page 54) and CXLVII respectively. CXLIII is a solid whereas CXLVII is a high boiling liquid which did not solidify on standing in the refrigerator or on seeding with CXLIII. This observation provides additional evidence that CXLII and CXLVII are different compounds.

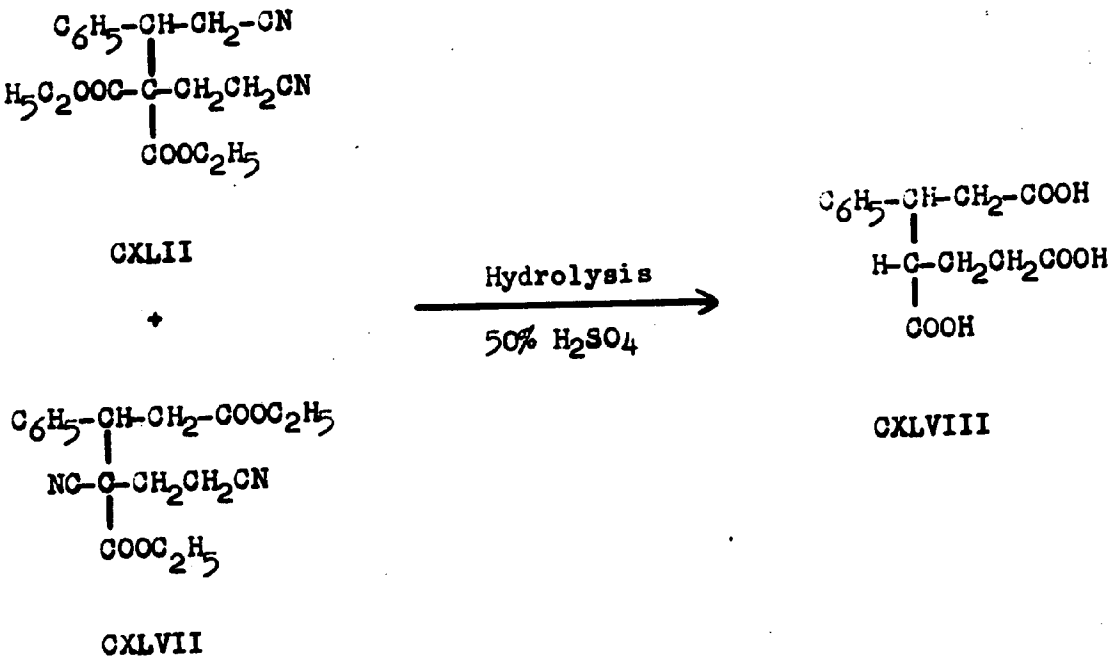


CXLVI CXLVII

Attempts to cyclicize CXLIII by means of the Ziegler modification (80) of the Thorpe reaction (79) were unsuccessful. Neither of the possible imino compounds (CXLIV and CXIV) nor the ketones derived from CXLIV and CXLV by acid hydrolysis were isolated.

Attention was then focused on the Dieckmann cyclization as a

method for obtaining the phenylketo acid (CXXXIX). It was noted that hydrolysis and decarboxylation of CXLII and CXLVII should yield the same triacid (CXLVIII). Hydrolysis of CXLII and CXLVII with 50% sulfuric acid gave oily mixtures from which small portions were crystallized from ethyl acetate. The mixtures were very difficult to crystallize. Thorpe and Udall (85) experienced the same difficulty with similar compounds. The portion which was crystallized had a wide decomposition range which was undoubtedly due to anhydride formation, but the range was the same for the products obtained from CXLII and CXLVII. Final confirmation that the same triacid was produced from CXLII and CXLVII was made on the basis of the admixture melting point and superimposable infrared spectra of the trimethyl esters (CXLVIIIa) which were prepared by the use of diazomethane.



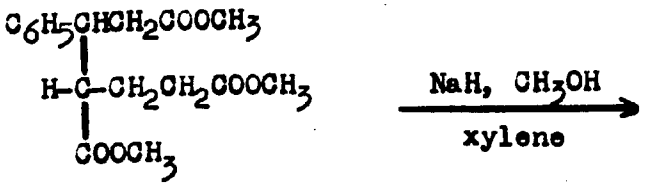
CXLII

CXLVII

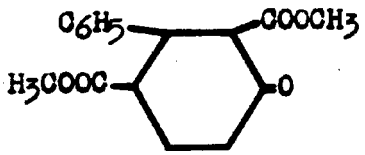
CXLVIII

CXLVIIIa was cyclicized by sodium hydride and a catalytic amount of methanol in refluxing xylene (86). While in most cases the

product from the cyclization reaction was a difficultly crystallizable oil a solid sharp melting compound (CXLIX or CL) was isolated; the elemental analysis of which showed it to be a cyclicized product. The product was assigned the structure CXLIX or CL rather than CLI or CLII because of the greater preference to form a six membered ring rather than a four membered ring.

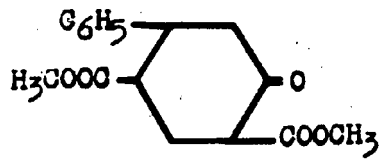


CXLVIIIa

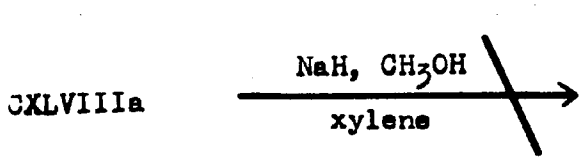


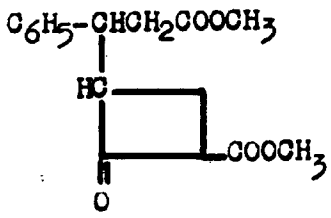
CXLIX

and/or



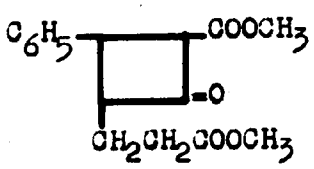
CL





CLI

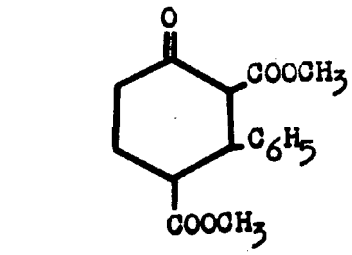
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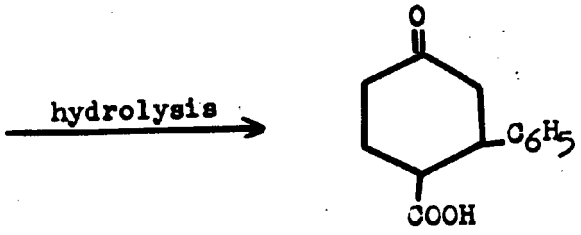
CL

No attempt was made to determine which of the possible products (CXLI or CL) was isolated. The melting point of the isolated β-keto ester did not agree with the melting point of the β-keto ester (CXXXVIII) obtained from the degradation of the chloroketo acid (CVII).

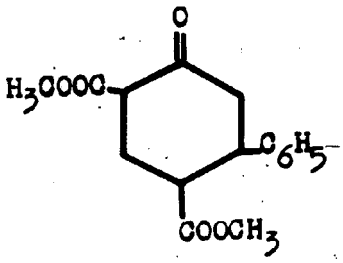
The β-keto acid (CXLIX or CL) was hydrolyzed and decarboxylated by refluxing it in a mixture of acetic acid, water, and hydrochloric acid (87). The product was assumed to be the desired 2-phenyl-4-keto-cyclohexanecarboxylic acid on the basis of elemental analysis and infrared spectrum. The melting point was not the same as the melting point of CXXXIX.



CXLIX



CLIII



CL

Although CLIII and CXXXIX do not have the same melting point, which indicates that they are different compounds, the possibility that only a <u>cis-trans</u> isomerism differentiates them was investigated. Attempts

to use the technique of Hückel and Goth (88) for the isomerisation of cyclohexanecarboxylic esters led only to unrecrystallizable, inseparable mixtures of compounds. The same results were obtained with both CLIII and CXXXIX. Attempts to separate the mixtures by means of derivatives were likewise unsuccessful for no well defined derivative common to both CLIII and CXXXIX was found. Thus, although the evidence indicates that CLIII and CXXXIX do not have the same basic structure, the possibility that they are similar cannot be eliminated.

SUMMARY

The bromination of the exo-acid reported by Ver Nooy and Rondestvedt (17) was repeated. While it is reported (17) that no bromolactone was formed in the reaction, trace amounts of a solid compound exhibiting a strong absorption bond at 1770 cm^{-1} in the infrared spectrum were isolated, which indicates a bromolactone was formed. The acidic products were investigated and two bromohydrin acids and a monobromo acid were isolated.

The chlorination of the endo-acid in sodium bicarbonate solution resulted in the formation of the expected chlorolactone and an unexpected chlorohydrin acid.

The chlorination of the exo-acid was investigated under a variety of basic conditions. The major products, a nortricyclene derivative, a chlorolactone, and a chlorohydrin acid, were isolated in all cases. In addition to these products another chlorohydrin acid and a monochloro acid were isolated.

Strong evidence was presented to show that the chlorolactone does not have the structure predicted in the basis of lactonization subsequent to a Wagner-Meerwein rearrangement (page 32). Investigation of the major chlorohydrin acid formed has shown that it is an epimer of the chlorolactone.

Structures consistent with experimental observations have been proposed for the nortricyclene derivative, chlorolactone, and one of

the chlorohydrin acids.

During investigation on the synthesis of 3-keto-5-phenylcyclohexanecarboxylic acid it was found that the boiling point of ethyl α-carbethoxy-γ-cyano-β-phenylbutyrate was incorrectly recorded in the literature. It was also determined that no abnormal Michael reactions occur in the reaction of cinnamonitrile and ethyl malonate and ethyl cinnamate and ethyl cyanoacetate. 2-Phenyl-4-ketocyclohexanecarboxylic acid was prepared and compared to the phenyl keto acid obtained from the degradation of the chlorolactone. The melting points are different but because of the possibility of cis-trans-isomerism the structural features of the two may still be the same. Attempts at the isomerization of both substances led only to inseparable mixtures.

EXPERIMENTAL[a, b]

Endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic Acid (XLIX). Method A.

To a solution of 222 g. (1.5 moles) of trans-cinnamic acid in 750 ml. of refluxing toluene were added dropwise, through the reflux condenser, 231 g. (3.5 moles) of freshly distilled cyclopentadiene. The cyclopentadiene was kept at 0° from the time of distillation to the time of addition. The solution was refluxed for sixty-two hours, cooled, and extracted with sodium hydroxide solution.

The basic water solution was made acid to Congo red with concentrated hydrochloric acid, cooled overnight in the refrigerator, and filtered. The crude solidified oil was iodolactonized (17,28). The iodolactone, 164 g., was filtered.

The filtrate was treated with 10% sodium thiosulfate solution to reduce the excess iodine and carefully neutralized with 10% hydrochloric acid. The following fractions were obtained. Crude weights which include occluded inorganic salts are given and pH measured by pH paper.

1) Thick viscous oil — pH -6.4

2) 44.5 g. — pH -6

---

[a] All melting and boiling points are uncorrected.

[b] Microanalyses were by Spang Microanalytical Laboratory, Ann Arbor, Michigan and Anna Griffin, University of Michigan.

3) 22.4 g. pH 6

4) 14.1 g. pH 6

5) 92.8 g. pH 2

Fractions 1-3 were recrystallized from methanol-water and 90-100° petroleum ether. After many recrystallizations there was isolated white crystals of the exo-acid (XLIX), 31.3 g. m.p. 112.5-115° and 9.5 g. m.p. 113-114.5°. Reported m.p. 113-113.5° (33), 115.5-116° (33), and 102-104° (7).

Endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic Acid (XLIX). Method B.

To a solution of 250 g. (1.69 moles) of trans-cinnamic acid in one liter of toluene maintained slightly under reflux temperature were added dropwise, through the reflux condenser, 400 ml. (322 g., 4.88 moles) of freshly distilled cyclopentadiene. The cyclopentadiene was kept at 0° from the time of distillation to the time of addition. The solution was refluxed for three days, cooled, and extracted with dilute sodium hydroxide solution.

The basic water solution was washed with ether to remove non-acidic organic material and made acid to Congo red with concentrated hydrochloric acid while hot and with stirring. On cooling the heavy viscous oil solidified. The solid was washed with water and iodolactonized (17,28). The iodolactone, 214 g. (0.63 moles), was filtered.

The filtrate was treated with solid sodium thiosulfate to reduce the excess iodine and allowed to cool overnight in the refrigerator. The precipitated sodium salt was filtered and partially

dissolved in water. The acid was liberated by the addition of concentrated hydrochloric acid and was extracted with ether. The ether solution was washed with 5% sodium bicarbonate solution. The basic water solutions were made acid to Congo red with concentrated hydrochloric acid, filtered, and the solid crystallized from 90-100° petroleum ether. The yield was 77 g. (0.36 moles, 21.0%) of white crystals, m.p. 112-115°. Reported m.p. 113-113.5 (33), 115.5-116° (33), and 102-104° (7).

Exo-3-phenyl-(2.2.1)-bicyclohept-5-ene-endo-2-carboxylic Acid (LIX).

LIX was prepared from the iodolactone (LXXVII) using the procedure of Rondestvedt and Ver Nooy (33).

Reaction of trans-Cinnamic Acid and Dicyclopentadiene to Give (LXXXIV).

A mixture of 91.0 g. (0.62 moles) of trans-cinnamic acid, 543 g. (4.45 moles) of 98% dicyclopentadiene, and 500 ml. of toluene was refluxed for eleven days. The solution was cooled and extracted with a dilute sodium hydroxide solution.The basic water solution was washed with 30-40° petroleum ether, then made acid to Congo red with concentrated hydrochloric acid. The viscous oil was extracted with 30-40° petroleum ether. The petroleum ether insoluble residual oil was crystallized from methanol-water giving 7.8 g. of material, m.p. 163-189°. An analytical sample, m.p. 193-194°, was prepared.

Anal. Calc'd. for $C_{19}H_{20}O_2$: C, 81.37; H, 7.19; N.E. 280. Found: C, 81,64; H, 7.07; N.E. 276.

Bromination of Exo-3-phenyl-(2.2.1)-bicyclohept-5-ene-endo-2-carboxylic Acid (LIX).

A 20% sodium hydroxide solution was added to 4.28 g. (0.02 moles) of LIX dissolved in 15 ml. of methanol until the solution was just basic to phenolphthalein. Thirty ml. of 5% sodium bicarbonate solution and 30 ml. of water were added to the slightly pink solution; a saturated solution of bromine in water was added dropwise until the bromine color was sustained. The mixture was filtered and 5.26 g. (90%) of bromo-lactone (LX) were obtained. After crystallization from ethanol-water (Norit), the melting point was 122.5-123°. Reported m.p. 123-123.5° (17,33).

The basic water solution was treated with 10% sodium thiosulfate solution, made acid with concentrated hydrochloric acid, cooled, and extracted with benzene. The benzene extract was dried over anhydrous calcium sulfate. After benzene was removed in an air stream 0.34 g. of a yellow oil was obtained. A few crystals, m.p. 117-160°, were obtained on crystallization from ethanol-water but no pure compounds could be isolated.

Chlorination of Exo-3-phenyl-(2.2.1)-bicyclohept-5-ene-endo-2-carboxylic Acid (LIX).

A 20% sodium hydroxide solution was added to 4.28 g. (0.02 moles) of LIX dissolved in 20 ml. of methanol until the solution was just basic to phenolphthalein. Fifty ml. of 5% sodium bicarbonate solution and 32 ml. of water were added to the slightly pink solution; chlorine water was added until a positive test with starch iodide

paper was obtained. The chlorine water was added in 50 ml. portions and the mixture was shaken after each portion was added. The mixture was extracted with one 100 ml. and two 50 ml. portions of benzene. The benzene extracts were dried over anhydrous calcium sulfate. After the removal of the benzene under reduced pressure, 2.8 g. of an oily residue, which solidified on trituration with 30-40° petroleum ether, were obtained. Crystallization of the solid from methanol-water yielded 1.5 g. (30%) of the chlorolactone (LXXXV), m.p. 126-128°. An analytical sample, m.p. 127-128°, was prepared.

Anal. Calc'd. for $C_{14}H_{13}O_2Cl$: C, 67.61; H, 5.27. Found: C, 67.58; H, 5.37.

The basic water solution was made acid to Congo red with concentrated hydrochloric acid and extracted with benzene. The benzene solution was dried over anhydrous calcium sulfate. After removal of the benzene under reduced pressure, 1.26 g. of oily residue were obtained. Crystallization from ethyl acetate-90-100° petroleum ether yielded a chlorohydrin acid (LXXXVI), white crystals, m.p. 153-155°. An analytical sample, m.p. 155-156.5°, was prepared from benzene-90-100° petroleum ether.

Anal. Calc'd. for $C_{14}H_{15}O_3Cl$: C, 63.06; H, 5.67; N.E. 266. Found: C, 63.36; H, 5.85; N.E. 267.

Bromination of Endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic Acid (XLIX).

A 10% sodium hydroxide solution was added to 2.14 g. (0.01 moles) of XLIX partially dissolved in 5 ml. of methanol until the

solution was just basic to phenolphthalein. One hundred ml. of 5% sodium bicarbonate solution and 10 ml. of water were added to the slightly pink solution. A saturated solution of bromine in water was added dropwise until the yellow color persisted. The excess bromine was reduced with 10% sodium thiosulfate solution. The mixture was extracted with ether. The ether extract was dried over anhydrous calcium sulfate. After removal of the ether under reduced pressure 1.44 g. of an oily residue was obtained. The residue was chromatographed over activated alumina (Merck). The bromophenylnortricyclene (LI), 0.87 g., was eluted with a 4:1 mixture of 90-100° petroleum ether: benzene. On vacuum sublimation it melted at 51-53°. Reported 52-53° (17). The bromolactone was eluted with methanol. The residue, after evaporation of the methanol in an air stream was crystallized from ethanol-water, m.p. 123-124.5°. The infrared spectrum showed a strong absorption at 1770 cm^{-1}.

The basic water solution was made acid to Congo red with concentrated hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous calcium sulfate. The ether was removed under reduced pressure leaving 1.12 g. of oily residue. Crystallization of the crude residue from ethyl acetate-90-100° petroleum ether yielded 0.11 g. of a bromohydrin acid (LXXXVII), m.p. 156-170°. An analytical sample, m.p. 173-174°, was prepared.

Anal. Calc'd. for $C_{14}H_{15}O_3Br$: C, 54.02; H, 4.86. Found: C, 54.14; H, 5.08.

Concentration of the filtrate yielded 0.28 g. of material,

m.p. 155-215°. Recrystallization from ethanol-water yielded a monobromo acid (LXXXVIII), m.p. 232-234°. An analytical sample, m.p. 233-234°, was prepared.

Anal. Calc'd. for $C_{14}H_{15}O_2Br$: C, 56.95; H, 5.12; Br, 27.07. Found: C, 56.95; H, 5.04; Br, 26.94.

Recrystallization of the residual oil from ethyl acetate-90-100° petroleum ether yielded another bromohydrin acid (LXXXIX), m.p. 142-144°. An analytical sample, m.p. 143-144°, was prepared.

Anal. Calc'd. for $C_{14}H_{15}O_3Br$: C, 54.02; H, 4.86; Br, 25.68. Found: C, 54.45; H, 4.79; Br, 26.34.

Chlorination of Endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic Acid (XLIX) with Chlorine Gas.

A 20% sodium hydroxide solution was added to 4.28 g. (0.02 mole) of XLIX partially dissolved in 16 ml. of methanol until the solution was just basic to phenolphthalein. Fifty ml. of 5% sodium bicarbonate solution and 75 ml. of water were added to the solution; chlorine gas was passed into the clear solution at a slow rate for twenty minutes. At the end of this time a positive starch iodide test was obtained. The excess chlorine was reduced with 10% sodium thiosulfate solution, 50 ml. of saturated sodium chloride solution was added, and the mixture was extracted continuously with ether for twenty hours. The ether was dried over anhydrous calcium sulfate. After the removal of the ether at the water pump, 3.16 g. of an oily residue were obtained. A few ml. of 30-40° petroleum ether were added and the mixture was cooled in the freezer compartment of the refrig-

erator. The precipitate was filtered. After crystallization from ethanol-water 0.53 g., m.p. 113-119°, of chlorolactone (XCI) was obtained. An analytical sample, m.p. 118-119°, was prepared.

Anal. Calc'd. for $C_{14}H_{13}O_2Cl$: C, 67.61; H, 5.27. Found: C, 67.37; H, 5.19.

The infrared spectrum showed a strong absorption at 1775 cm^{-1}.

The filtrate was evaporated to dryness in an air stream to give 2.09 g. of oily residue, which was dissolved in 30-40° petroleum ether and passed over activated alumina (Merck). The nortricyclene derivative (XC) was eluted with 30-40° petroleum ether. The first 40 ml. of eluent contained 1.66 g. of clear colorless XC. On distillation 1.0 g., b.p. 119-120° at 0.7 mm. $n_D^{25.5}$ 1.5662 of XC was obtained.

Anal. Calc'd. for $C_{13}H_{13}Cl$: C, 76.28; h, 6.40. Found: C, 76.19; H, 6.46. The infrared spectrum showed peaks at 1940, 1860, 1800, 820, and 800 cm^{-1}.

The basic water solution was made acid with concentrated hydrochloric acid and was extracted continuously with ether for thirty-six hours. The ether was washed with water and dried over anhydrous calcium sulfate. After the removal of the ether under reduced pressure, 1.18 g. of an oily residue were obtained. Crystallization from benzene gave 0.5 g. of the chlorohydrin acid XCII. An analytical sample, m.p. 172.5-173.5°, was prepared from ethyl acetate-90-100° petroleum ether.

Anal. Calc'd. for $C_{14}H_{15}O_3Cl$: C, 63.06; H, 5.67; Cl, 13.29; N.E. 267 . Found: C, 63.10; H, 5.70; Cl, 13.11; N.E. 267.

The methyl ester was prepared by the use of diazomethane. An analytical sample, m.p. 96-97°, was prepared from cyclohexane.

Anal. Calc'd. for $C_{15}H_{17}O_3Cl$: C, 64.14; H, 6.13; Cl, 12.62. Found: C, 64.10; H, 6.23; Cl, 12.74.

The remainder of the residue was not investigated.

Chlorination of Endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic Acid (XLIX) with Chlorine Water and 5% Sodium Bicarbonate Solution.

A 20% sodium hydroxide solution was added to 8.56 g. (0.040 moles) of XLIX partially dissolved in 30 ml. of methanol until the solution was just basic to phenolphthalein. Fifty ml. of 5% sodium bicarbonate solution and 100 ml. of water were added; chlorine water was added until a positive test with starch iodide paper was obtained. The pH was measured with a Coleman Model 3 pH meter.

ml. Cl_2 water added	pH
0	9.90
100	9.45
200	8.31
300	7.37
400	7.01
500	6.80

at this point 25 ml. of 5% sodium bicarbonate solution were added

600	7.10
700	6.92

at this point 25 ml. of 5% sodium bicarbonate solution were added

ml. Cl_2 water added	pH
830	7.20

Two ml. of 20% sodium hydroxide solution were added to insure that all the acidic material was in the form of the sodium salt. The mixture was extracted continuously with ether for thirty-six hours. The ether was washed with water and dried over anhydrous calcium sulfate. After the removal of the ether at the water pump, 3.94 g. of an oily residue were obtained. A few ml. of 30-40° petroleum ether were added and the mixture was cooled in the freezer compartment of the refrigerator. The solid was filtered. After two crystallizations from ethanol-water 0.80 g. of the chlorolactone (XCI), m.p. 116-119°, were obtained.

The filtrate was evaporated to dryness, redissolved in 30-40° petroleum ether and passed over activated alumina (Merck). The nortricyclene derivative (XC) was eluted with 30-40° petroleum ether and distilled; 1.54 g., b.p. 114-118° at 0.5 mm, were obtained.

The basic mother liquor was made acid with concentrated hydrochloric acid and was continuously extracted with ether for thirty-nine hours. The ether was washed with water and dried over anhydrous calcium sulfate. After the removal of the ether at the water pump, 3.73 g. of an oily residue was obtained. The residue was crystallized from benzene (Norit) yielding the following fractions.

1) 0.69 g. m.p. 165-171.5°

2) 0.44 g. m.p. 162-169°

3) 0.45 g. m.p. 130-140°

4) oily residue

The first two fractions were combined and recrystallized from benzene; 0.82 g., m.p. 170-172°, of the chlorohydrin acid (XCI) were obtained.

Fraction 3 was recrystallized from benzene and the chlorohydrin acid (XCII), m.p. 146-147.5°, was obtained. An analytical sample, m.p. 148-149°, was prepared.

Anal. Calc'd for $C_{14}H_{15}O_3Cl$: C, 63.06; H, 5.67; Cl, 13.29. Found: C, 63.12; H, 5.78; Cl, 13.32.

After two recrystallizations of the oily residue from ethanol-water (fraction 4), 0.12 g. of the monochloro acid (XCIV), m.p. 231-235°, were obtained. An analytical sample, m.p. 236-237.5°, was prepared.

Anal. Calc'd for $C_{14}H_{15}O_2Cl$: C, 67.14; H, 6.03; Cl, 14.14. Found: C, 67.46; H, 5.33; Cl, 13.92.

The infrared spectrum showed a doublet at 1680-1690 cm^{-1}. No band which may be assigned to a hydroxyl group or a lactone was present.

The remainder of the residue produced on crystallization a mixture of compounds having a melting point range of 130-140°. No separation of this mixture was achieved in further crystallizations.

Chlorination of Endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic Acid (XLIX) in the Presence of a Large Excess of Sodium Bicarbonate.

A solution of the sodium salt of 12.84 g. (0.060 moles) of XLIX was prepared as before (page 70). Forty-two grams of solid sodium bicarbonate and 200 ml. of water were added. Chlorine water was added until a positive starch iodide test was obtained. The pH was not measured. The reaction mixture was extracted continuously with ether for sixty hours. The ether was washed with water and dried over anhydrous calcium sulfate. After the removal of the ether on a steam bath, 7.25 g. of an oily residue were obtained. A few ml. of 40-60° petroleum ether were added and the mixture was cooled in the freezer chest of the refrigerator. The mixture was filtered. After two recrystallizations from ethanol-water 1.4 g. of the chlorolactone (XCI), m.p. 115-118°, were obtained.

The petroleum ether filtrate was evaporated to dryness to give 5.7 g. of the crude nortricyclene derivative (XC).

The basic water solution was made acid to Congo red with concentrated hydrochloric acid and was extracted continuously with ether for sixty hours. The ether solution was washed with water and dried

over anhydrous calcium sulfate. After the removal of the ether on a steam bath 7.8 g. of an oily residue were obtained. Crystallization of the residue from benzene gave 3.0 g. of the chlorohydrin acid (XCII), m.p. 163-169°. One recrystallization from benzene raised the melting point to 170-173°.

Crystallization of the residue from the initial benzene crystallization from ethanol-water gave 0.4 g. of the monochloro acid (XCIV), m.p. 220-235°.

Crystallization of the remaining material gave only mixtures of compounds. No effort was made to separate the mixture further.

Chlorination of Endo-3-phenyl-(2.2.1)-bicyclohept-5-ene-exo-2-carboxylic Acid (XLIX) in a Standard Buffer Solution.

A solution of the sodium salt of 12.84 g. (0.06 moles) of XLIX was prepared as before (page 70). One liter of a buffer solution composed of 0.95 M sodium hydroxide and 0.95 M potassium dihydrogen phosphate was added. Chlorine water was added until a positive starch iodide test was obtained. The pH was measured with a Coleman Model 3 pH meter.

ml. Cl_2 water added	pH
0	7.20
200	7.20
500	7.10
800	7.00
1100	6.98

The reaction mixture was extracted continuously with ether for sixty hours. The ether solution was washed with water and dried over anhydrous calcium sulfate. After the removal of the ether on a steam bath, 10.3 g. of an oily residue were obtained. The residue was treated with petroleum ether, b.p. 40-60°, cooled, and the liquor decanted. Evaporation of the petroleum ether in an air stream yielded the nortricyclene derivative (XC).

Crystallization of the petroleum ether insoluble material yielded a mixture of compounds. However, 0.62 g. of the chlorolactone (XCI), m.p. 116-119°, was isolated. The infrared spectra of various crystallization samples showed the presence of acidic compounds. The melting points of the various fractions indicated that the monochloro acid (XCIV) was one of the acidic compounds present.

The water solution was made acid to Congo red with concentrated hydrochloric acid and was extracted continuously with ether for seventy hours. The ether solution was washed with water and dried over anhydrous calcium sulfate. After the ether was removed on a steam bath, 3.12 g. of a solid residue was obtained. The residue was crystallized from benzene to give 2.10 g. of the chlorohydrin acid (XCII), m.p. 168-171°. After one recrystallization the melting point was raised to 172-173°.

The residue was not investigated.

Attempted Hydrolysis of the Chlorohydrin Acid (XCII).

A. A mixture of 0.14 g. (0.52 mmoles) of the chlorohydrin acid (XCII)

and 20 ml. of 2.5% sodium hydroxide solution was refluxed for six hours. The solution was made acid to Congo red with 10% sulfuric acid and cooled. The white crystals were filtered and recrystallized from water. The melting point was 171-174° and did not depress the melting point of XCII.

B. A mixture of 0.14 g. (0.52 mmoles) of the chlorohydrin acid (XCII) and 20 ml. of 20% sodium hydroxide solution was refluxed for seventeen and a half hours; 10 ml. of water was added and the solution was refluxed for an additional twenty-four hours. After cooling, 50 ml. of water was added and the solution was made acid to Congo red with 10% sulfuric acid. The precipitate was filtered and crystallized from water. The melting point and infrared spectrum were identical with those of XCII.

Attempted Dehydrohalogenation of the Chlorohydrin Acid (XCII).

A solution of 0.27 g. (1.0 mmoles) of the chlorohydrin acid (XCII) and 25 ml. of 20% alcoholic potassium hydroxide solution were refluxed for twenty-two hours. The solution was cooled, diluted with water, made acid with 20% sulfuric acid, and extracted with ether. The ether solution was dried over anhydrous calcium sulfate. The volatile compounds were removed on a steam bath leaving 0.26 g. of solid residue. On crystallization of the residue from benzene the melting point was 168-171°. The white crystals gave a positive Beilstein test and did not depress the melting point of XCII.

Attempted Reductive Dehalogenation of the Rearranged Chlorolactone (XCI).

A mixture of 590 mg. (2.37 mmoles) of the rearranged chlorolactone (XCI), 50 mg. (3.0 mmoles) of anhydrous sodium acetate, 100 mg. of 5% palladium on carbon, and 40 ml. of absolute ethanol were stirred under hydrogen for six days. The mixture was filtered and the filtrate was evaporated to dryness. The solid residue was triturated with water and filtered; 547 mg. of the rearranged chlorolactone (XCI), m.p. 118-120°, was recovered.

The filtrate gave a negative test for chloride ion with silver nitrate.

Attempted Reductive Dehalogenation of the Chlorohydrin Acid (XCII).

A. A mixture of 290 mg. (1.1 mmoles) of the chlorohydrin acid (XCII), 164 mg. (2.0 mmoles) of anhydrous sodium acetate, 150 mg. of 5% palladium on carbon, and 30 ml. of absolute ethanol was stirred under hydrogen for four days. The mixture was filtered and the filtrate was evaporated to dryness in an air stream. The residue was triturated with water and filtered. A quantitative recovery of the chlorohydrin acid (XCII), m. p. 169-172°, was obtained.

The filtrate gave a negative test for chloride on with silver nitrate.

B. A mixture of 1.92 g. of sodium ethoxide, prepared from 0.7 g. (0.03 g. atoms) of sodium and 50 ml. of absolute ethanol, 801 mg. (3.0 mmoles) of the chlorohydrin acid (XCII), and 0.7 g. of Raney nickel (W-4), was stirred under hydrogen for two days. The mixture

was filtered and the filtrate evaporated to dryness in an air stream. A small sample of the residue was acidified with nitric acid; no precipitate formed on the addition of silver nitrate. The remainder of the residue was triturated with 10% hydrochloric acid. The solid was filtered, 635 mg. of material, m.p. 170-173°, was obtained. The solid did not depress the melting point of the starting chlorohydrin acid (XCII).

Attempted Dehalogenation of the Chlorohydrin Acid (XCII).

The procedure of Alder and Brockhagen (90) was adopted. To a solution of 100 mg. (0.384 mmoles) of the chlorohydrin acid (XCII) in 5 ml. of glacial acetic acid was added portionwise, with shaking, 240 mg. of zinc dust. The mixture was allowed to remain at room temperature for seventeen hours. The mixture was filtered, and the solid was washed with acetic acid, then with hot water. The filtrate was cooled and extracted with ether. The ether was dried over anhydrous magnesium sulfate. The ether was evaporated in an air stream leaving 107 mg. of solid residue. Crystallization of the residue from benzene yielded 78 mg. (78%) of the starting chlorohydrin acid (XCII), m.p. 170-172.5°.

Reaction of the Chlorohydrin Acid (XCII) with Sodium Iodide in Acetone.

A mixture of 1.50 g. of sodium iodide, 0.14 g. (0.52 mmoles) of the chlorohydrin acid (XCII), and 20 ml. of reagent acetone was refluxed for twelve days. The solution was diluted with water and the solid filtered. Crystallization of the solid from water yielded 0.12 g.

of material, m.p. 168-174°; N.E. 272. Neutralization equivalent of XCII is 267 and that of the iodohydrin acid 358.

Oxidation of the Rearranged Chlorolactone (XCI).

A mixture of 0.75 g. (3.0 mmoles) of the rearranged chlorolactone (XCI), 35 ml. of water, and 0.85 g. of potassium hydroxide was refluxed for fourteen hours. The solution was cooled and sufficient water was added to dissolve the precipitated potassium salt of the hydroxy acid. A solution of 2.5 g. (2.0 mmoles) of sodium permanganate trihydrate in 20 ml. of water was added and the mixture stirred at room temperature for seventeen and a half hours. The mixture was made acid to Congo red with 20% sulfuric acid. A saturated solution of sodium bisulfite was added to reduce the excess sodium permanganate and manganese dioxide and the mixture was extracted with ether. The ether solution was washed with dilute sodium hydroxide solution and dried over anhydrous calcium sulfate. The ether was removed at the water pump leaving 0.29 g. of crude rearranged chlorolactone (XCI).

The basic wash solution was made acid to Congo red with 20% sulfuric acid and extracted with ether. The ether extract was washed with water and dried over anhydrous calcium sulfate. After removing the ether at the water pump, 0.55 g. (68%) of the chloroketo acid (CVII) was obtained. After one recrystallization from water the melting point was 153-155°. An analytical sample, m.p. 154-156°, was prepared.

Anal. Calc'd for $C_{14}H_{13}O_3Cl$: C, 63.53; H, 4.95; Cl, 13.40. Found: C, 63.36, 63.40; H, 5.28, 5.26; Cl, 13.34, 13.39.

The 2,4-dinitrophenylhydrazone was prepared according to Shriner, Fuson, and Curtin(91). An analytical sample, m.p. 166-167°, was prepared from ethanol-water.

Anal. Calc'd for $C_{20}H_{17}N_4O_6Cl$: N, 12.57. Found: N, 12.55.

Reaction of 3-Chloro-5-phenylnortricyclene (XC) with Silver Nitrate.

A small sample of XC was dissolved in methanol and ethanolic silver nitrate was added. In a short time (approximately 15 minutes) a precipitate was noted. The mixture was allowed to remain for an additional two hours. The supernatant liquid was decanted off. The precipitate was found to be insoluble in nitric acid but soluble in 2% aqueous ammonia.

Reaction of the Rearranged Chlorolactone (XCI) with Sodium Hydroxide.

A mixture of 0.27 g. of XCI and 30 ml. of 7% sodium hydroxide solution were refluxed until a homogenous solution was obtained. The mixture was cooled and made acidic with hydrochloric acid. The acid mixture was rapidly extracted with ether. The ether was dried over anhydrous calcium sulfate and the ether was rapidly evaporated. Crystallization of the residue from benzene-petroleum ether, b.p. 90-100°, gave a small amount of a solid compound. m.p. 172-184°. The infrared spectrum of these crystals indicated the presence of a hydroxy group. On remaining in the refrigerator in petroleum ether

the material relactonized to XCI.

Reaction of the Chlorohydrin Acid (XCII) with Silver Nitrate.

A small amount of XCII was dissolved in ethanol and ethanolic silver nitrate was added. No precipitate was obtained on remaining at room temperature for one hour. The solution was then refluxed for 48 hours. At the end of this time no precipitate of silver chloride was noticed.

Oxidation of the Chlorohydrin Acid (XCII).

A solution of 0.30 g. (3.0 mmoles) of chromium trioxide in 5 ml. of water and 10 ml. of glacial acetic acid was added dropwise to a stirred solution of 0.81 g. (3.0 mmoles) of the chlorohydrin acid (XCII) in 15 ml. glacial acetic acid. The mixture was stirred at room temperature for 0.75 hours, then stirred and heated on a steam bath for 3 hours. The solution was diluted with water, cooled, and extracted with ether. The ether extract was washed with water and dried over anhydrous calcium sulfate. The ether was stripped at the water pump leaving 0.59 g. of an oily residue which solidified on trituration with 90-100° petroleum ether. Crystallization of the solid from ethyl acetate-90-100° petroleum ether produced 0.45 g. (56%) of material, m.p. 152-156°. On recrystallization from water the melting point was raised to 154-156°. The infrared spectrum was identical to the infrared spectrum of the chloroketo acid (CVII) obtained from the rearranged chlorolactone (XCI). An admixture melting

point showed no depression.

The 2,4-dinitrophenylhydrazone, m.p. 166-168°, was crystallized from ethanol-water. An admixture melting point with 2,4-dinitrophenylhydrazone of the chloroketo acid obtained from the rearranged chlorolactone showed no depression.

Reaction of the Chloroketo Acid (CVII) with Silver Nitrate.

A mixture of 100 mg. of the chloroketo acid (CVII) and a saturated alcoholic solution of silver nitrate was refluxed for 48 hours. No precipitate of silver chloride was obtained and the starting chloroketo acid (CVII) was recovered quantitatively.

Acetate Lactol (CVIII) from the Chloroketo Acid (CVII).

A sealed tube containing a mixture of 1.861 g. (6.98 mmoles) of the chloroketo acid (CVII), 18 ml. of acetic anhydride, and 2 ml. of acetyl chloride was heated in a steam bath for 12 hours. The volatile material was removed at the water pump. The residual oil was triturated with 90-100° petroleum ether and the solid was crystallized from benzene-90-100° petroleum ether; 1.649 g. (87%) of the acetate lactol (CVIII), m.p. 136.5-138°, was obtained.

Anal. Calc'd for $C_{16}H_{15}O_4Cl$: C, 62.51; H, 4.93; Cl, 11.56. Found: C, 62.40, 62.45; H, 4.91, 4.95; Cl, 11.55, 11.61.

Attempted Reaction of the Chloroketo Acid (CVII) and Selenium Dioxide.

A. A mixture of 100 mg. (0.376 mmoles) of the chloroketo acid

(CVII), 100 mg. (0.911 mmoles) of freshly sublimed selenium dioxide, and 5 ml. of xylene was refluxed for four hours. The reaction mixture was cooled and extracted with 2% sodium hydroxide solution. The basic water solution was made acid to Congo red with 10% hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous calcium sulfate. The ether was evaporated on a steam bath and the residual oil was crystallized from benzene-90-100° petroleum ether giving white crystals, m.p. 154.5-156°. The infrared spectrum was identical with the infrared spectrum of CVII.

B. A mixture of 1.35 g. (5.5 mmoles) of the chloroketo acid (CVII), 0.67 g. (6.0 mmoles) of freshly sublimed selenium dioxide, and 45 ml. of pseudocumene was refluxed and stirred for 11.5 hours. The mixture was cooled, 1.3 g. of finely powdered silver was added, and the mixture refluxed and stirred for an additional 3 hours. The mixture was cooled and filtered. The filtrate was extracted with 5% sodium bicarbonate solution. The basic water solution was washed with ether and made acid to Congo red with dilute hydrochloric acid. On scratching with a stirring rod the oil solidified; wt. 0.96 g., m.p. 139-152°. The infrared spectrum indicated the absence of a 1,2-diketone and is very similar to the infrared spectrum of CVII. Crystallization from water raised the melting point to 154-156°.

Attempted Condensation of the Chloroketo Acid (CVII) with Ethyl Formate.

To a stirred suspension of 0.1 g. of sodium hydride in 10 ml. of reagent benzene in a nitrogen atmosphere was added a solution of

0.342 g. (0.127 moles) of the chloroketo acid (CVII) in 10 ml. of benzene and 10 ml. of anhydrous ether. The mixture was stirred for 1.5 hours and one ml. of freshly distilled ethyl formate was added. The mixture was stirred at room temperature for 48 hours under a nitrogen atmosphere. The mixture was cooled, 10 ml. of ethanol and then water was added. The layers were separated and the water layer was washed with benzene. The water solution was made acid to Congo red with 10% hydrochloric acid. On cooling and scratching with a stirring rod 0.220 g. of solid material, m.p. 145-154°, was obtained. One crystallization from benzene 90-100° petroleum ether raised the melting point to 152-155°. The infrared spectrum was identical with the infrared spectrum of the chloroketo acid (CVII).

Reaction of the Chloroketo Acid (CVII) with Ethyl Formate and Butyl Nitrite.

The procedure of Meyer and Vaughan (67) was modified. To a stirred suspension of 0.100 mg. (4.2 mmoles) of sodium hydride and 10 ml. of benzene and 10 ml. of ether in a nitrogen atmosphere were added 483 mg. (1.82 mmole) of the chloroketo acid (CVII). The mixture was stirred for one hour, then one ml. of ethyl formate was added. The mixture was stirred for 36 hours. After 8 hours and 24 hours had elapsed an additional 0.5 ml. of ethyl formate was added. The mixture was cooled in an ice bath and 5 ml. of absolute ethanol were added followed by the addition of 0.5 ml. of freshly distilled n-butyl nitrite. The mixture was stirred under nitrogen at room temperature for 14 hours Twenty ml. of water were added and the layers separated.

The benzene-ether layer was washed with 10 ml. of water. The combined water layers were washed with ether. The water solution was made acid with concentrated hydrochloric acid. The white solid, 352 mg., m.p. 153-155.5°, was filtered. On admixture melting point with CVII it showed no depression.

Oxidation of the Methyl Ester of the Chlorohydrin Acid (XCIIa).

To a solution of 2.7 g. (9.6 mmoles) of XCIIa in 25 ml. of glacial acetic acid was added dropwise a solution of 1.0 g. (10.0 mmoles) of chromium trioxide in 4 ml. of water and 20 ml. of glacial acetic acid. The mixture was stirred and heated on a steam bath for 2.5 hours and poured into a mixture of ice and water. On scratching with a glass rod, the oil solidified; 2.5 g. (90%) of the methyl ester of the chloroketo acid (CVIIa), m.p. 84-87°, were obtained. An analytical sample, m.p. 86.2-87.2°, was prepared from cyclohexane.

Anal. Calc'd for $C_{15}H_{15}O_3Cl$: C, 64.61; H, 5.42; Cl, 12.72. Found: C, 64.63; H, 5.46; Cl, 12.81.

Attempted Reaction of the Methyl Ester of the Chloroketo Acid (CVIIa) with Isopropenyl Acetate.

A. A mixture of 1.509 g. (5.51 mmoles) of CVIIa, 32 ml. of isopropenyl acetate, and 1 drop of concentrated sulfuric acid was refluxed for 3.5 hours. The mixture was cooled, 0.5 g. of anhydrous sodium acetate was added, and the volatile components were removed at the water pump. Benzene was added to the residue, the mixture was filtered, and the filtrate was evaporated to dryness in an air stream. On

crystallization of the residue from cyclohexane (Norit) 1.191 g. of CVIIa, m.p. 85-88°, was obtained. The infrared spectrum was identical to the infrared spectrum of CVIIa.

B. A mixture of 200 mg. (0.717 mmole) of CVIIa, 6 ml. of isopropenyl acetate, and a few crystals of p-toluenesulfonic acid was heated on a steam bath for 4 hours. The solution was cooled, ether was added, and the solution was washed with 5% sodium bicarbonate solution. The ether solution was dried over anhydrous magnesium sulfate and the volatile components were evaporated in an air stream. A solid residue, 184 mg. (92%), m.p. 78-86°, was obtained. Crystallization of the solid from cyclohexane yielded 106 mg. of white crystals, m.p. 85-87°, which did not depress the melting point of CVIIa. The infrared spectrum was identical to the infrared spectrum of CVIIa.

Cleavage of the Methyl Ester of the Chloroketo Acid (CVIIa).

A mixture of 4.8 g. (1.7 mmoles) of CVIIa and 80 ml. of 10% sodium hydroxide solution was refluxed for 3 hours. The solution was cooled, made acid to Congo red with concentrated hydrochloric acid, and extracted continuously with ether for 24 hours. The ether was evaporated in an air stream and the residue crystallized from water yielding 3.7 g. of white crystals, m.p. 132-139°, which gave a negative Beilstein test. On recrystallization from water the melting point was raised to 137-139° (fast heating) (CXXVI or CXXVII). The neutralization equivalent was determined.

Calc'd for $C_{14}H_{14}O_4$: N.E., 123. Found: N.E., 125.

The di-p-bromophenacylester was prepared according to Shriner, Fuson, and Curtin (91). An analytical sample, m.p. 151.8-153°, was prepared from acetone-methanol.

Anal. Calc'd for $C_{30}H_{24}O_6Br_2$: C, 56.29; H, 3.78; Br, 24.96. Found: C, 56.57; H, 4.01; Br, 24.87.

The dimethylester (CXXVIa or CXXVIIa) was prepared using diazomethane. An analytical sample, m.p. 51-53°, was prepared from 60-75° petroleum ether.

Anal. Calc' d for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.67; H, 6.41.

Oxidation of CXXVI and CXXVII with Sodium Permanganate.

To a solution of 0.750 g. of a mixture of the sodium salts of CXXVI and CXXVII and 20 ml. of water was added, dropwise, a solution of 1.725 g. of sodium permanganate trihydrate in water. The reaction was very rapid. The manganese dioxide was filtered and the filtrate was acidified with sulfuric acid. A saturated solution of sodium sulfite was added to reduce the excess sodium permanganate and any manganese dioxide which had come through the filter paper. No precipitate was noted. The aqueous solution was extracted continuously for 24 hours. The ether was dried over anhydrous magnesium sulfate. The ether was removed in an air stream to give 0.559 g. of an oily residue. A positive 2,4-dinitrophenylhydrazine test was obtained, however, no crystalline products could be isolated.

Oxidation of a Mixture of Diacids (CXXVI, CXXVII) with Perbenzoic Acid.

A solution of 0.60 g. (2.44 mmoles) of CXXVI or CXXVII in 18 ml. of chloroform containing perbenzoic acid was allowed to remain in the refrigerator for 20 days. At the end of this time perbenzoic acid was still present as evidenced by the formation of iodine when a small sample of the reaction mixture was added to a mixture of sodium iodide, glacial acetic acid, water, and chloroform. The precipitate formed was filtered; 170 mg., m.p. 182-186° (dec.), were obtained. The solid was recrystallized from ethyl acetate-chloroform yielding 83 mg., m.p. 191-194° (dec.). The bath was preheated to 180° and the melting point was raised to 195-199° (dec.). An analytical sample, m.p. 203-205° (dec.) (bath preheated to 180°, fast heating), was prepared.

Anal. Calc'd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Calc'd for $C_{27}H_{28}O_{10}$: C, 63.27; H, 5.51. Found: C, 63.14, 63.17; H, 5.48, 5.42.

The filtrate was evaporated to dryness. The residue was washed with carbon tetrachloride and with benzene. The residue weighed 266 mg. and the melting point was 134-142°. An analytical sample, m.p. 140-141°, was prepared.

Anal. Calc'd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Calc'd for $C_{27}H_{28}O_8$: C, 67.48; H, 5.87. Found: C, 67.50; H, 5.74.

Reaction of the Methyl Ester of the Diacid (CXXVIa) with Perbenzoic Acid.

A solution consisting of 1.45 g. (5.28 mmoles) of CXXVIa and 25 ml. of chloroform which contained 0.00705 g. of perbenzoic acid per ml. of chloroform was allowed to remain in a refrigerator for 5

days. The chloroform solution was washed rapidly with 5% sodium hydroxide solution and water. The chloroform was dried over anhydrous sodium sulfate and the chloroform was removed at the water pump. The solid residue was crystallized from cyclohexane to yield 540 mg. of white crystals, m.p. 104-109°. No solid material could be obtained from the filtrate. Aa analytical sample, m.p. 111-112°, was prepared.

Anal. Calc'd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.22; H, 6.21.

Reaction of Mixture of Methyl Esters of Diacids (CXXVIa and CXXVIIa) with Prevost's Reagent.

Prévost's reagent was prepared by refluxing 1.120 g. (4.92 mmoles) of silver benzoate and 0.624 g. (2.46 mmoles) of iodine in 40 ml. of benzene for 0.5 hours. To the prepared reagent was added 673 mg. of CXXVIa and CXXVIIa. The mixture was refluxed for 41 hours. The mixture was cooled and the silver iodide was filtered. The benzene was washed with 5% sodium bicarbonate solution and water. The benzene was dried over anhydrous magnesium sulfate. After the removal of the benzene under reduced pressure, 631 mg., m.p. 50-53°, of solid residue was obtained. The residue did not depress the melting point of the starting material.

Reaction of the Epoxide (CXXXIa) with Magnesium Bromide Etherate.

To a stirred solution of magnesium bromide etherate, formed by the reaction of 96.5 mg. (3.98 mg. atoms) of magnesium and 835 mg. (4.45 mmoles) of ethylene bromide in 10 ml. of reagent ether, was

added dropwise a solution of 1.139 g. (3.94 mmoles) of the epoxide (CXXXIa) in 15 ml. of dry benzene and 5 ml. of reagent ether. The mixture was stirred at room temperature for 11 hours. One ml. of water was added; the mixture was stirred for an additional 15 minutes, then evaporated to dryness in an air stream. The solid residue was extracted with two 20 ml. portions of hot benzene. Evaporation of the benzene in an air stream left 1.368 g. of a semi-solid residue which solidified on trituration with 60-75° petroleum ether. Crystallization from cyclohexane yielded 1.005 g. (69%) of the bromohydrin (CXXXII), m.p. 101-104°. An analytical sample, m.p. 104-105°, was prepared.

Anal. Calc'd for $C_{16}H_{19}O_5Br$: C, 51.77; H, 5.16; Br, 21.53. Found: C, 51.87; H, 4.74; Br, 21.76.

The acetate was prepared by heating the bromohydrin (CXXXII) with an excess of isopropenyl acetate and a few crystals of p-toluenesulfonic acid on the steam bath for one hour. An analytical sample, m.p. 110-111°, was prepared from 60-75° petroleum ether.

Anal. Calc' d for $C_{18}H_{21}O_6Br$: C, 52.30; H, 5.12; Br, 19.34. Found: C, 52.51; H,5.16; Br, 19.26.

Reductive Debromination of the Bromohydrin (CXXXII) to the Alcohol (CXXXVII).

A mixture of 783 mg. (2.11 mmoles) of the bromohydrin (CXXXII), 180 mg. (2.19 mmoles) of anhydrous sodium acetate, 100 mg. of 5% palladium on carbon, and 40 ml. of absolute ethanol was stirred under hydrogen for 25 hours. Forty-one ml. (S.T.P.) of hydrogen were taken up (89%). The mixture was filtered and evaporated to dryness in an air

stream. The solid residue was stirred with water and filtered. On titration of the filtrate with standard silver nitrate (Fajans method) 2.03 mmoles (98%) of the bromide ion were found. The solid alcohol (CXXXVII) remaining on the filter was dried and gave a negative Beilstein test. The yield was 562 mg. (92%), m.p. 93-97°. An analytical sample was prepared from cyclohexane.

Anal. Calc'd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.30; H, 6.63.

Oxidation of the Alcohol (CXXXVII) to the Ketone (CXXXVIII).

Jones' reagent (54,55) was added dropwise to a stirred solution of 423 mg. (1.45 mmoles) of the alcohol (CXXXVII) in 20 ml. of reagent acetone at room temperature. The addition was continued until the yellow color persisted; the solution was stirred an additional 15 minutes. Water was added; most of the acetone was removed in an air stream and the mixture was extracted with ether. After drying the ether solution over anhydrous magnesium sulfate and evaporating the ether in an air stream, 357 mg. (85%) of a solid residue, m.p. 88-90°, giving a positive ferric chloride test, were obtained. An analytical sample, m.p. 89.5-90.5°, was prepared from cyclohexane-60-75° petroleum ether.

Anal. Calc'd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.55; H, 6.43.

The p-nitrophenylhydrazone, m.p. 197.5-198.5°, was crystallized from ethanol.

Anal. Calc'd for $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 62.22; H, 5.47; N, 9.87.

Hydrolysis of Degraded β-Keto Ester (CXXXVIII).

A mixture of 88 mg. of CXXXVIII and 15 ml. of 0.1 N sulfuric acid was refluxed for 18 hours. Barium carbonate was formed in a barium hydroxide trap. The mixture was cooled and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. After the removal of the ether on a steam bath 62 mg. of a semi-solid residue was obtained. The residue gave a negative ferric chloride test and a positive 2,4-dinitrophenylhydrazone test. The residue was triturated with 60-75° petroleum ether, heated to reflux, and cooled. A white solid, 41 mg. m.p. 110-112.5°, was obtained. An analytical sample, m.p. 112-113°, was prepared from benzene-cyclohexane.

Anal. Calc'd for $C_{13}H_{14}O_3$: C, 71.55; H, 6.46. Found: C, 71.38; H, 6.43.

Ethyl α-Carbethoxy- γ-cyano- β-phenylbutyrate (CXLII).

A. The procedure of Koelsch (78) was used. However, the boiling point of the product was 148-150° at 0.3 mm. instead of 190-195° as reported (77).

B. To a solution of sodium ethoxide, formed by the reaction of 0.96 g. (0.042 g.atoms) of sodium and 80 ml. of absolute alcohol, was added 32.2 g. (0.25 mole) of diethyl malonate. The mixture was refluxed for 4 hours, cooled, neutralized with dilute acetic acid, and poured into water. The viscous oil was separated and the water layer was extracted with ether. The combined organic fractions were washed

twice with 10% potassium chloride solution and dried over magnesium sulfate. After removal of the volatile components at the water pump, distillation of the residual liquid gave 39.0 g. (54%) of colorless ethyl α-carbethoxy- γ-cyano- β-phenylbutyrate (CXLII), b.p. 152-155° at 0.4 mm, $n_D^{21.5°}$ 1.4972. Reported b.p. 190-195° at 5mm. (77). On standing the liquid solidified. On crystallization from ether-60-75° petroleum ether it melted at 43-45°. Reported m.p. 41-44° (77).

Ethyl α-Cyano- β-phenylglutarate (CXLVI).

To a solution of sodium ethoxide, formed by the reaction of 0.48 g. (0.021 g.atoms) of sodium and 50 ml. of absolute ethanol, was added 14.1 g. (0.125 moles) of ethyl cyanoacetate followed by 22.0 g. (0.125 moles) of ethyl cinnamate. The mixture was refluxed for 5 hours, cooled, neutralized with dilute acetic acid, and poured into water. The viscous oil was separated and the water layer extracted with ether. The organic material was then washed with water and dried over anhydrous magnesium sulfate. After the removal of the volatile material at the water pump, distillation of the residual liquid gave 23.9 g. (66%) of colorless ethyl α-cyano- β phenylglutarate (CXLVI), b.p. 142-144° at 3 mm, $n_D^{21.5}$ 1.4990. Reported b.p. 208-210° at 18 mm (78) and 172-175° at 2 mm (77).

Ethyl α-Cyano- β-phenylglutarate (CXLVI).

To a solution of sodium ethoxide, formed by the reaction of 2.9 g. (0.125 g. atoms) of sodium and 50 ml. of absolute ethanol, were

added 14.1 g. (0.125 mole) of ethyl cyanoacetate followed by 22.0 g. (0.125 mole) of ethyl cinnamate. The mixture was refluxed, cooled, neutralized with dilute acetic acid, and poured into water. The viscous oil was separated and the water layer extracted with ether. The organic material was then washed with water and dried over anhydrous magnesium sulfate. After the removal of the volatile material at the water pump, distillation of the residual liquid gave 23.3 g. (65.4%) of colorless ethyl α-cyano-β-phenylglutarate (CXLVI), b.p. 143-145° at 0.3 mm, $n_D^{21.5}$ 1.4990. Reported b.p. 208-210° at 18 mm (78) and 172-175° at 2 mm (77).

Hydrolysis of γ-γ-Dicarbethoxy-δ-phenylsuberic Dinitrile (CXLIII).

A mixture of 4.5 g. (0.0125 mole) of CXLIII and 45 ml. of 50% sulfuric acid was refluxed for 12 hours. The mixture was cooled, diluted with 200 ml. of water, and made basic with a concentrated sodium hydroxide solution. The basic solution was washed with ether to remove non-acidic material. The water solution was concentrated in an air stream then made acid to Congo red with concentrated hydrochloric acid and extracted continuously for 19 hours. The ether was washed with a small amount of water and dried over anhydrous magnesium sulfate. After the removal of the ether on a steam bath, 3.9 g. of a viscous oil were obtained. The residue was triturated with ethyl acetate, cyclohexane was added, then the mixture was heated to reflux, cooled, and filtered; 0.9 g. of material, m.p. 165-172° (dec.), were obtained. The solid was esterified with diazomethane After one

crystallization from ether-60-75° petroleum ether, the melting point of the triester was 50-53°. An admixture melting point with the triester obtained from CXLVII showed no depression. The infrared spectra of the triester from the two sources were superimposable.

Ethyl δ-Carbethoxy-δ,ω-dicyano-γ-phenylcaproate (CXLVII).

To a stirred solution of 25.0 g. (0.096 mole) of ethyl α-cyano-β-phenylglutarate (CXLVI) in 80 ml. of dioxane was added 4 ml. of 35% aqueous Triton B solution followed by a solution of 4.58 g. (0.086 mole) of acrylonitrile in 10 ml. of dioxane. The solution was stirred for 11 hours, then poured into a mixture of ice, water, and hydrochloric acid. The viscous oil was separated and the water solution was extracted with two 50 ml. portions of chloroform. The oil and chloroform extracts were combined, washed with water and dried over anhydrous magnesium sulfate. The chloroform was removed at the water pump. Distillation of the residual oil gave 16.3 g. (55.5%) of ethyl δ-carbethoxy-δ,ω-dicyano-γ-phenylcaproate, b.p. 192-194° at 0.4 mm.

Anal. Calc'd for $C_{19}H_{22}N_2O_4$: C, 66.64; H, 6.48; N, 8.18. Found: C, 65.64; H, 6.68; N, 8.42.

γ,γ-Dicarbethoxy-δ-phenylsuberic Dinitrile (CXLIII).

To a stirred solution of 14.0 g. (0.048 mole) of ethyl α-carbethoxy-γ-cyano-β-phenylbutyrate in 100 ml. of dioxane was added 4 ml. of 35% aqueous Triton B solution followed by a solution

of 2.6 g. (0.049 mole) of acrylonitrile in 10 ml. of dioxane. The solution was stirred at room temperature for 12 hours, then poured into a mixture of ice, water, and hydrochloric acid. On trituration in the acid solution, the oil solidified. Crystallization of the solid from benzene-60-75° petroleum ether gave 9.4 g. (63.0%), m.p. 80-83°, of γ,γ-dicarbethoxy-δ-phenylsuberic dinitrile. An analytical sample, m.p. 81.5-83.5°, was prepared from benzene-cyclohexane.

Anal. Calc'd for $C_{19}H_{22}N_2O_4$: C, 66.64; H, 6.48; N, 8.18. Found: C, 66.63; H, 6.24; N, 8.00.

Hydrolysis of Ethyl δ-Carbethoxy-δ,ω-dicyano-γ-phenylcaproate (CXLVII).

A mixture of 10 g. (0.028 mole) of CXLVII and 85 ml. of 50% sulfuric acid was refluxed for 19 hours. The mixture was cooled, diluted with 250 ml. of water, and made basic with a concentrated sodium hydroxide solution. The basic water solution was washed with ether to remove any non-acidic material. The basic water layer was made acid to Congo red with concentrated hydrochloric acid. The mixture was concentrated in an air stream; then extracted continuously with ether for 17 hours. The ether was washed with a small amount of water and dried over anhydrous magnesium sulfate. After the removal of the ether on a steam bath 7.2 g. of a viscous oil were obtained. The oil was partially crystallized from ethyl acetate-cyclohexane to give 2.0 g. of the triacid (CXLVIII). The melting point could not be sharpened to better than 165-172° (dec.). The trimethyl ester (CXLVIIIa)

was prepared using diazomethane. An analytical sample, m.p. 52-53°, was prepared from ether-petroleum ether (60-75°).

Anal. Calc'd for $C_{17}H_{22}O_6$: C, 63.33; H, 6.88. Found: C, 63.40; H, 6.87.

Cyclization of the Triester (CXLVIIIa).

The procedure of Blicke (86) was modified. A solution of 631 mg. (1.96 mmole) of CXLVIIIa in 10 ml. of xylene was added dropwise to a refluxing stirred mixture of 10 ml. of xylene, some glass beads, 100 mg. (4.17 mmole) of sodium hydride, and one drop of absolute methanol. A slow stream of nitrogen was constantly passed through the reaction flask. The mixture was stirred and refluxed for 7 hours. The reaction mixture was cooled in an ice bath, an excess of acetic acid was added dropwise, then water was added. The two phase mixture was stirred and allowed to warm at room temperature. The layers were separated and the xylene layer was washed with water, 5% sodium bicarbonate solution, and water. The xylene was dried over anhydrous magnesium sulfate. After the removal of the xylene in an air stream, 511 mg. of a semi-solid residue were obtained. The residue was triturated with 60-75° petroleum ether and filtered. A white solid, 207 mg., m.p. 138-144°, was obtained. On crystallization from cyclohexane 119 mg. of white crystals , m.p. 144-145°, were obtained. An analytical sample was prepared.

Anal. Calc'd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.02; H, 6.41.

Hydrolysis of the Synthetic β-Keto Ester (CL).

A solution of 2.60 g. of oily residue from a cyclization reaction in 40 ml. of glacial acetic acid, 10 ml. of water, and 4 ml. of concentrated hydrochloric acid was refluxed for 38 hours. Most of the acetic acid was removed at the water pump. The residue was dissolved in chloroform. The chloroform solution was washed with 5% sodium bicarbonate solution. The basic extracts were made acid to Congo red with concentrated hydrochloric acid. The acid solution was heated to reflux, filtered while hot, then cooled and concentrated in an air stream. White crystals, 0.80 g. m.p. 141-144°, were obtained. An analytical sample, m.p. 146.5-147.5°, was prepared from benzene-cyclohexane.

Anal. Calc'd for $C_{13}H_{14}O_3$: C, 71.55; H, 6.46. Found: C, 71.15; H, 6.40.

The p-bromophenylacyl ester was prepared (92). An analytical sample, m.p. 134-135°, was prepared from ethanol-water.

Anal. Calc'd for $C_{21}H_{19}O_4Br$: C, 60.74; H, 4.61; Br, 19.25. Found: C, 60.64; H, 4.61; Br, 19.45.

Attempted Equilibration of Degraded Keto Acid (CXXX).

The methyl ester of (CXXX) was prepared using diazomethane. A solution of 147 mg. of the methyl ester in 10 ml. of 10% sodium methoxide in methanol was refluxed for 7 hours. The solution was cooled, 1 ml. of water was added, and the mixture heated for one hour and allowed to remain overnight. Most of the methanol was removed in an air stream, water was added, and the water solution was washed

with ether. The basic water solution was made acid to Congo red with concentrated hydrochloric acid. The acid solution was extracted with ether, the ether was washed with water, then 5% sodium bicarbonate solution. The basic solution was made acid with concentrated hydrochloric acid and filtered. An orange solid, 62 mg., m.p. 80-160° (dec.), was obtained. Attempts at purification of this solid were unsuccessful.

Attempted Equilibration of the Synthetic Keto Acid (CLIII).

The methyl ester was prepared using diazomethane. A solution of 197 mg. of the methyl ester in 10 ml. of 10% sodium methoxide in methanol was refluxed for 7 hours. The solution was cooled, one ml. of water was added and the solution was heated for one hour and allowed to remain overnight. Water was added and most of the methanol was removed in an air stream. The solution was washed with ether and made acid to Congo red with concentrated hydrochloric acid. The acid solution was extracted with ether. The ether extract was washed with water, then with 5% sodium bicarbonate solution. The basic wash solution was made acid with concentrated hydrochloric acid. On filtration, 150 mg., m.p. 170-210° (dec.), of white solid were obtained. Attempts to purify the solid further were unsuccessful.

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