SPIRO(3,3)HEPTANE

THE HUNSDIECKER DEGRADATION OF CARBOXYLIC ACIDS

Thesis by

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It is my privilege gratefully to acknowledge the inspiration and leadership of this research by Dr. Edwin R. Buchman.

I want also to thank my fellow workers in the laboratory, Dr. R. M. Badger for his help with the infra-red work, and The Office of Naval Research for its financial support of the work.

Most especially I want to thank my ever-loving wife, Gladys, for her patience and assistance (and her financial support).

Abstract

A general method for the synthesis of polyspiranes containing cyclobutane rings is described. The method involves condensation of sodiomalonic esters with derivatives of trimethylene glycol to give cyclobutane-1,1-dicarboxylates, reduction of these esters with lithium aluminum hydride to the corresponding 1,1-dimethylol cyclobutane, and the use of this substituted trimethylene glycol for a repetition of the cycle. By means of this series of reactions spiro-(3,3)-heptane has been made.

The degradation of silver salts of certain types of aliphatic carboxylic acids with bromine has been investigated. Halogen-substituted acids were found to give results that were dependent upon the position of the halogen and the technique that was employed. Polycarboxylic acids, contrary to some previous reports, were found to undergo the reaction in fair yields, giving alkyl polybromides. The cyclobutane ring was found to be cleaved during the degradation if carried out as customarily described, but use of low temperature techniques gave cyclobutyl bromides in good yields. The mechanism of the reaction is the subject of some speculation, but its synthetic usefulness seems considerable.

Table of Contents

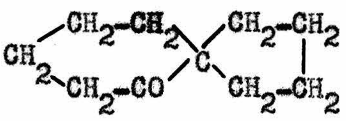
PART I

SPIRO(3,3)HEPTANE

PART I

SPIRO-(3,3)-HEPTANE

The first formation of a spirane system was reported in 1899 by Meiser (1). He isolated spiro-(4,5)-decanone-6* (I) as the product of a pinacolone rearrangement carried out on 1,1'dihydroxy-dicyclopentyl, a result which was later confirmed by Hückel (2), Zelinsky (3) and others (4). Fecht (5) produced, in 1907, spiro-(3,3)-heptane-2,6-dicarboxylic acid starting from pentaerythrityl



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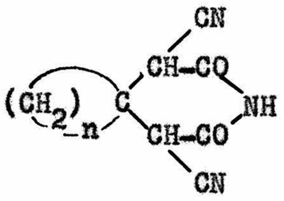

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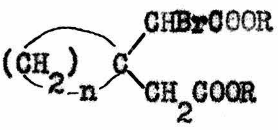

III

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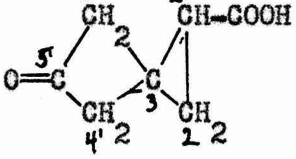
*A note on nomenclature: There are two systems in popular use for naming and numbering the spiranes. The approved system now names them as spiro-(n,n')-alkanes, where n and n' are the number of carbon atoms between the carbon common to the two rings. The atoms are numbered clockwise, starting immediately to the right of the spiro atom and giving the lowest possible number to the spiro atom. An example, (IVa) is spiro-(2,3)-hexan-5-one-1-carboxylic acid.

The older system is still used in some cases; the compound is named as the spiro derivative of a cyclic system. That is, (IVb) would be called cyclopropane-1-spirocyclobutane-3'-one-2-carboxylic acid. In some cases it is easier to use the second type of nomenclature, as for example, in naming a series of spiranes based on cyclopropane. (Continued, bottom of page 2.)

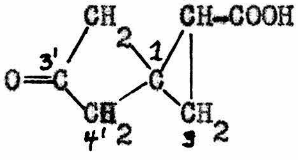
tetrabromide and malonic ester. This compound was the subject of considerable debate over the possibility of its existing in optically active d- and l-forms as do the allenes. In the 1930's Backer and Shurink (6), and Janson and Pope (7) succeeded in isolating the optically active acids and several derivatives of higher rotatory power, illustrating clear-cut cases of "molecular" asymmetry causing optical activity, even in the absence of what would ordinarily be considered an asymmetric carbon atom.

The English school under Ingold and Thorpe, in an effort to correlate reactivity of glutaric acids with the angles assumed by substituents in the β-position, synthesized and tested the stability of a series of spirane dicarboxylic acids. They made 2,3-dicarboxycyclopropane-1-spirocyclopentane (8), (9), -spirocyclohexane (10), (11), -spirocycloheptane (12), (old nomenclature), and some others, mostly by means of the sodio derivatives of the Guareshi imides (II) with iodine, or by dehydrobromination of the cycloalkane-1-acetic, 1-α-bromoacetic esters (III).

Dispiranes are named according to the first system above. Dispiro-(3,1,3,1)-decane is V



IVa



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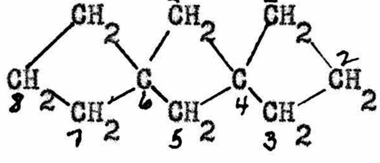
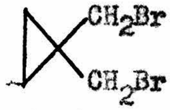


V

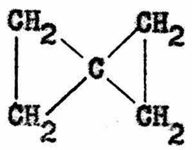
The unsubstituted hydrocarbons have proved to be considerably more difficult to make and only the ones listed below had been reported previous to the time of this investigation.

VI Cyclopropane-spirocyclopropane (13), (14)
VII Cyclopropane-spirocyclohexane (15)
VIII Cyclopentane-spirocyclopentane (3),(16)
IX Cyclopentane-spirocyclohexane (17),(18),(19)
X Cyclohexane-spirocyclohexane (20)

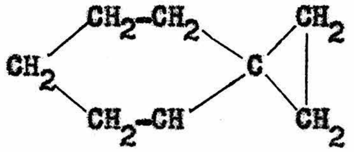
No authentic dispirane hydrocarbons have been reported.

The simplest member of the spirane series, spiro-(2,2)-pentane (VI), is easily accessible in a direct manner from a readily available starting material. By treatment of pentaerythrityl tetrabromide with zinc in acetamide with sodium iodide-sodium carbonate catalyst (Hass-McBee procedure), yields of the spirane as high as 60% (21) have been reported. Zelinsky (22) had claimed the preparation of the compound as early as 1913, from  with zinc in aqueous ethanol, but his compound reacted vigorously with bromine at 25°; the authentic material does not. He probably had methylene cyclobutane, from a Whitmore-type rearrangement of the intermediate carbonium ion. This type of rearrangement is known to occur in the reaction of pentaerythrityl tetrabromide with zinc in aqueous alcohol. The presence of spiropentane in the mixture of hydrocarbons from the reaction was first deduced by Murray and Stevenson (14) from Raman spectra studies. Its structure was confirmed by electron diffraction studies in these laboratories (23).

The API group (15) at the Ohio State University, in preparing a series of cyclic hydrocarbons, made spiro-(2,5)-octane (VII) by essentially the same procedure, using 1,1-dibromomethylcyclohexane as starting material. Presumably the method can be extended to other cyclopropane-containing spiranes.

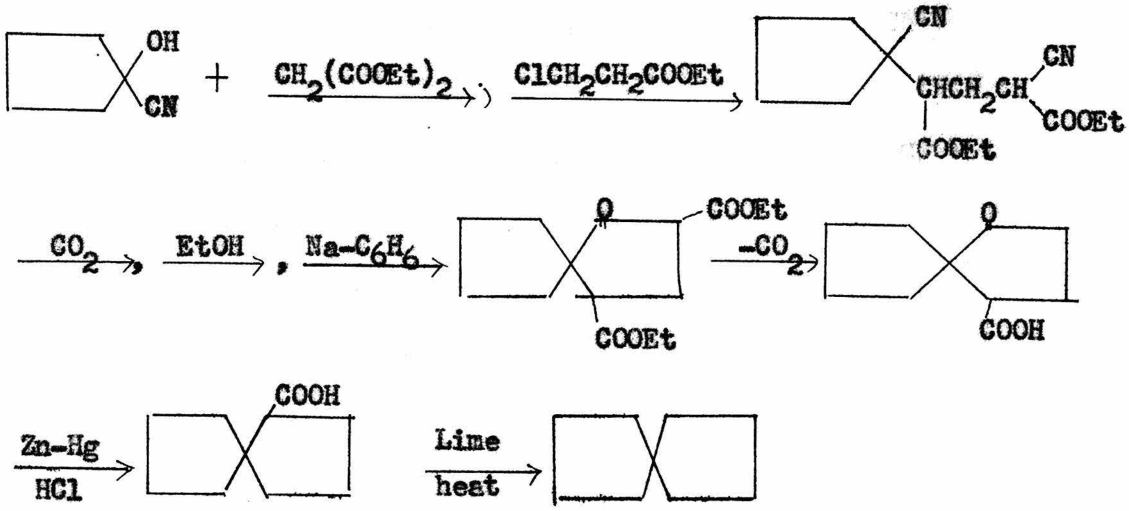


VI



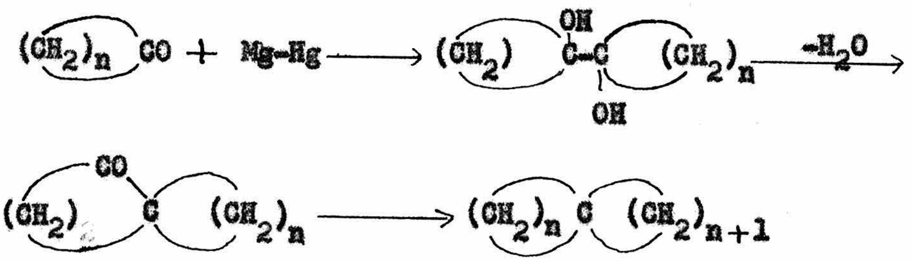
VII

Much more devious procedures have been used in preparing the other reported spirane hydrocarbons. Chatterjee (16) has claimed the preparation of two cyclopentane spiranes by the following scheme, which, in theory, can be used to make others.



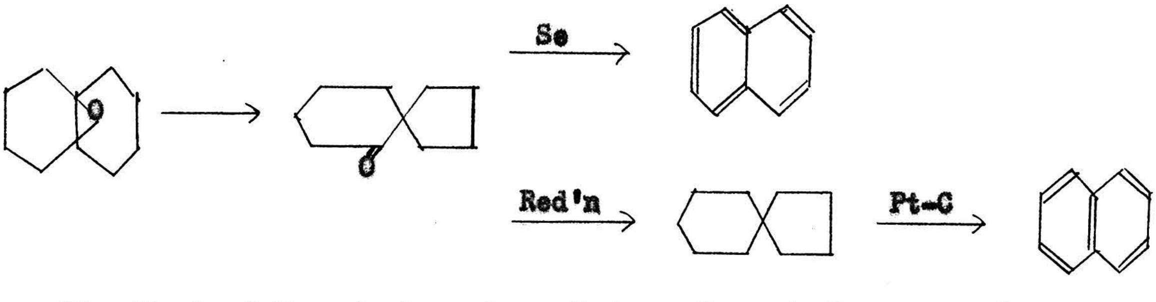
As can be easily understood from the scheme, the yields overall are minute and the method will remain a laboratory curiosity

The same can be said for another method which is of interest as a general method for the preparation of n, n + 1-spiranes (VIII). The pinacol reduction products of the cyclic ketones can be obtained (in yield of 1-5%) by the action of magnesium or aluminum amalgams (17), (24), (25). Such a pinacol can then be rearranged by 50% sulfuric acid to the corresponding pinacolone, an unsymmetrical spiranone, which can, in turn, be reduced by the Wolff-Kishner or the Clemmensen technique to the corresponding spirane.

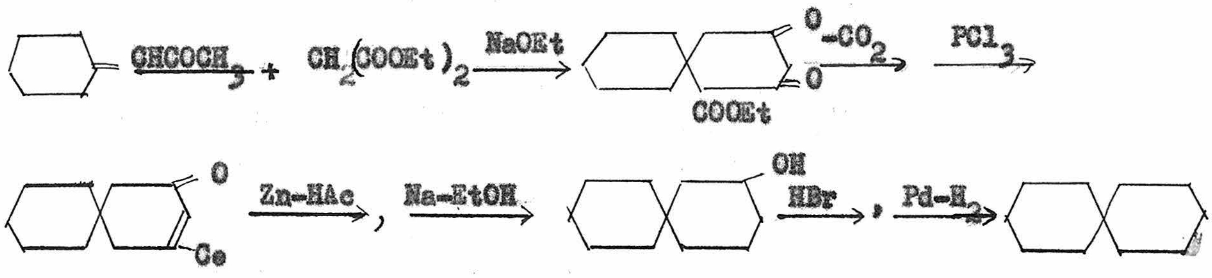


VIII

It is of interest that an example of the same type of spiranone (n = 4) has been produced (in much better yield) by the rearrangement of 5,10-dihydroxy decalin or of octalin oxide under various conditions by Hückel (2) and by Clemo (4). This type of rearrangement, from a bicyclic to a spirocyclic system, is reversible under dehydrogenating conditions, and the spiro-(4,5)-decane and -decanone yield naphthalene at temperatures of 275-300° in the presence of platinum-charcoal or selenium catalysts, respectively (18), (19).



The first of the simple spirane hydrocarbons to be prepared was reported by Norris (20) in 1926, and its preparation, shown below, well illustrates the difficulties that were overcome in the early work in this field. The yields were small. Obviously a better procedure is needed for the reduction of the cyclic β-diketones that are often intermediates in these syntheses.



Since the start of this research, four spiranes not previously reported have been synthesized in this laboratory under the direction of Dr. E. R. Buchman. Dr. G. I. Fujimoto has made spiro(3,3)heptane by the conversion of spiro(3,3)-heptane-2,6-dicarboxylic acid to the corresponding dibromide and reduction to the hydrocarbon. He has also made spiro-(3,5)-nonanone by the reaction of pentamethylene ketene with diazomethane. This reaction gives the two isomeric ketones, spiro-(3,5)-nonanone-1 and -nonanone-2, and these may be reduced to the hydrocarbon, spiro-(3,5)-nonane, by the Wolff-Kishner technique.

Simultaneously, D. H. Deutsch made spiro-(3,5)-nonane by the reaction of 1,1-dibromomethylcyclohexane with malonic ester, followed by decarboxylation, conversion to the 2-bromospiro-(3,5)-nonane, and reduction to the hydrocarbon, which proved to be identical with that prepared by Fujimoto.

Dr. Harry Walborsky was able to produce two dispiranes, dispiro-(3,1,3,1)-decane (V) and dispiro(5,1,5,1)-tetradecane by a method described later, which involves dimerization of the monocyclic ketenes. The resulting diketones were reduced by Raney nickel desulfurization of the thioketals. Dr. Hershel Herzog has also been able to reduce dispiro-(3,1,3,1)-decane-5,10-dione to the hydrocarbon (V) by the Ruzicka and Goldberg (28) modification of the Wolff-Kishner technique.

A complete description of the spiranes and substituted spirocarbon systems that have been reported is given in Elsevier's Encyclopedia (26), so only a list of the systems that have been synthesized previously to this research need be given here.

Cyclopropane spirocyclo-propane, -pentane, -hexane, -heptane

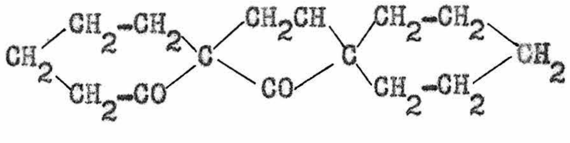
Cyclobutane spirocyclo-butane, -pentane, -hexane

Cyclopentane spirocyclo-pentane, -hexane

Cyclohexane spirocyclo-hexane, -heptane

Cycloheptane spirocyclo-octane.

No reliable reports of any polyspiranes, with the possible exception of (IX), have been reported.



IX

The spiranes so far mentioned have been investigated with respect to their interesting optical properties, their Raman spectra and electron diffraction patterns, the stability of their acids, and their rearrangements into aromatic systems. However, they have much greater general interest than is represented by any one of the specific studies that have been made. They present a very interesting problem in pure synthetic chemistry, since very little is known about the orientation and entropy relationships that are involved in the closure of a second ring, and about the energy of that ring once formed as evidenced by its stability towards reagents. It is especially interesting in the chemistry of spiranes containing three and four carbon rings, where strain factors are important, to gather information as to the reactions that can be employed, since in this way valuable light can be shed on the mechanisms involved.

The chemical properties of the hydrocarbons and their functional derivatives need to be studied further. The spirane system, involving, as it does, atoms that are tied rigidly into definite spatial relationships that can be relatively easily determined, presents an ideal system for the study of certain types of reaction, just as the bridgehead systems have been put to good use in the study of reactions involving displacements and rearrangements.

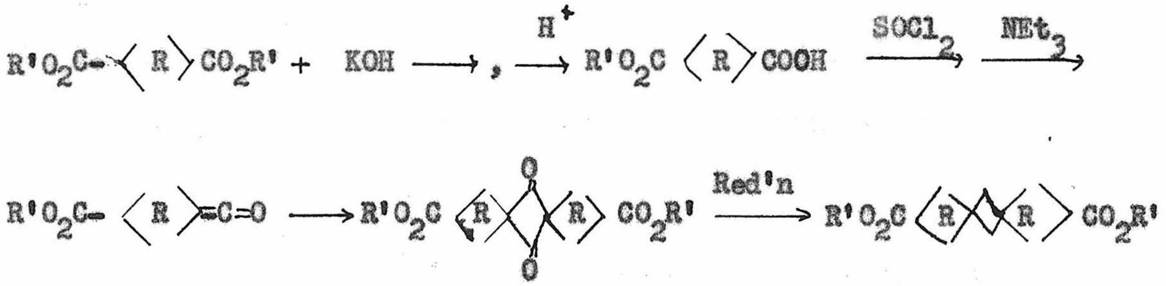
The rigidity and linearity of the molecules, especially in the polyspirobutane series, ought to lead to unusual physical properties as well. The spectra - infra-red and Raman- ought to show very characteristic features due to the elimination of certain modes of vibrations involving rotation and carbon-carbon bending. The molecules should have restricted forms of internal vibrations, since the position or motion of any carbon atom at any time is determined and limited to an unusual extent by its rigid connections to all the others. On the intermolecular scale, the motion of the molecules will be restricted in some ways by the ease of approach and the resultant closeness of other molecules, and in some ways increased by the lack of tangling of freely rotating side chains. The viscosity-temperature relationships should be quite unusual, especially in the case of the longer polyspiranes now being prepared. The boiling points of the hydrocarbons may be anomalous and the melting points and densities should certainly be high due to the extreme symmetry and the ease of fitting together of the molecules. Especially the crystals of the higher members should be easily formed and have very interesting packing patterns.

General Methods of Synthesis

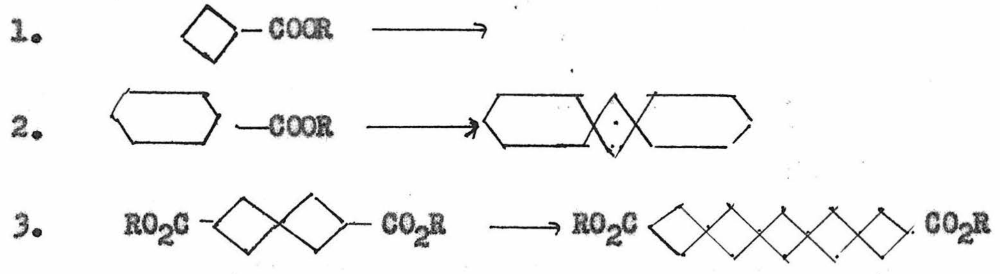
Some general methods of synthesis of monospiranes (that is, two joined rings) have been suggested in the historical description above. It is of interest, however, to have methods that can be used for extending the chain of rings beyond just two. The interesting properties of the two-ring spiranes ought to be accentuated in the higher members. It is the purpose of this research to find a method that will enable the chain to be extended indefinitely.

In the preparation of cyclobutane spiranes two general methods have proved of considerable value. Briefly, they are: (1) condensation of sodiomalonic esters with substituted trimethylene halides; and (2) dimerization of ketenes. In the study of method (1), the preparation of the starting materials, the finding of the optimum condition for ring formation, and the conversion of the products into starting materials for the next step have made up the three phases of the present work.

The second method will be considered first briefly, since it is not the author's work and will be reported at length elsewhere (29). The scheme is shown below applied to the problem of building up polyspirane molecules:

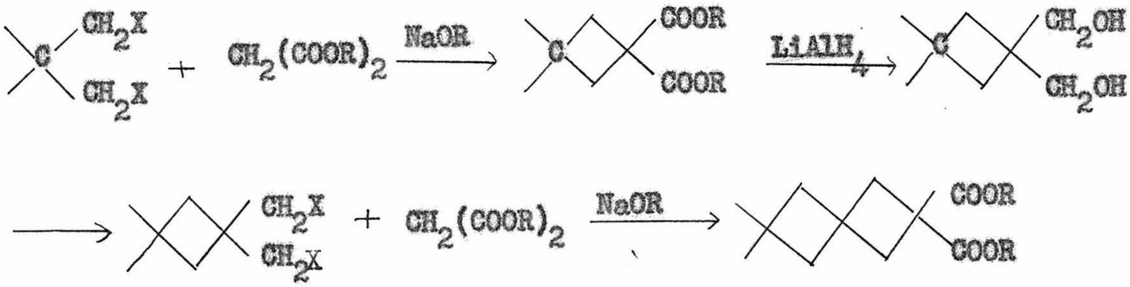


The starting material can be a cycloalkane dicarboxylic acid diester (if it is available) in which case ⟨R⟩ can represent cyclobutane, cyclohexane, etc. Or it may itself be a spirane diacid, such as Fecht's spiro-(3,3)-heptane-2,6-dicarboxylic acid. At this date three cases have been studied (see above).



The reduction step is the critical one. A Raney nickel desulfurization of an intermediate thioketal has been successful in cases (1) and (2), and in case (1) the Wolff-Kishner method is known to be applicable. The synthesis of eleven and twenty-three ring -containing spiranes will be attempted by Dr. Buchman's group. Not all members of the series are available by this method. Only the three, seven, fifteen, etc., ring spiranes would be obtainable from cycloalkane diacids; only five, eleven, twenty-three, etc. ring spiranes from an initial monospirane diacid.

The second method is completely general. It can be outlined as follows:



If the starting material is trimethylene bromide, the reactions will result in adding one cyclobutane ring at a time. If the starting material is pentaerythrityl tetrabromide, two cyclobutane rings will be added each time.

In both methods the final step to a parent hydrocarbon is the replacement of the carboxyl groups by hydrogen. This can be carried out by the degradation of the silver salt of the acid with bromine to give the alkyl bromide, which can in turn be reduced by hydrogen at atmospheric pressure using Raney nickel catalyst in the presence of sodium methylate in methanol.

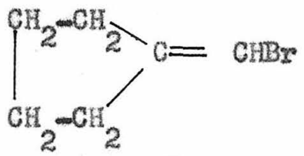
In the process of this research we have successfully made 1,1-dimethylcyclobutane from 1,1-dicarbethoxycyclobutane by lithium aluminum hydride reduction, and have converted this glycol to the ditosylate, which was then reacted with malonic ester to give the diester of spiro-(3,3)-heptane-2,2-dicarboxylic acid. The diacid was readily decarboxylated to the monoacid, which was, by use of the Hunsdiecker technique, converted to the bromide. The hydrocarbon was obtained from the bromide by catalytic hydrogenation at atmospheric pressure, in alkaline solution. The physical properties , including the infra-red spectrum, of the hydrocarbon were determined, and were found to be practically identical with those of the spiro-(3,3)-heptane prepared from the Fecht acid by Dr. Fujimoto. The overall yield from trimethylene bromide was only 2.3%, with the quantities used, but the yield of  $(COOEt)_2$ from  $(COOEt)_2$ was 28.5%. That is, one cyclobutane ring can be added to a spirane chain by this method with an expected yield of 28.5%.

Experimental Observations

The preparation of 1,1-dicarbethoxycyclobutane has been described many times, most recently and with the best yields (60%) by Cason (30). In addition to the standard preparation from trimethylene bromide, the condensation using trimethylene tosylate and sodiomalonic ester was tried in a single run. The reaction was more sluggish than with bromide, but the yield was fair (25% as compared with 35-37% from the bromide under the usual conditions).

The glycol, 1,1-dimethylolcyclobutane, has been reported only once previously (31), made by a Bouveault-Blanc reduction of the 1,1-diester, from which it was a minor product (10%) with methylolcyclobutane the principal product. Lithium aluminum hydride reduction of the 1,1-diester gave 81% of the desired glycol. The product is extremely soluble in water and very hygroscopic, however it could be extracted with ether from a concentrated salt solution made by adding sodium chloride to the sulfuric acid solution obtained in the working up of the lithium aluminum hydride reduction product. The glycol, as obtained under ordinary conditions, is a viscous liquid, which can be purifed to yield a low-melting solid. The ditosylate of this is easily made by reaction at 0° of tosyl chloride and the glycol in pyridine. It is a white crystalline material, obtainable in 94% yield from the glycol.

Several efforts were made to obtain the 1,1-dibromomethylcyclobutane, but with no success. Although successful reaction of 2,2-dimethylolpropane (32), 1,1-dimethylolcyclopropane (22) and 1,1-dimethylolcyclohexane (15) with phosphorus tribromide have been reported, all efforts to carry out this reaction, or the corresponding one with thionyl bromide resulted only in tarry masses. Reaction with 60% hydrogen bromide in a sealed tube at 25°, using acetic acid as solvent, led to a dark-blue material which lost hydrogen bromide spontaneously and gave rise to a monobromide of uncertain constitution. A picrate made from the reaction product of this monobromide and trimethylamine (a very slow reaction) gave analytical figures in agreement with the composition $C_{15}H_{20}N_4O_7$, which possibly indicates rearrangement to a compound of structure (X).



X

The exchange reaction of sodium bromide with the glycol ditosylate was tried in diethylene glycol and in diethylene glycol dimethyl ether, but only decomposition resulted. Evidently the resultant dibromide, if formed at all, is unstable. It is interesting to note that 1,1-dimethylolcyclohexane ditosylate undergoes the exchange readily (29). However, several examples of rearrangements of cyclobutyl carbinols under acid conditions have been reported (33), (34).

Since the dibromide was not available, the condensation of the ditosylate with sodiomalonic esters was attempted. (Braber, Pribyl and Lott (35) have reported the successful formation of disubstituted malonates from the tosylate of cyclobutyl carbinol and substituted malonic esters in 18-87% yields.) The reaction was successful in this case also, giving 34%(with diethyl malonate) and 38%(with di-isoamyl malonate) of somewhat impure spiro-(3,3)-heptane-2,2-dicarboxylic acid esters.

The impure diester was saponified and gave 58% of pure crystalline diacid. The diacid was decarboxylated by heating to 200° and gave a 95% yield of liquid monoacid. The silver salt of this monoacid, after drying thoroughly, was reacted with bromine in carbon tetrachloride at 10°, under which conditions decarboxylation took place slowly to give 2-bromospiro-(3,3)-heptane.

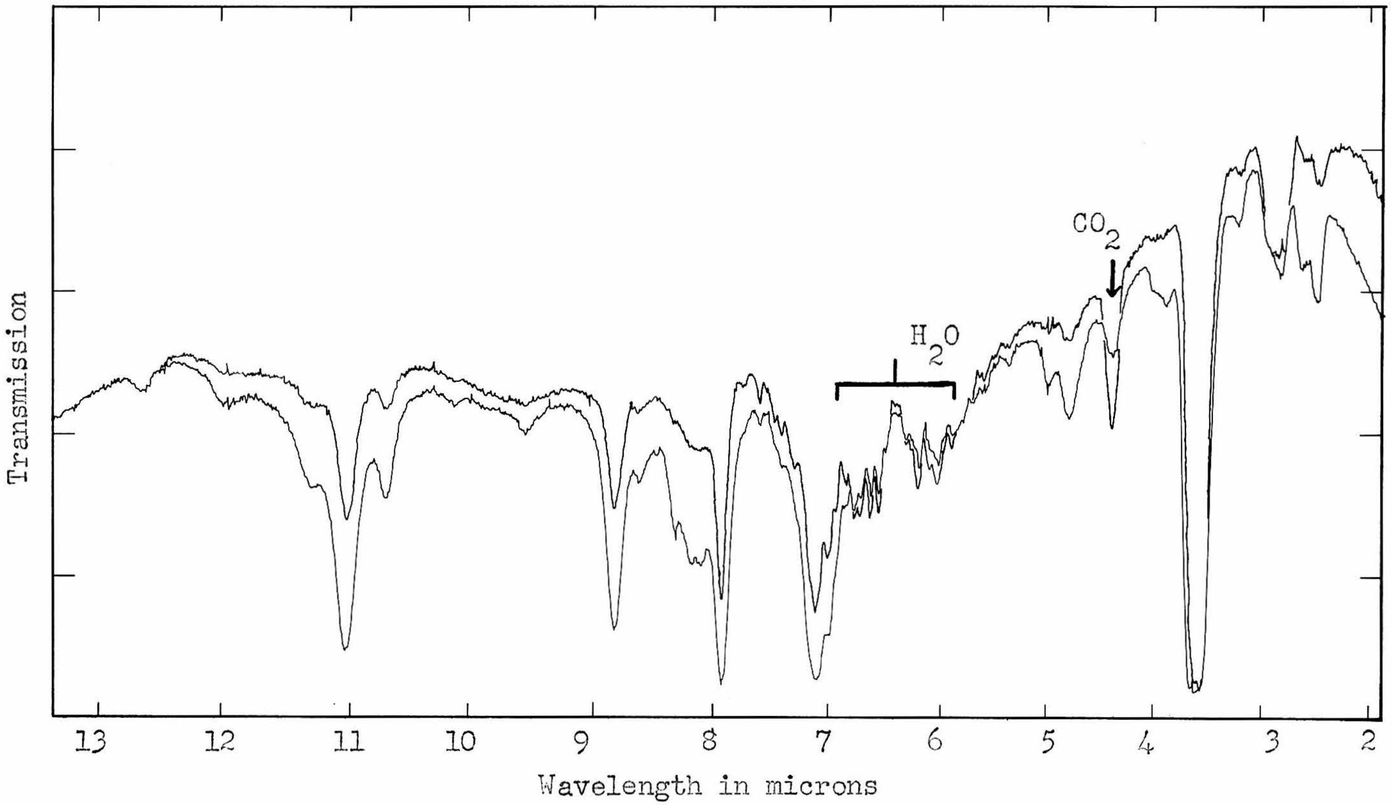


Fig. 1.- Infrared absorption of spiro(3,3)-heptane. Upper curve, .03 mm. layer; lower curve, .1 mm. layer.

The monobromide, by use of a catalytic hydrogenation method described by Prelog and Seiwerth (36) to reduce 1,3-dibromoadamantane to the hydrocarbon, took up 90% of the theoretical amount of hydrogen and gave rise to a 57% yield of the spirane hydrocarbon. The infra-red absorption of .03 and .1 mm. layers of the material in similar cells are shown in Figure 1.

Experimental Procedures.*

1,1-Dicarbethoxycyclobutane:

I. (37) Sodium (176 g., 7.6 moles) was dissolved in 3 l. of absolute ethanol in a five-liter, three-necked flask fitted with a "trubore," half-moon stirrer and two reflux condensers topped by calcium chloride drying tubes. Eli Lilly and Co. diethyl malonate (607 g., 3.8 moles) was poured in and the mixture stirred for a few minutes. To the warm (50-60°) solution was added through a dropping funnel which had been put in place of one of the condensers, 768 g. (3.8 moles) of Eastman Kodak Co. white label trimethylene bromide, over about a ten minute period. The reaction mixture warmed to about 75°. The flask was heated on the steam bath about two hours, with stirring. Sodium bromide precipitated after about two to three minutes. The condenser is replaced with a takeoff head and ethanol was stripped off at about 100 mm. pressure. When ethanol had practically ceased to come off, heating was discontinued and the mixture was cooled. The insoluble organic layer was washed once with water in a separatory funnel, and the water washed once

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*Analyses by Dr. A. Elek, Los Angeles. Unless otherwise noted, melting points are uncorrected.

with ether. The organic layers were combined and dried with calcium chloride. The ether was stripped off and the product was distilled. Some dibromide was recovered (ca. 20 g.), some diethyl malonate (ca. 40 g.), and the desired product was collected at 64-70° at 1.5 mm. The yield was 34-8%, ca. 250-70 g., n_D^{25} 1.432. If the recovered ethanol, malonate and dibromide are used in a subsequent run the yield can be raised about 5%.

II. Sodium (4.6 g., 0.2 mole) was dissolved in 100 ml. of absolute ethanol, then, while the solution was refluxed, 16 g. (0.1 mole) of diethyl malonate and 38.4 g. (0.1 mole) of trimethylene tosylate (38), m.p. 92-3°,mixed with 100 ml. of absolute ethanol, were added through the condenser. After addition, refluxing was continued for four hours. The contents of the flask were cooled to 10° and filtered. The sodium tosylate, after washing once with cold ethanol, weighed 37.5 g., calculated 38.8 g.; this salt was completely soluble in cold water, i.e., no unreacted tosylate. From the filtrate, ethanol was removed through a 12" Vigreux column at atmospheric pressure. The residue was transferred to a Claisen flask and distilled through 2" of glass helices. There was obtained 7.8 g. of diethyl malonate, and 5 g. (25%) of product, b.p. 67-8°/2 mm., n_D^{25} 1.431.

III. (39). Sodium (23 g., 1.0 mole) was dissolved in 250 ml. of absolute ethanol, 160 g. (1.0 mole) of diethyl malonate was next added and then finally 157.5 g. (1.0 mole) of trimethylene chlorobromide, b.p. 140-2°/760 mm., was added over a period of ten minutes at 15-20° with cooling. The flask was slowly heated to 70° over a period of two hours and maintained at 70° for two additional hours. A solution of 23 g. (1.0 mole)of sodium in 325 ml. of absolute ethanol was then added, using suction, through the dropping funnel. The flask-contents were heated to reflux and maintained at this temperature for four hours. The mixture was worked up as in I; yield 94 g. (47%), n_D^{25}1.4325.

1,1-Dimethylolcyclobutane (cf. 40):

1,1-Dicarbethoxycyclobutane,(100 g., 0.5 mole), b.p. 67-8°/1.5 mm., n_D^{25} 1.4320, was dissolved in 100 ml. of dry ether (dried over sodium), and dropped into a solution of 22.8 g. (0.6 mole) of lithium aluminum hydride (Metal Hydrides Corp.) powder in dry ether (600 ml.), in a two-liter, three-necked flask equipped with a "tru-bore" half-moon stirrer and a reflux condenser topped with a calcium chloride tube and a dropping funnel. Addition was at such a rate that a slow reflux of ether was maintained even with good stirring and external ice-water cooling. About one hour sufficed for the addition. The reaction was very vigorous, especially initially. After the addition was completed the reaction mixture was allowed to warm to room temperature and was stirred for about forty-five minutes. Then water (about 20 ml.) was added cautiously through the dropping funnel, with external cooling. Then enough 25% sulfuric acid was added to make the solution acid to congo red paper, again with cooling. There was a voluminous precipitate of lithium and aluminum basic sulfates. About 50 g. of sodium chloride was added and the mixture stirred to dissolve as much as possible. The ether was then siphoned off, 500 ml. more added and this procedure was repeated twice, giving a total volume of about two liters of ether. The ether solution was stripped of solvent on the steam bath and the viscous residue was put into a Claisen flask and distilled. Water was taken off up to 50°/1 mm.; then some traces of unchanged ester came off at about 60°/1 mm.; and product was taken off at 80°-2°/1 mm. The yield was 81.9%, n_D^{25} 1.4781, m.p. 32.5-33.5° (corr.), after recrystallization from isopropyl ether at 0°.

Anal. Calcd. for $C_6H_{16}O_2$: C, 62.02; H, 10.43. Found: C, 61.91; H, 10.48.

An alternative procedure for working up the lithium aluminum hydride reduction product was to bring the salt solution after the initial addition of water to pH 4 with hydrochloric acid and then to evaporate to dryness with a stream of air on the steam bath. The resultant moist salts were extracted with boiling ethanol two or three times. The combined extracts were then distilled as above. The yield was approximately the same.

<u>Ditosylate of 1,1-Dimethylolcyclobutane:</u>

1,1-Dimethylolcyclobutane (116 g., 0.1 mole) was dissolved in 70 ml. of Merck reagent pyridine and the solution was cooled to 0° in a large-mouthed Erlenmeyer flask. Recrystallized p-toluenesulfonyl chloride (45.5 g., 0.22 mole), (Eastman Kodak Co. white label, recrystallized from ligroin, discarding insoluble material) was added portionwise over about one-half hour with stirring. Pyridine hydrochloride precipitated after about five to ten minutes. The mixture was allowed to stir and warm to room temperature overnight. Ten milliliters of water was added to destroy any excess sulfonyl chloride and the mixture was allowed to stir for one-half hour. Finally it was poured into 500 ml. of cold water; after a few minutes the product crystallized out. It was filtered off and dried, yield 39 g. (94%), m.p. 82-92°. This material was recrystallized from 70-95% ethanol giving an 85% recovery of pure ditosylate, m.p. 92-3°.

Anal. Calcd. for $C_{20}H_{24}O_6S_2$: C, 56.60 ; H, 5.66 . Found: C, 56.75; H, 5.76.

1,1-Dibromomethylcyclobutane:

I. 1,1-Dimethylolcyclobutane was mixed at 0°, according to Whitmore (32), with phosphorus tribromide. At this temperature no reaction occurred. On heating to 10-15° an explosive reaction took place and insoluble tar was produced. An attempt was made to carry out this reaction at 60°, and again only insoluble tars were found.

II. 1,1-Dimethylolcyclobutane (11.6 g., 0.1 mole), 41.6 g. (0.2 mole) of thionyl bromide and 100 ml. of pyridine were mixed and the resultant product allowed to stand overnight at room temperature. After removal of the remaining thionyl bromide at 50°, only a dark brown, totally insoluble polymeric tar was left.

III. Sodium bromide (10 g., 0.08 mole) was suspended in redistilled Eastman Kodak Co. white label diethylene glycol and the suspension heated to 135-140°. Ditosylate of 1,1-dimethylolcyclobutane (16.9 g. 0.04 mole) was added portionwise. The mixture turned black after about ten minutes; heating was continued for three to four hours. The product was poured into water and extracted with carbon tetrachloride. The extract, after removal of solvent was distilled in vacuo yielding a fraction, b.p. ca. 40°/75 mm.,

d_4^{25} 1.20, n_D^{25} 1.44. Obviously this material is too low-boiling and too low in molecular refraction to be the desired dibromide; it may be a rearranged product of dehydrobromination. (See below, IV).

When this reaction was tried at lower temperatures, unchanged tosylate was recovered. It was also tried in diethyl carbitol (decomposition of the solvent occurred using diethylene glycol) but without success.

IV. An approximately 60% hydrobromic acid solution, obtained by saturating 100 ml. of water at -5° with gaseous hydrogen bromide, was placed in a relatively thin-walled pyrex ampule. There was added 11.6 g. (0.1 mole) of glycol and, after sealing, the ampule was allowed to rise slowly to room temperature. After about one hour a second phase had developed, which reached its maximum volume in about twenty-four hours. At the end of this time, this oily top-layer was brown in color; after forty-eight hours it was blue-black. The ampule was cooled and opened and the contents extracted with carbon tetrachloride. The extract was washed with bicarbonate solution and with water and the still deeply colored solution was dried with magnesium sulfate. The solution apparently loses hydrogen bromide spontaneously; it was distilled taking off solvent at atmopheric pressure. The material collected at 83-6° at 10 mm. weighed 10 g. (41%); a second fraction which later solidified, b.p. 95-105°/1 mm., was also obtained. The above 10 g. fraction lost hydrogen bromide spontaneously on standing and was partially converted to a dark tar. On redistillation after two months an apparently homogeneous monobromide, 3.35 g., b.p. 39-41°/1 mm., was obtained. Based on the slow reaction of this material with trimethylamine, and an analysis of a picrate, m.p. 132-3°, formed from the product of this reaction, (Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.8; H, 5.46. Found: C, 49.0; H, 5.38) it was assumed to be a vinyl bromide formed by rearrangement, possibly to 1-bromo-1-bromomethylcyclopentane, with subsequent loss of hydrogen bromide.

Spiro-(3.3)-heptane-2,2-dicarboxylic Acid Ester:

After dissolving 68 g. (3.0 moles) of sodium in two liters of iso-amyl alcohol (redistilled Eastman Kodak Co. practical grade) in a five-liter, three-necked-flask fitted with a "tru-bore" half-moon stirrer and a total-reflux, variable-takeoff condenser, 232 g. (1.45 moles) of Eli Lilly and Co. diethyl malonate was added. The flask and contents were heated, taking off ethanol for about two hours at a slow rate, until the temperature at the head reached 130°; the total amount taken off was about 300 ml. Next there was added 526 g. (1.25 moles) of ditosylate of 1,1-dimethylolcyclobutane through a third neck while the malonate solution was maintained at about 100°. The mixture was refluxed with stirring for forty-two hours, then cooled and filtered to separate the sodium tosylate precipitate. The filtrate was stripped of iso-amyl alcohol on the steam bath at 20 mm. down to a total volume of about 400-500 ml. and the residue was cooled and washed with water. The wash water was extracted once with ether and the extract added to the organic phase and the ether solution was dried with magnesium sulfate. On distillation, alcohol, etc. came off up to 110°/15 mm., then about 70 g. of recovered malonate, etc. up to 110°/1 mm. A good middle cut of di-isoamyl spiro-(3,3)-heptane-2,2-dicarboxylate was taken at 123-5°/1 mm., 153 g. (37.6%), n_D^{25} 1.4770, d_4^{25} 0.980.

Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.31; H, 9.95. Found: C, 70.04; H, 10.30.

This presumably pure material turned out, upon saponification, to be contaminated with some ester or lactone of undetermined constitution. However, yields reported of the diacid and of the monoacid are based upon assumption of 100% purity for this material.

Spiro-(3,3)-heptane-2,2-dicarboxylic Acid:

Potassium hydroxide (56.0 g., 1.0 mole) was dissolved in 500 ml. of absolute ethanol. The solution was placed in a beaker, cooled to about 50-60° and 81 g (0.25 mole) of the di-isoamyl ester was poured in with stirring. About thirty seconds after the addition was completed the mixture set to a semi-solid mass, which was then heated in the steambath for forty-five minutes. The reaction mixture was cooled, filtered and the di-potassium salt was washed once with about 500 ml. of absolute ethanol to remove any residual potassium hydroxide and also isoamyl alcohol. The salt was then dissolved in a minimum amount of water, and hydrochloric acid, diluted with enough water to dissolve all of the potassium chloride formed, was added with cooling. The solid diacid precipitated and was recrystallized from hot water. The yield, after recrystallization, was 26.5 g. (57.6%), m.p. 200-2° (dec.). The diacid crystallized from hot water in pure white ziggurat-shaped crystal agglomerations, pyramids of square blocks of decreasing size with a square hole in the center of each, except for the top block, which is solid.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.49. Found: C, 58.69; H, 6.58.

The p-bromophenacyl ester of this diacid was made by the reaction of the sodium salt and p-bromophenacyl bromide in dilute ethanol. It was recrystallized from 70% ethanol, m.p. 140.5-141° (corr.).

Anal. Calcd. for $C_{25}H_{22}O_6Br_2$: C, 52.10; H, 3.83. Found: C, 52.17; H, 3.96.

An oily layer was noticed upon acidification of the solid potassium salts. This was originally assumed to be the monoacid, resulting from partial decarboxylation, but subsequent study of its reactions and physical properties proved it not to be, although it has approximately the same boiling point and is acidic. Its constitution has not been determined.

<u>Spiro-(3.3)-heptane-2-carboxylic Acid</u>:

A 20.5 g. (0.11 mole) portion of the above dicarboxylic acid was heated at 205° for fifteen minutes, until carbon dioxide evolution had ceased. The product was distilled at reduced pressure through a one-inch helix-packed column; there was collected 14.4 g. (95% yield) of monocarboxylic acid, m.p. 22.75-23° (corr.), b.p. 79.5-80.0°/1 mm., n_D^{25} 1.4657, d_4^{25} 1.042, M.R.^{25} calculated: 37.25; found: 37.22.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.52; H, 8.64. Found: C, 68.50; H, 8.65.

The anilide of this acid was made by heating the acid with aniline at 170° for two hours, m.p. 125-6°.

Anal. Calcd. for $C_{14}H_{17}ON$: C, 78.1; H, 7.91. Found: C, 78.05; H, 7.86.

2-Bromospiro-(3,3)-heptane: (cf. 41)

Potassium hydroxide (6 g., 0.11 mole) in 30 ml. of water was added to 13.25 g. (0.098 mole) of spiro-(3,3)-heptane-2-carboxylic acid until a pH of 7 was reached. The resulting solution of potassium salt, diluted to 75 ml., was added slowly to a vigorously stirred solution of 17 g. (0.1 mole) of reagent grade silver nitrate in 200 ml. of water. The white precipitate was centrifuged off, washed once each with water, methanol, acetone, and ether and dried overnight at 25° at the vacuum of a Cenco Hyvac pump. Before using the silver salt, it was ground, put in the vessel in which it was to be used, and dried in vacuo to constant weight. The yield was 24 g. (ca. 100%).

Merck reagent bromide, (16 g., 0.1 mole), which had been washed with concentrated sulfuric acid and filtered through a filter bed of phosphorus pentoxide, was dissolved in 150 ml. of dry carbon tetrachloride (dried by distillation and standing over "drierite") in a 300 ml., three-necked, standard-tapered flask, equipped with "trubore" half-moon stirrer, and bulb-type reflux condenser. Before turning on the water in the condenser, the solution was heated until some of it boiled out of the top of the condenser, thus eliminating the last traces of water from the apparatus. The condenser was fitted with a calcium chloride tube and a bubble-counter, and the cooling-water was turned on. The 50 ml. round-bottomed flask containing the silver salt was now connected by means of a flexible rubber tube to the third neck of the flask and the flask cooled to -20 to -25°. The silver salt was slowly introduced into the reaction vessel over a period of six hours. Carbon dioxide evolution was slow, especially at first. When about 90% of the silver salt had been added, the bromine color had been nearly discharged, so five grams extra of bromine was added. At the end of addition the flask was allowed to warm to 25° overnight. Some bromine color persisted. The silver bromide was filtered off and washed once with carbon tetrachloride. The filtrate was washed with 10% aqueous sodium bisulfite and with 10% aqueous sodium bicarbonate solution, and dried with magnesium sulfate. Carbon tetrachloride was removed by distillation through a six-inch helix-packed column and the residue was distilled from a Claisen flask with a one-inch helix column. There was obtained 7.5 g. (43%) of monobromide, b.p. 59.5-60.5°/14 mm., m.p. (macro), -38 to -36°, n_D^{25} 1.4935, d_4^{25} 1.334.

Anal. Calcd. for $C_7H_{11}Br$: C, 48.00; H, 6.34. Found: C, 48.4; H, 6.53.

Spiro-(3,3)-heptane: (cf. 36).

The solution prepared by dissolving 1.9 g. (0.08 mole) of clean sodium in 25 ml. of special reagent grade methanol (distilled from magnesium) in a 125 ml. centrifuge tube was cooled to 0°, and there was added 7 g. (0.04 mole) of spiroheptyl bromide and three grams of freshly prepared Raney nickel (Adkin's W-6) in three to four ml. of methanol. The tube was connected to an atmospheric pressure hydrogenation apparatus and put in a shaker. Before shaking, the air space above the reaction mixture was evacuated and filled with hydrogen. It was found that the reaction vessel became noticeably warm upon shaking, so occasionally during the first part of the reaction the shaker was stopped and the vessel cooled with ice-water. The reaction temperature never exceeded 40°. In the first forty minutes 480 ml. of hydrogen were taken up (roughly 50% of theory) and a total of 840 ml. (90.5%) in three hours and twenty minutes, by which time the uptake had practically ceased.

The catalyst was centrifuged off and washed with methanol. The combined methanol solutions were distilled and a binary mixture of methanol and the hydrocarbon, boiling at 56.5-8°, collected. The binary separated into two phases and the bottom oily layer was removed with a pipette. Upon addition to the other phase of twice its volume of water, an oily phase came to the top and was separated. The water phase was extracted with alcohol-free ether and the combined oily phases were dried with calcium chloride. The ether was taken off up to 45° and nothing else came over up to 91.75°. Ninety per-cent of the distillate boiled in the range 93.5-93.75°/750 mm. and there was no higher boiling fraction. The yield was 2.12 grams, 57.3% of theory; n_D^{25} 1.4331, d_4^{25} 0.816; M.R.^{25} calculated: 31.10; Found: 30.61. (Compare these constants with those found for Fujimoto's spiro-(3,3)-heptane, n_D^{25} 1.4323, d_4^{25} 0.797, M.R.^{25} found: 31.30.)

The infra-red spectra of this compound and that of Fujimoto were measured and compared. They were found to be so similar that, to avoid repetition, only the curve obtained with the sample described here is illustrated. (Figure 1.)

Summary:

1. Spiro-(3,3)-heptane has been made and a few of its physical properties determined. The synthesis was accomplished via 1,1-dicarbethoxycyclobutane, 1,1-dimethylolcyclobutane, and the new compounds spiro-(3,3)-heptane-2,2-dicarboxylic acid, the corresponding monocarboxylic acid and 2-bromospiro-(3,3)-heptane.

2. Cyclobutane rings have been made by the reaction of trimethylene glycol tosylates and sodiomalonic esters.

3. A general method and an experimental technique for making polyspirocyclobutanes are described.

Literature cited:

1. Meiser, *Ber.*, *32*, 2055 (1889).
2. Hückel, et al., *Ann.*, *474*, 121 (1929).
3. Zelinsky and Elagina, *Compt. rend. Acad. Sci. U.R.S.S.*, *49*, 568 (1945).
4. Clemo and Ormston, *J. Chem. Soc.*, *1932*, 1778.
5. Fecht, *Ber.*, *40*, 3883 (1907).
6. Backer and Shurink, *Rec. trav. chim.*, *50*, 926 (1931).
7. Janson and Pope, *Chem. and Ind.*, *51*, 316 (1932); *Proc. Roy. Soc.*, *A154*, 53 (1936)
8. Ingold, Lanfear, and Thorpe, *J. Chem. Soc.*, *123*, 3140 (1923).
9. Backer and Thorpe, *J. Chem. Soc.*, *117*, 1579 (1920).
10. Beesley, Ingold and Thorpe, *J. Chem. Soc.*, *107*, 1080 (1915).
11. Birch, Gough and Kon, *J. Chem. Soc.*, *119*, 1315 (1921).
12. Baker and Ingold, *J. Chem. Soc.*, *123*, 122 (1923)
13. Murray and Stevenson, *J. Am. Chem. Soc.*, *66*, 314 (1944).
14. Murray and Stevenson, *J. Am. Chem. Soc.*, *66*, 812 (1944)
15. Shortridge, et al., *J. Am. Chem. Soc.*, *70*, 946 (1948).
16. Chatterjee, *J. Ind. Chem. Soc.*, *14*, 259 (1938).
17. Zelinsky and Shuikin, *Ber.*, *62*, 2180 (1929).
18. Clemo and Ormston, *J. Chem. Soc.*, *1933*, 352.
19. Marvel and Brooks, *J. Am. Chem. Soc.*, *63*, 2630 (1941).
20. Morris, *J. Chem. Soc.*, *1926*, 245.
21. Slabey, *J. Am. Chem. Soc.*, *68*, 1335 (1946).
22. Zelinsky (and Krawetz), *Ber.*, *46*, 160 (1913).
23. Donohue, Humphrey and Schomaker, *J. Am. Chem. Soc.*, *67*, 332 (1945).
24. Qudrat-i-Khuda, *J. Ind. Chem. Soc.*, *16*, 525 (1939).

25. Godchot and Cauquil, *Compt. rend.*, **186**, 767 (1928).

26. "*Elsevier's Encyclopedia of Organic Chemistry*," Elsevier Publishing Co., New York, N.Y., Volume 12A, 1948, page 1085 ff.

27. Mannich, *Ber.*, **74**, 1007 (1941).

28. Ruzicka and Goldberg, *Helv. Chim. Acta*, **18**, 668 (1935).

29. Buchman, et al., to be published.

30. Cason and Way, *J. Org. Chem.*, **14**, 31 (1949).

31. Zelinsky and Kazansky, *Ber.*, **60**, 711 (1927).

32. Whitmore, et al., *J. Am. Chem. Soc.*, **63**, 124 (1941).

33. Dojarenko, *J. Russ. Phys.-chem. Soc.*, **58**, 27 (1926).

34. Tatevosyan, et al., *Bull. Armen. Acad. Sci., U.S.S.R.*, 5/6, 23, (1944).

35. Braber, Pribyl and Lott, *J. Am. Chem. Soc.*, **69**, 866 (1947).

36. Prelog and Seiwerth, *Ber.*, **74**, 1769 (1941).

37. Perkin, *Ber.*, **16**, 208 (1883).

38. Gough and King, *J. Chem. Soc.*, **1928**, 2426.

39. Kishner, *J. Russ. Phys.-chem. Soc.*, **37**, 507 (1905).

40. Nystrom and Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947).

41. Allen and Wilson, "*Organic Syntheses*," John Wiley and Sons, Inc., New York, N.Y., Volume 26, 1946, page 52.

PART II

THE HUNSDIECKER DEGRADATION OF CARBOXYLIC ACIDS

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The designation "Hunsdiecker degradation" has been given to the reaction

$$RCOO\text{-}Ag + X_2 \longrightarrow RX + AgX + CO_2$$

where X represents halogen, usually bromine; the metal usually used is silver. The reaction is more general than is sometimes recognized; its usefulness is still being extended. It should be noted that the above equation may be only a special case of the more general equation

$$RCOO\text{-}Ag + XY \longrightarrow RY + AgX + CO_2.$$

The metal may be any of several of the alkali metals, silver, mercury or thallium (I). In the cases studied to date, X has been a halogen ion carrying a positive charge, and Y a negative ion or radical. Examples in addition to the halogens, are ICl (1) and ClCN (2). Research is also in progress in this laboratory on the cases in which XY is NOCl and NO_2Cl.

Variation in the R-group presents possibilities that have not yet been investigated widely. The researches of Hunsdiecker, Hunsdiecker and Vogt that led to their basic patent (3) in 1937 and the full report that followed in 1942 (4) constitute the only general studies yet made. In these they described the reaction of several types of substituted silver alkylcarboxylates with bromine and chlorine. It has been the purpose of this research to extend our understanding of the reaction and to find in what ways it can be appropriately used for the synthesis of various types of alkyl bromides.

Following the report of Peligot in 1836 (5) that silver benzoate, when treated with bromine, gives rise to meta-bromobenzoic acid, the early investigators expected that silver alkylcarboxylates would produce α-bromoacids on similar treatment. Therefore, when such a famous investigator as Kekulé (6), in 1861, was unsuccessful in brominating succinic acid by this technique, not much attention was given to Borodine's (7) report in the same year that propyl bromide was obtained from silver butyrate and methyl bromide from silver acetate. The following year Schutzenberger reported that iodine monochloride with silver acetate gave silver iodide and methyl chloride, but the significance of the observation was not grasped at that time.

It remained for Simonini (8), in the 1890's, to develop the first workable technique for carrying out the reaction that is commonly referred to by his name. He discovered that in a considerable number of cases iodine would react with silver alkylcarboxylates to form quite stable complexes, which in turn could be relatively easily decomposed, by heating to 100°, to give the alkyl alkylcarboxylate, by a loss of one molecule of carbon dioxide from two molecules of silver salt.

$$2RCOOAg + I_2 \longrightarrow RCOOR + 2AgI + CO_2$$

The ester could be transformed by standard methods to yield some of the starting acid, RCOOH, and the alcohol, ROH, which in turn could be converted to the alkyl halide. This method provided a fair conversion from a given acid to a product containing one less carbon atom.

Birnbaum and Gaier (9) had attempted somewhat earlier to carry out this type of degradation, but their interest was in dibasic acids and since their technique involved rather extreme conditions, they isolated a miscellany of dehydration, decarboxylation and substitution products. Further studies of Birnbaum (10) carried out at the time of Simonini's work, dealt with aromatic acids, which, under the conditions used, underwent for the most part substitution in the aromatic ring.

The Simonini reaction has been the subject of a considerable amount of research and speculation (11). The initial product of the reaction between a silver salt and iodine at 80° or below is an ether-soluble complex containing silver, iodine and acyloxy radicals in varying proportions. In the simple case of lower members of the aliphatic series the predominant species is $(RCOO)_2AgI$. There are other varieties of this type of intermediate present also, the amounts of which vary with the character of R and the temperature (12, (13). If excess iodine be present, a silver-free complex is formed, which has been described as $(RCOO)_3I$. The species mentioned are isolable and are stable under anhydrous conditions for a considerable period of time. They react with water, regenerating the original acid. With excess of iodine at 80-120°, carbon dioxide is lost and the principal product is the alkyl iodide, although some ester is always produced. On the other hand, the silver containing complex is soluble in inert organic solvents and is relatively stable in solution up to about 80°. Above this temperature decomposition gives rise to 50-70% of the ester, RCOOR, and usually to some of the starting acid. Dibasic acids under these same conditions (14) can give rise to lactones as a principal product, with anhydride formation in some cases where steric factors lessen the likelihood of lactonization.

It is interesting to note in this connection that in lactone formation from dibasic acids with substitution on only one α-carbon, the carboxyl group is lost preferentially from the secondary carbon atom. Windaus and Klanhardt (14) report that α-ethylglutaric acid gives only γ-caprolactone, and not α-ethyl-γ-butyrolactone.

The decomposition of the intermediate complex is evidently almost completely a displacement reaction in the ordinary case. Wieland and Fisher (12) decomposed the silver-iodide-containing complexes of types such as triphenylacetic acid, reasoning that the intermediate triphenylmethyl radical, or triphenylacetoxy radical, if such were produced, would either be visible or give rise to characteristic reaction products. They could find no sign of free-radical intermediates, triphenylmethyl triphenylacetate being produced in good yield. Similarly, Oldham and Ubbelohde (13) conducted a search for free-radical dimerization products - i.e., R-R and

$(RCOO)_2$, but were able to isolate neither. Even though R• radicals would probably have too short a life to meet another R• and form the doubled hydrocarbon, it was demonstrated that the RCOO• radicals under consideration were stable enough so that diacyl peroxides should have been detectable if the reaction proceeded according to a free-radical mechanism.

A large number of complex iodine-containing molecules, of structure related to the Simonini complexes, were investigated by Birckenbach and coworkers (15), (16). They found that the reaction $AgY + I_2 \longrightarrow AgI + IY$ (or IY_3) was quite a general one, and that compounds could be formed not only where Y = RCOO, but also when Y = CNO, CN, IO_3, NO_2, etc., giving a variety of interesting reagents. Birckenbach's group and Prevost (17), (18), with his coworkers, almost simultaneously, found that these iodine complexes, in which iodine acts as a positive ion, would add to olefinic double bonds very rapidly even at -80°. Birckenbach investigated the addition to cyclohexene of the non-organic type preponderantly and his work will not be discussed further here. Prevost's researches were devoted to those complexes containing acyloxy groups. He found that in the presence of a minimum amount of the silver iodide complex the addition to ethylenic bonds gave predominantly the iodohydrin ester adduct, but with an excess of the complex the iodine was displaced giving a glycol diester. This proved to be a good method for the synthesis of otherwise difficultly accessible glycols and their derivatives, such as 1,2-dihydroxybutene-3.

The discovery that iodine in these complexes acted like a positive ion - that it would, for example, react with silver methylacetylide to give the iodine-substitution product, 1-iodopropyne - led Prevost to investigate the properties of the corresponding derivatives containing the other halogens to see if they, too, contained positive halogen. He found that they behaved in a very similar way, but that they contained no silver. He formulated them as RCOOBr and RCOOCl, a view which is generally accepted today. They, too, add to olefins and react with alkynes as do the iodine complexes, but they are much more reactive and unstable, and decompose readily, even at fairly low temperatures.

Bockemüller and Hoffmann (19) investigated the kinetics of the decomposition of the compounds formed by the reaction between silver alkylcarboxylates and bromine or chlorine. Their major thesis was that organic hypohalogenites play an important part in many reactions. The addition of chlorine to allyl chloride in acetic acid, for example, gives 1,2-dichloro-3-acetoxypropane, according to them, through an acyl hypochlorite intermediate. They stated that these acyl hypohalogenites are more reactive than the free halogens; a statement born out by the reaction of RCOOBr with chloroform to give trichlorobromomethane, and by the reaction, noted in this research, of cyclobutyryl hypobromite with the cyclobutane ring to give open-chain compounds although under similar conditions free bromine will not cleave the ring.

Bockemüller and his coworker carried out studies of considerable theoretical interest for the elucidation of the mechanism of the decomposition of the intermediate hypohalogenites. They discovered that the decomposition was of second or somewhat higher order with respect to the concentration of the intermediate (filtered free of silver bromide), and that it was exceedingly sensitive to heat and light. They found also that the hypobromite could be decomposed to give yields of the alkyl bromide as high as 80%. A major side-reaction is the case of compounds that can be easily substituted with bromine is the reaction of the by-product hydrogen bromide with either the silver salt or the intermediate, removing it from the reaction sphere. He noted the decomposition of CH_3COOBr at 0°, giving rise to a 69% yield of methyl bromide. Silver adipate was reacted to give tetramethylene bromide, and silver benzoate gave 80% of the theoretical yield of bromobenzene.

The definitive work on the synthetic uses of this reaction was carried out by Hunsdiecker, Hunsdiecker and Vogt simultaneously with the work of Bockemüller and Hoffmann. In a series of patents (3), (20), (21), (22), and in an article in 1942 (4), the Hunsdiecker group illustrate the application of the reaction to a variety of compounds, with good yields reported in almost all of the cases. A few representative types, with the products that were formed, are listed below:

$$RCOOAg + Br_2 \longrightarrow RBr$$

$$RCHNH_2COOAg \longrightarrow (RCHNH_2Br) \longrightarrow RCHO$$

$$RCHNH_2CH_2COOAg \longrightarrow RCHNH_2CH_2Br$$

$$\mathrm{RCHOHCOOAg} \longrightarrow (\mathrm{RCHOHBr}) \longrightarrow \mathrm{RCHO}$$

$$\mathrm{RCOCOOAg} \longrightarrow \mathrm{RCOBr}$$

$$\mathrm{ROOC(CH_2)_nCOOAg} \longrightarrow \mathrm{ROOC(CH_2)_nBr}, \text{ where } n > 3$$

$$\mathrm{RCHBrCOOAg} \longrightarrow \mathrm{RCHBr_2}$$

$$\mathrm{RCHClCHCl(CH_2)_6COOAg} \longrightarrow \mathrm{RCHClCHCl(CH_2)_6Br}$$

They describe the use of carbon disulfide and carbon tetrachloride as solvents, and the use of silver, mercury, thallous and potassium salts of the acids. The silver salts were found to be the best, decomposing at the lowest temperatures and giving the smallest yield of ester by-products. It is unfortunate that most of this material is reported only in patents; certain of the broader claims can only be accepted after experimental details have been presented in a publication in a recognized journal.

There has been a great deal of discussion of the mechanism of the Hunsdiecker degradation, and the controversy has not yet been resolved. There is an impressive array of evidence in favor of a scheme such as that recently proposed by Arcus, Campbell and Kenyon (23), (24).

$$\mathrm{RCOO{-}Br} + \mathrm{R{-}COO{-}Br} \longrightarrow \mathrm{RCOO^-} + \mathrm{BrR} + \mathrm{Br^+} + \mathrm{CO_2}$$

$$\mathrm{RCOO^-} + \mathrm{Br^+} \longrightarrow \mathrm{RCOOBr}$$

and, in the case of free bromine being present:

$$\mathrm{Br{-}Br} + \mathrm{R{-}COO{-}Br} \longrightarrow \mathrm{Br^-} + \mathrm{BrR} + \mathrm{CO_2} + \mathrm{Br^+}$$

$$\mathrm{Br^-} + \mathrm{Br^+} \longrightarrow \mathrm{Br_2}$$

$$\mathrm{Br^+} + \mathrm{R{-}COO{-}Br} \longrightarrow \mathrm{BrR} + \mathrm{CO_2} + \mathrm{Br^+}$$

One of the lines of evidence in favor of this is based on the results of the kinetics-study of Bockemüller (mentioned above), in which he found an order of reaction higher than first, and a very high sensitivity to light and heat - greater than that of a first order reaction. The second, and more conclusive, line is that of Arcus and his coworkers, who have reported inversion of configuration of optically active material in at least two cases. While other experimenters have reported only racemization in such cases (25), (26), no contradiction is entailed, since Kenyon's group found that bromine in carbon tetrachloride in the presence of silver bromide would cause racemization at a rapid rate. The lability of the carbon-carbon bond in the presence of these reagents has also been reported by Doering and Farber, (27), who found, attempting a Hunsdiecker degradation of bicyclo(2,2,2)octane-2-carboxylic acid, that their product was 2-bromobicyclo(1,2,3)octane. Authentic 2-bromobicyclo(2,2,2)-octane, under identical conditions, underwent the same rearrangement. If the Kenyon scheme is the correct one, it represents, according to the English authors, (23), the first case of an S_E2 mechanism that has been reported.

On the other hand, there is some evidence that is impossible to reconcile with a mechanism involving a Walden inversion. One case of a Hunsdiecker degradation involving carboxyl groups located on bridgehead carbons has been reported by reliable investigators. Prelog and Seiwerth (28), degraded 1,3-dicarboxyadamantane to the corresponding dibromide; in this case two bridgehead carbon atoms participated. The structure of the final product was well established.

Whether this reaction proceeded through an ionic or a free radical mechanism cannot be said at this time, but it is not unlikely to suppose that a Br$^+$ ion can be formed (they are included in Kenyon's scheme), and the bridgehead carbon, made highly negative by hyperconjugation, ought to eject the negative COO very readily. That the COO loss takes place at a highly substituted carbon atom more readily than at one not highly substituted is suggested by the work of Windaus and Klänhardt (14) (see above) and also by the finding of Cason and Way[29] that during the degradation of cyclobutanecarboxylic acid, loss of carbon occurs at -25°. In this work it was also found that an α-bromoacid loses carbon dioxide more easily than a β-bromoacid. However, negative substituents, on the α-carbon atom would increase the ease of decarboxylation by either mechanism, so a definite conclusion cannot be reached from this. Price (30) considers the degradation a free-radical reaction, but his scheme takes no account of the intermediate hypohalite, the existence of which is generally conceded by workers in the field. Furthermore, the work of Wieland and Fisher (12), and Oldham and Ubbelohde (13), on the iodine complexes cannot be ignored. The failure of these investigators to find any of the products of free-radical reaction, and the similar results of the workers experimenting with the bromine containing intermediates, indicates that, if other than a displacement reaction is involved, it is probably an ionic dissociation into Br$^+$ and RCOO$^-$, with subsequent loss of carbon dioxide.

It is quite possible to conceive of two mechanisms that can operate, the bimolecular displacement predominating in the simple ordinary case, and an ionic first-order reaction in the case of the highly substituted tertiary carbons of adamantane. Kinetic studies on trimethylacetic acid would be very interesting in this light.

However, as in the case of many reactions in the field of organic chemistry, the present interest in the Hunsdiecker degradation lies to a great extent in its use as a synthetic method. An idea of the scope of the reaction can be seen in the types of carboxylic acids that have been degraded to alkyl halides by the various workers, especially by Wieland and Fisher and by the Hunsdieckers.

Many examples of polyfunctional molecules, including such varied types as aminoacids, hydroxyacids, ketoacids, esteracids, dibasic acids, alicyclic acids, aromatic acids, and halogen-substituted acids have been reported as undergoing this degradation successfully. The indications are from the work that has been done to date, that almost any acid of even moderate stability towards halogen can be decarboxylated using the appropriate technique and conditions.

This reaction has been of special value in a few cases where the resultant product is difficult of access by conventional methods (31). Also, in this work it was found that cyclobutane acids can undergo this decarboxylation smoothly and with good yields, while ordinary methods fail to yield the same products with equal ease because of the susceptibility of the four-ring to cleavage or rearrangement. This degradation, using the refined techniques that are described here and elsewhere, (29), seem further to be fitted for use in the conversion of optically active acids, which are relatively easily resolved, to the corresponding active bromides, which can themselves be directly resolved only with difficulty. On the preparative side again, the easily available disubstituted malonic acids should, by means of this reaction, be readily convertible to dibromides, which, in turn, are easily transformed into the corresponding ketones in good yields; ketones which may not be as easily accessible by other means of approach. It is important that a technique suited to the particular case be used; otherwise misleading results may be obtained (26), (27).

The reaction may be varied also by the use of other than simple halogens, as suggested above. The use of ICl has been mentioned (1); cyanogen chloride has also been used (2) to give silver chloride and the corresponding cyanide. While this latter case may seem to have little practical value, it is certainly of considerable theoretical interest. The variety of pseudohalogens made by the group working with Birckenbach (15), (16), (see above), may prove to be desirable reagents leading to an interesting variety of substituted organic molecules. An approach to this field is only now being made.

Purpose of this research.

The original aim of this research was to find a practical means for the conversion of cyclobutanecarboxylic acids to the corresponding bromides, with the intention of converting these bromides, in turn, into the hydrocarbons. Previous to the start of the work described below, no good routes to cyclobutane and cyclobutene had been described. Willstätter's preparations, (32) (33), which were still generally in use, were lengthy and tedious and resulted in poor overall yields. Since the cyclobutane carboxylic acids are the most easily available of the four-ring derivatives, their degradation to the bromides, and subsequent reduction of these, seemed to provide a good route to the hydrocarbons, if suitable conditions could be worked out.

A rather extensive program of synthesis of spirane hydrocarbons containing cyclobutane rings is currently being undertaken by Dr. E. R. Buchman and his collaborators at this Institute (34), (see Part I of this thesis). Spiro(3,3)heptane-2-carboxylic acid, spiro(3,5)nonane-2-carboxylic acid and spiro(3,3)heptane-2,6-dicarboxylic acid, were synthesized by this group, and a general method for the transformation of these and other polyspiranecarboxylic acids to the corresponding hydrocarbons was needed.

The synthesis of other difficultly accessible cyclobutane derivatives may be facilitated by the Hunsdiecker degradation also. 1,1-Dibromocyclobutane should result from the degradation of 1,1-dicarboxycyclobutane, a readily made material, and this dibromide may serve as a source of cyclobutanone, through a hydrolysis such as is described below. Many projected schemes for the synthesis of cyclobutadiene involve the degradation of cyclobutanepolycarboxylic acids. Such degradations, previously unknown, become feasible if a satisfactory technique for the application of the Hunsdiecker degradation can be worked out.

The degradation of one α-bromoacid and of one 8,9-dichlorocarboxylic acid is described by Hunsdiecker, but no technique that is applicable in general to halogen-containing acids is described. It was of interest to see if the acids containing halogen in the α, β, α, and δ, positions could be successfully converted to the dihaloalkanes in reasonable yields. It was somewhat doubtful whether or not this could be done, since the silver salts of some of these acids are commonly described as unstable under the conditions of the reaction as described by Hunsdiecker.

In the older literature, certain degradations involving two carboxyl groups less than four carbon atoms apart has been described as unsuccessful, (11), but there appears little justification for accepting this result as final. The work of previous investigators with malonic, (9), succinic, (9), and glutaric, (12), (35), acids was carried out by the Simonini technique, in some cases under very adverse conditions. A re-investigation seemed desirable. Substituted malonic acids offer attractive routes to many different types of compounds, and thus have great synthetic interest. Succinic acids are of special interest too, since some of the common degradative methods that might be suggested as leading to ethylene bromides are not usable. (For example, ethylene diamine, formed by a Curtius degradation of succinic acid, cannot be transformed to ethylene bromide by the von Braun technique (36).) In the cyclobutane series no conversion of 1,2-dicarboxycyclobutane to 1,2-dibromocyclobutane was known. (Although nitrosyl chloride will convert ethylene diamine to ethylene chloride, similar reagents cause rearrangements in the four-ring series.)

Further, an extension of the degradation to polybasic acids seemed of interest, both for the synthesis of polybromides of unambiguous structure, and also to find a practical limit to the use of the reaction.

Results

The silver salts of the halogen-containing acids proved to be quite unstable, as had been expected. The silver salts of α-, β, and δ-bromoacids could be made successfully if the temperature during their precipitation, drying and storage was kept below 10°, but the silver salt of γ, δ-dibromovaleric acid proved to be unstable, even at 0°, and could not be used. The reaction of the more stable of the above salts with bromine in refluxing carbon tetrachloride proved to give mostly lactones and polyesters, but reduction of the reaction temperature to 0° gave reasonable yields of the desired dibromoalkanes.

The silver salts of ethylmalonic acid and succinic acid underwent the Hunsdiecker degradation with a fair degree of success, also. A side-reaction, the simultaneous bromination of the α-carbon atom of the malonic acid, gave, in addition, considerable quantities of the tribrominated product, (37), (38). Tricarboxybutane gave a low yield of tribromide; tetracarboxybutane gave no detectable amount of tetrabromide.

It was found that cyclobutanecarboxylic acids gave quite good yields of the corresponding bromides (both cis and trans 1,2-dicarboxycyclobutane gave trans-1,2-dibromide) if the reaction was carried out at low temperatures. High temperatures led to cleavage of the four-ring on the side away from the substituents, giving straight-chain products. Extension of the low-temperature reaction to the spirane-carboxylic acids gave bromides from which spiro(3,3)heptane and spiro(3,5)nonane were made.

Experimental Findings

α-Bromovaleric acid was converted to its silver salt by mixing solutions of silver nitrate and of the ammonium salt of the acid at 0°. The salt was dried at 0° and converted to 1,1-dibromobutane (39), in 54% yield by reaction with bromine in carbon tetrachloride at 0°. When the reaction was attempted in refluxing carbon tetrachloride, polyesters were the only product. The authenticity of the dibromide was established by converting it to butyraldehyde which was characterized by the 2,4-dinitrophenylhydrazone. Similarly, β-bromopropionic acid was transformed in 55% yield to ethylene bromide by reaction of the silver salt with bromine at 0°. At 25° silver β-bromopropionate spontaneously went over to β-propiolactone (identified as the thioureide (40) derivative) and silver bromide.

Allylacetic acid (41), was made in 44% overall yield by reacting allyl bromide with sodiomalonic ester and decarboxylating the resultant allylmalonic ester. Hydrogen bromide was added in the presence of peroxide to the allylacetic acid to give δ-bromovaleric acid (42), in 71% yield. The silver salt of this material was successfully made and dried at below 10°, but on standing at 25° it decomposed. Bromine was added to allylacetic acid to give γ, δ-dibromovaleric acid (43), in 59% yield. The silver salt of this material, even though handled with care and kept below 5°

at all times, spontaneously went over to silver bromide and a bromlactone. Evidently Hunsdiecker degradation of bromo-substituted acids cannot be carried out under these conditions on the γ- and possibly not on the δ-bromoacids.

In an effort to see if allylacetic acid, the silver salt of which was easily made and proved to be stable, could be transformed in one step to 1,2,4-tribromobutane, the bromine degradation was carried out with it. However, at the temperature used (75°) the only product of the reaction was bromolactone.

Ethylmalonic ester was converted to the disilver salt in practically quantitative yield. The silver salt was treated with bromine at 0° and 28% of the theoretical amount of 1,1-dibromopropane was isolated from the reaction products. In addition, 25% of 1,1,1-tribromopropane was found to be present, caused by bromination, presumably before decarboxylation, of the silver malonate. The products were identified by hydrolyzing off the bromine atoms; the first product gave propionaldehyde (identified as the 2,4-dinitrophenylhydrazone), the second gave propionic acid. It is thought that much better yield of dibromoalkane would be obtained from a disubstituted malonic acid.

Succinic acid disilver salt was converted to ethylene bromide in 37% yield at 0° and at 60°. At 135° only polyesters were formed. 1,2,4-Tricarboxybutane (45), at 75°, gave only small yields (approximately 4%) of the corresponding tribromide. Some bromolactones were also isolated. 1,2,3,4-Tetracarboxybutane, using the same technique, gave no isolable amount of 1,2,3,4-tetrabromobutane.

The 1,2,4-tricarboxybutane mentioned above was produced by a nitric acid oxidation of 1-vinylcyclohexene-3, donated for this research by the Koppers Co. This reaction proceeded very smoothly, giving yields (62%) comparable with those reported for a similar permanganate oxidation (48), (70%), with much greater ease of handling.

Trimethylene bromide and sodiomalonic ester were reacted and the product saponified and decarboxylated to give cyclobutanecarboxylic acid in 29% overall yield (cf. 49). The acid was converted to the silver salt in 98% yield, and this latter reacted with bromine at 10° to give 46% of the theoretical amount of cyclobutyl bromide. Originally it was intended to convert the halide to cyclobutane by catalytic hydrogenation in alkaline solution at atmospheric pressure, but the appearance of an article by Cason and Way (29) reporting a similar series of reactions leading from cyclobutane carboxylic acid to cyclobutane made unnecessary the carrying out of this last step.

Preliminary attempts to carry out the Hunsdiecker degradation on silver cyclobutanecarboxylate gave rise to products other than those expected (cf. 29). When a bromine solution was added to a suspension of the silver salt at 25° the principal product (62% of theory) turned out to be the ester, cyclobutyl cyclobutanecarboxylate, previously reported by Demjanow and Dojarenko (50), as the result of a Simonini degradation of the same acid. This ester was also prepared by the reaction of cyclobutyl bromide with silver cyclobutanecarboxylate and the two samples were shown to be identical.

When the degradation was attempted at 75°, cleavage of the four-ring took place and 1,2,4-tribromobutane (46), (47), was isolated as the major product, in 65% yield. This material was identified by comparison of its absorption in the infra-red with material made from 1,2,4-tricarboxybutane (see above) and with authentic material made by the method of Pariselle (47). In addition, the 1,2,4-tribromobutane was converted to allylacetic acid by carbonation of the Grignard reagent produced by its reaction with magnesium (cf. von Braun (51)); a crystalline derivative of the allylacetic acid was compared with authentic material.

The silver salts of the cis and trans cyclobutane-1,2-dicarboxylic acids (prepared according to the method of Fuson and Kao (52), (cf. 53)), were submitted to treatment with bromine in carbon tetrachloride at reflux temperature, and in each case the same dibromide was isolated, in almost identical yield (40.6% from the cis acid; 39.4% from the trans acid). The dibromide was shown to have the trans configuration by comparison with authentic trans dibromide obtained from the bromination of cyclobutene. The dibromide obtained via the Hunsdiecker reaction also contained a small amount of 1,4-dibromobutene-2. In order to purify the product, the crude dibromide was dehalogenated with zinc in ethanol and the fractionated hydrocarbon rebrominated (recovery 66%). In an attempt to reduce the 1,2-dibromocyclobutane to cyclobutane, a reduction in alkaline solution using Raney nickel catalyst and hydrogen at atmospheric pressure was carried out. However, only 50% of the theory of hydrogen was absorbed, and the volatile product contained both cyclobutane and cyclobutene.

The Hunsdiecker degradation of spiro(3,3)heptane-2-carboxylic acid which gave 2-bromospiro(3,3)heptane in 46% yield is reported in Part One of this Thesis.

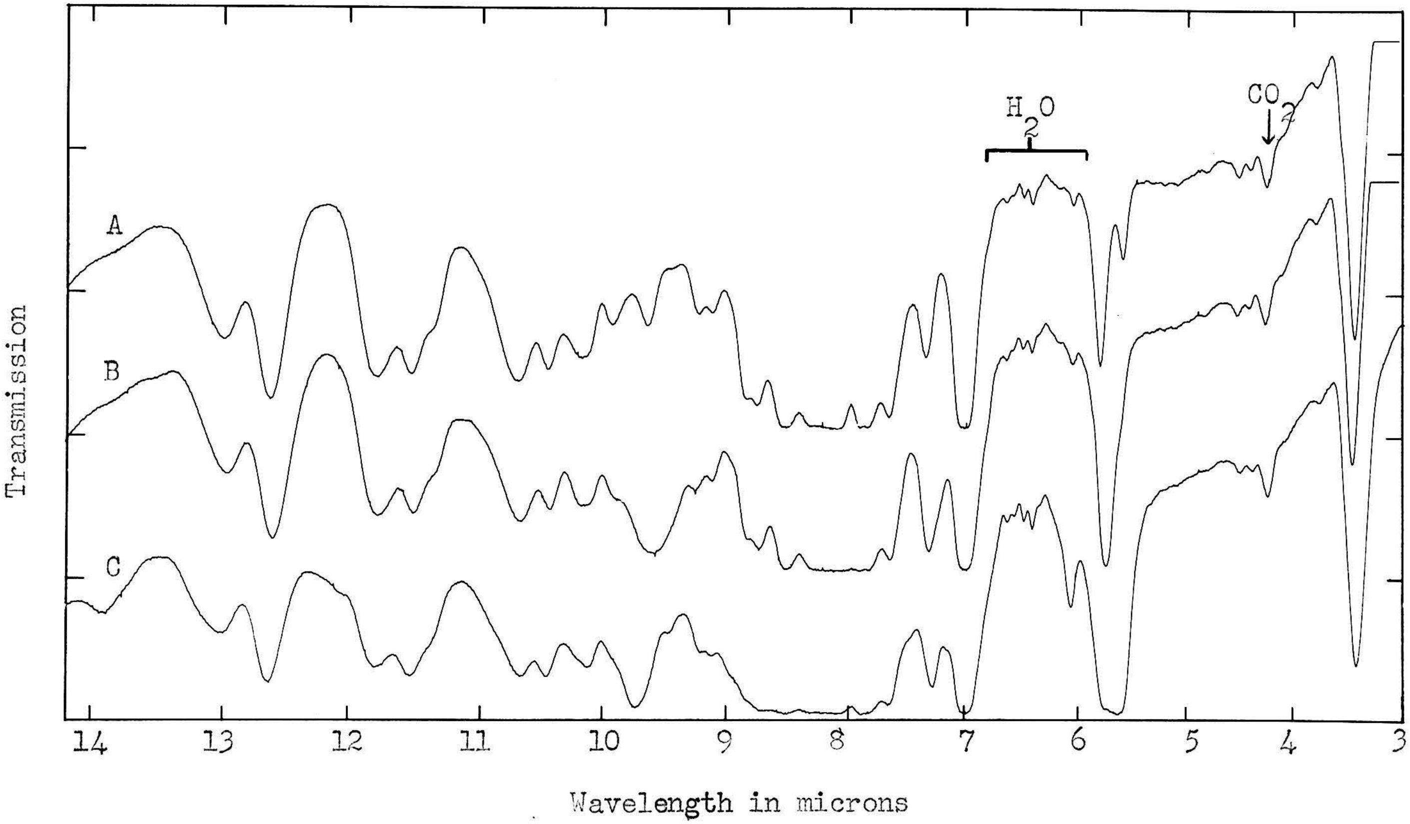

Fig. 2.- Infra-red absorption of 1,2,4-tribromobutane from: (A) degradation and ring cleavage of cyclobutane carboxylic acid, (B) 1,2-dibromo-4-hydroxybutane with hydrobromic acid; and (C) degradation of 1,2,4-tricarboxybutane. Curves A and B displaced upwards two and one scale divisions respectively.

Experimental Procedure*

Degradation of α-bromovaleric acid to 1,1-dibromobutane: (cf. (54)).

It was discovered in making salts of halogen-containing acids that considerable care must be exercised to keept the salt from lactonizing; but, with care, the salts can in most cases be made successfully. The temperature must at all times be kept below 10°, even for the dry salt, and, of course, the use of excess base must be avoided during the formation of the salt.

α-Bromovaleric acid (0.132 mole, 24.0 g.) Eastman Kodak Co. white label, redistilled, was cooled to 0° and mixed with 50 ml. of ice-water, Three normal ammonium hydroxide solution, also at 0°, was added until a pH of 7 was reached. The ammonium salt solution was poured in a thin stream into an ice-cold solution of silver nitrate, 22.4 g. (0.132 mole), Goldsmith reagent grade, with good stirring. The resultant precipitate was hurriedly transferred to pre-cooled centrifuge tubes and centrifuged. It was washed with water, acetone and ether, all of which solvents had been previously cooled to approximately 0°. The residual ether was removed on the aspirator and the silver salt dried at 0° overnight. This treatment gives a very fine powder, so that it is unnecessary to do more than break up the large lumps, which fall apart easily. The drying was done in the centrifuge bottle (250 ml.) and in the subsequent reaction the salt was used directly from this bottle. At no time did the temperature of the ammonium salt or the silver salt exceed 10°. At 20° the lactonization reaction occurs

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*Unless otherwise noted,melting points are uncorrected. Microanalyses reported are by Dr. A. Elek, Los Angeles.

rapidly, with evolution of considerable heat, polyesters are formed, and the silver salt turns yellow. The yellow color and the light-sensitivity of the silver bromide formed are very characteristic of decomposed material; the organic silver salts when properly prepared are pure white and not very light sensitive.

Merck reagent bromine (17 g., 0.108 mole, dried by shaking with concentrated sulfuric acid, separating and filtering through a bed of phosphorus pentoxide) was dissolved in 200 ml. of dry reagent grade carbon tetrachloride (dried by distillation and standing over drierite) in a 300 ml. three-necked, standard-taper-equipped flask, fitted with a "trubore" half-moon stirrer and a bulb-type reflux condenser. The solution was boiled, with no cooling water going through the condenser, until a few ml. had distilled out the top, carrying out any remaining water from the apparatus. Then a calcium chloride drying tube was fitted to the top of the condenser, the heat removed and the cooling water turned on. The silver salt, dried to constant weight (0.108 mole, 31.8 g.), was attached to the third neck of the reaction flask by means of a flexible rubber coupling. The reaction vessel was cooled to 0° and addition was made, raising the vessel containing the silver salt and shaking in the salt in small portions with good stirring over a period of about four hours.

At first reaction was very slow, but at the end of a one-half hour induction period the reaction proceeded so that about one bubble of carbon dioxide per second was evolved. By the end of addition the rate had increased to 5-10 bubbles per second. External cooling was necessary, and the silver salt being added needed also to be chilled during this time. At the end of addition the reaction was allowed to stir for one-half hour at 0°. Then sodium bisulfite solution was added dropwise at 0° until the bromine color had disappeared. The silver bromide was filtered off and washed with carbon tetrachloride and the combined organic layers were washed with cold, dilute sodium bicarbonate, solution,dried and distilled. 1,1,-Dibromobutane, 12.44 g. (53.6%), b.p. 90.5-92°/100 mm., n_D^{25} 1.4985, d_4^{25} 1.800, was collected.

Anal. Calcd. for $C_4H_8Br_2$: C, 22.20 ; H, 3.71 . Found: C, 22.21 ; H, 3.70 .

The identity of this material was established by refluxing 1.5 g. of it with 2.5 g. of silver acetate in 15 ml. of glacial acetic acid for six hours, decomposing the diacetate thus formed by boiling a few minutes with ten ml. of dilute hydrochloric acid (after filtering off the silver salts), and distilling the product. About 0.25 g. of butyraldehyde was obtained, distilling as a binary with water at 68°, and this was converted to the 2,4-dinitrophenylhydrazone according to the procedure described by McElvain (55), m.p. 121-2° (uncorr.).

<u>Degradation of β-bromopropionic acid to ethylene bromide</u>: (see also below, degradation of <u>succinic acid</u>)

The silver salt was prepared exactly as described above. β-Bromopropionic acid, 32 g. (0.21 mole), Eastman Kodak Co., white label, gave 46.5 g. (0.18 mole) of dry silver salt. The actual yield of the silver salts is usually quantitative, but there is considerable mechanical loss in the rapid handling procedure that is necessary. The silver salt was added to 65 g. (0.4 mole-125% excess) of dry bromine over a period of eight hours. The reaction was very slow at all times; the carbon dioxide evolution never exceeded one bubble per second. After a total of sixteen hours at 0°, evolution of carbon dioxide had practically ceased and the mixture allowed to warm up to 25° overnight. It was cooled to 0°, then sodium bisulfite was added to the solution until it was colorless. The silver bromide was filtered off and the precipitate washed with carbon tetrachloride. The organic layer was washed with sodium bicarbonate solution and with water, dried and distilled at atmospheric pressure. After removing solvent, 32.2 g. of ethylene bromide (68%) was collected, b.p. 128-29°/750 mm., n_D^{25} 1.5350, m.p. 7.5-9.0° (corr.).

An earlier attempt to make this silver salt had resulted in decomposition at 25° while drying at the vacuum of a Hyvac pump. A considerable quantity of a water-white liquid collected in the dry-ice trap. This proved to be β-propiolactone, as shown by its reaction with thiourea to give β-thioureidopropionic acid, m.p. 178-9° after air-drying (this is the m.p. reported by Gresham, et al. (40), who, however, dried the derivative at 100°; when the material obtained in this research was dried at 100°, it decomposed).

When the silver salt degradation described above was carried out at the temperature of refluxing carbon tetrachloride instead of at 0°, the principal product of the reaction was a non-distillable polyester. A small amount (4%) of somewhat impure ethylene bromide was obtained.

Allylmalonic acid:

Sodium (115 g., 5.0 moles) was dissolved in 2150 ml. of absolute ethanol in a five-liter, three-necked flask, fitted with reflux condenser, trubore stirrer and dropping funnel. Redistilled Eli Lilly and Co. diethyl malonate (800 g., 5.0 mole) was added while the solution was still hot. Then 605 g. (5.0 moles) of Eastman Kodak Co. white label allyl bromide was added over three-quarters of an hour to the hot solution, maintained at gentle reflux by the heat of the reaction. The mixture was heated during five hours while ethanol was slowly removed. After about two liters of ethanol had been taken off, the reaction mixture was cooled and washed with about 1.5 liters of water, which was extracted in turn with 200 ml. of ether. The combined organic layers were dried with magnesium sulfate, the ether was stripped off and the residue was distilled. Allylmalonic ester, 400 g. (40%), was obtained, b.p. 55-60°/1 mm., n_D^{25} 1.4290. In addition 115 g. (23%) of allylacetic acid was obtained upon saponification and acidification of fore- and after-runs. Upon saponification of the after-run (b.p. 60-90°/1 mm.), 42 g. (12%) of diallylacetic acid was obtained, b.p. 110-115°/30 mm.

Allylmalonic ester (200 g., 1.0 mole) was poured with good stirring into a solution of 225 g. (ca 4 moles) of potassium hydroxide in absolute ethanol at 50°. In about thirty seconds the mixture set to a semi-solid mass which was heated in the steam bath for one-half hour.

At the end of this time it was filtered, washed with absolute ethanol and then with ether. It was then dissolved in the minimum amount of water and made acid with cooling. After removal of water at 20 mm., the remaining dry salts were extracted with acetone and the acetone evaporated to give an almost quantitative yield of allylmalonic acid, m.p. 165° (dec.).

Allylacetic acid:

Allylmalonic acid, 72 g. (.5 mole), from the above reaction was used without further purification. Concentrated hydrochloric acid (2-3 ml.) was added and the mixture heated to 165° for one hour, or until carbon dioxide evolution had practically ceased. If the acid is very pure, or if no mineral acid is added, decarboxylation is very slow, requires higher temperatures, and the yield is correspondingly low. Even at 165° there was considerable side-reaction-lactone and polyester formation-and on distillation only about 70% (35 g.) of allylacetic acid, b.p. 95-7°/25 mm. was obtained.

The p-bromophenacyl ester of allylacetic acid was prepared from its sodium salt and p-bromophenacyl bromide, according to McElvain (57). After recrystallization from dilute ethanol it melted at 59.5-60.5° (corr.)

δ-Bromovaleric acid:

Gaseous hydrogen bromide was bubbled into 30 ml. of C.P. toluene at 0° until the saturation point was reached. Eastman Kodak Co. white label benzoyl peroxide (0.1 g.) was added, and then 22 g. (0.22 mole) of allylacetic acid was dropped with good stirring at 0°. More hydrogen bromide was added until a total of 30 g. (0.37 mole) had been absorbed.

After a few minutes the solution was allowed to warm to room temperature and was stirred for three hours. The toluene solution was then washed with water several times, extracting the water washings with ether. The combined organic layers were stripped free of ether and distilled. Allylacetic acid (6 g. 27%) was recovered unchanged and 28.1 g. (71%) of a fraction, b.p. 102-110°/1 mm, was obtained which solified to a white solid, m.p. 35-40°. This acid after a single recrystallization from ligroin melted at 39.5-40.5° (corr.). The isomer, γ-bromovaleric acid, is reported to melt at 21° (56).

Attempted degradation of δ-bromovaleric acid to tetramethylene bromide:

An attempt to carry out the silver salt degradation of δ-bromovaleric acid was made before the technique of using these heat-sensitive bromine-containing silver salts had been properly worked out, and as a result, none of the desired product was obtained. The silver salt was made at 10° from the ammonium salt without any noticeable decomposition, but upon drying overnight at 25° it decomposed into a liquid (presumably the lactone) and silver bromide. Later work indicates that since the silver salt can be made, the degradation with bromine probably can also be carried out successfully at 0°.

γ, δ-Dibromovaleric acid:

Allylacetic acid (50 g., 0.5 mole) was dissolved in dry reagent carbon tetrachloride and the solution was cooled to 0°. Bromine, 80 g. (0.5 mole) was added dropwise with stirring over a two-hour period. When the addition was about two-thirds complete, the bromine color persisted and two phases had formed. The reaction mixture was then allowed to warm to room temperature and was stirred for two hours. The excess bromine was destroyed by warming with formic acid and the organic phases were extracted with dilute aqueous sodium bicarbonate solution. The aqueous extract was acidified and extracted in turn with ether. From the ether extract the low-boiling materials were stripped off in vacuo on the steambath (some allylacetic acid can be recovered) and, on cooling, the orange oily residue crystallized. This crude product melted at 45-50°. One crystallization from 30-60° petroleum ether gave 77.65 g. (59.6%) of white crystals, m.p. 56-8°.

Degradation of γ,δ-dibromovaleric acid to 1.2.4-tribromobutane: (see also below).

The silver salt of γ,δ-dibromovaleric acid was made by the low-temperature technique described above under the silver salt degradation of α-bromovaleric acid. Throughout the precipitation and centrifugation, and during most of the drying at 0°, the silver salt remained pure white in color. However, after 16 hours of drying, the centrifuge bottle was opened to break up the lumps with a spatula, even though the salt was maintained at 0° then and thereafter, it decomposed rapidly into a liquid and silver bromide. The degradation could not be carried out. Evidently preparation of a silver salt of a γ-bromoacid requires a special technique if lactonization is to be avoided.

Attempted Degradation of allylacetic acid to 1.2.4-tribromobutane:

The silver salt of allylacetic acid was made in the usual way, by addition of the potassium salt to a silver nitrate solution. The minimum amount of water was used because of the high solubility of silver allylacetate. After the customary washing and drying the yield of silver salt was only 35.5 g. (59%) from 25 g. (0.25 mole) of the acid.

The dry silver salt , 35.5 g. (0.17 mole), was added to 54.4 g (0.34 mole) of dry bromine in 200 ml. of dry reagent grade carbon tetrachloride portionwise at reflux temperature over a period of two hours; the mixture was refluxed for an additional one-half hour after addition. The reaction was vigorous, but no carbon dioxide was evolved. On working up in the usual fashion, destroying the rather large excess of nromine remaining and distilling, 9.8 g. of material boiling at 98-9°/1.5 mm. was obtained. Thus was determined to be a bromolactone by the fact that it dissolved in concentrated hydrobromic acid and, upon dilution of the resulting solution, γ , δ -dibromovaleric acid was obtained. Possibly this reaction could be carried out successfully at lower temperatures (0° or below).

<u>Degradation of ethylmalonic acid to 1,1-dibromo and 1,1,1-tribromopropanes:</u>

Eli Lilly and Co. ethylmalonic ester,(94 g., 0.5 mole), was saponified by pouring into a solution of 100 g. (1.78 mole) of C.P. potassium hydroxide in 700 ml. of ethanol at 50° with stirring and subsequent heating in the steambath for one-half hour. The resultant semi-solid mass was filtered, washed once with absolute ethanol and once with ether. After sucking dry on a Buchner funnel, the quite pure dipotassium salt was dissolved in a minimum amount of water and, with cooling, the solution was made acid to congo red with nitric acid. The water solution was extracted several times with alcohol-free ether and the ether removed at 25° in the vacuum of the water aspirator. The crystalline white diacid was air dried on a porcelain plate, yield ca. 100%. No odor of butyric acid could be detected.

Alternatively, the water solution of the potassium salt could be brought to the neutral point with nitric acid and this solution used directly in the preparation of the silver salt.

The pure diacid (31 g., 0.23 mole) was dissolved in 50 ml. of water and enough 15% potassium hydroxide solution added to bring it to pH 7. This potassium salt solution was added slowly in a fine stream, with vigorous stirring, to a solution of 40 g. (0.23 mole) of Goldsmith reagent grade silver nitrate in 200 ml. of water. The precipitated silver salt was centrifuged and was washed successively with acetone, methanol, and ether, centrifuging relatively free of solvent each time. The ether was taken off at 25° at the vacuum of the water aspirator and the resulting silver salt was dried over-night at 25° on a Cenco Hyvac pump, yield, 37 g. (95%).

Dry Merck reagent bromine, (42 g. 0.132 mole) was dissolved in 125 ml. of dry reagent grade carbon tetrachloride in the apparatus described above. The silver salt, which had been dried to constant weight (37 g., 0.117 mole), in the 100 ml. round-bottomed flask in which it was to be used, was attached to the third neck with a flexible rubber tube. The reaction vessel was cooled to 0° and addition was started by raising the flask containing the silver salt and shaking in the salt in small portions.

About 2-3 g. was added and the mixture was stirred for about one hour before reaction was at all noticeable, as evidenced by carbon dioxide evolution. This gas evolution can be conveniently followed by attaching a bubble counter to the exit tube of the calcium chloride drying tube. Small portions of the silver salt were added over a period of several hours. The rate of carbon dioxide evolution slowly increased until a steady rate of 2-3 bubbles per second was reached. The remainder of the silver salt was then added and the suspension allowed to stir for eight hours at 0°, and then gradually the mixture was warmed over a period of three to four hours to 55°. Some evolution of hydrogen bromide was noted.

The suspension was again cooled to 0° and 10% aqueous sodium bisulfite solution was added dropwise until the bromine color was destroyed. Only a few drops were needed in this case. The silver bromide was filtered off in the cold and the precipitate washed with carbon tetrachloride. The combined organic phases were washed with aqueous bicarbonate to remove any brominated or unbrominated free acids formed by the reaction of the silver salt and hydrogen bromide. A brown alkaline layer was formed, which was not further investigated but which probably contained appreciable amounts of acidic substances. The organic layer was washed once with cold water, and then dried over calcium chloride.

The carbon tetrachloride was taken off at atmospheric pressure and the residual material fractionated. 1,1-Dibromopropane, b.p. 86-88°/155 mm., and a fraction, mostly 1,1,1-tribromobutane, b.p. 70-80°/25 mm. were obtained upon distillation of this residue. This represented a yield of 28% of the dibromopropane and 24.7% of the tribromopropane. These materials were redistilled; dibromopropane, b.p. 133.25-134.0°/751 mm.; n_D^{25} 1.5063, d_4^{25} 1.960, was collected, and analyzed.

Anal. Calcd., for $C_3H_6Br_2$: C, 17.81; H, 3.00. Found: C, 18.03; H, 2.94.

Tribromopropane, b.p. 77-83°/25 mm., n_D^{25} 1.5606; d_4^{25} 2.439, was also collected and analyzed.

Anal. Calcd. for $C_3H_5Br_3$: C, 12.81; H, 1.79. Found: C, 13.25; H, 1.95.

To prove the structure of the two products they were treated in the following ways; The dibromopropane (1.5 g.), 2.5 g. of silver acetate, and 15 g. of glacial acetic acid were refluxed vigorously for six hours. The mixture was cooled and the silver salts were filtered off and washed with a little acetic acid. The acetic acid solution was put into a Claisen flask fitted with a short glass-bead-column and 10 ml. of dilute hydrochloric acid was added. The flask was heated rapidly to boiling and the propionaldehyde produced, together with some water, was taken off at 48-52°. About 0.25 g of aldehyde was produced in this way which was converted to the 2,4-dinitrophenyl hydrazone by the method described by McElvain (55). After two recrystallizations from ethanol, the derivative melted at 153.5-154.5°.

The tribromide (0.75 g.) was refluxed with 20% aqueous potassium hydroxide solution for twenty-four hours. After extracting the alkaline solution with ether an orange - colored solution was obtained. The solution, after bringing to pH 8 with hydrochloric acid, was then evaporated to dryness on the steambath and the resultant mixture of salts was extracted with 70% ethanol. This extract was brought to pH 7, and 0.25 g. of p-phenylphenacyl bromide added. The ethanol solution was refluxed for two hours; the product* after several recrystallizations from ethanol melted at 102-3°, and showed no depression of the melting point when mixed with authentic p-phenylphenacyl propionate (57).

Degradation of succinic acid to Ethylene bromide: (see above also, degradation of β-propionic acid)

Pure dry white silver succinate was prepared in 98-9% yield by the addition with good stirring of a neutral solution of sodium succinate to a slight excess of a solution of silver nitrate. The resultant precipitate was washed successively with water, acetone and ether, removing the solvent each time by filtration or centrifugation. After stripping off the major part of the residual ether on the aspirator, the silver salt was dried overnight at temperatures

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* It was found convenient, when making phenacyl esters, to use an excess of the phenacyl halide to insure a maximum amount of product. The excess phenacyl bromide remaining at the conclusion of the reaction can be easily removed from the desired ester derivative by warming a benzene solution of the mixed precipitates and adding a benzene solution of trimethyl amine until precipitation of the quaternary bromide salt stops. The quaternary bromide may be filtered off or removed by washing with water, leaving relatively pure phenacyl ester.

up to 75° on a Cenco Hyvac pump. Before use it was ground and dried to constant weight in the container in which it was to be used.

Silver succinate (99.5 g., 0.3 mole) was added, in the system described above, portionwise over a period of one hour to a stirred solution of 96 g. (0.6 mole) of dry bromine in 300 ml. of dry carbon tetrachloride. Initially at reflux temperature, the system maintained itself there at first; later external heat was applied. After the addition was complete, the solution was refluxed for an additional hour, was then filtered, washed with 10% sodium bisulfite solution and finally was distilled in vacuo. The yield of ethylene bromide was 18 g. (31.9%), b.p. 60-60.5°/67 mm., d_4^{25} 2.172, n_D^{25} 1.534, m.p. 6.5-9.0° (corr.), mixed m.p. with authentic dibromide, 7.5-9.0° (corr.).

Several other runs at different temperatures were made. When the addition was made at 0°, with subsequent warming, in one case the decarboxylation occurred with explosive violence at about 40°. In another case of addition made at 0°, the intermediate decomposed smoothly and evenly at about 10-15° (with external cooling); the yield was 37%. Some unreacted silver succinate was also recovered in this case, even though an excess of bromine was used. In several runs at higher temperatures the yields were always lower. For example, in one run at 135°, using tetrachloroethane as the solvent, the starting material was completely accounted for as polyesters, for the most part insoluble in the chlorinated solvent but soluble in boiling ethanol.

1,2,4-Tricarboxybutane:

An attempt was made to oxidize 1-vinylcyclohexene-3 (butadiene dimer) by the conventional method using permanganate, but such large volumes of solution were involved, and the product obtained was so contaminated with intermediate oxidation products which were difficult to remove, that a more convenient method was desired.

Nitric acid was suggested (by Dr. H. L. Herzog), as a concentrated oxidizing agent of considerable power that produces only gaseous by-products, so a procedure was tried patterned somewhat after that described in Organic Syntheses (58) for the oxidation of cyclohexanone. Similar oxidations have also been described in a British patent (59).

1-Vinylcyclohexene-3 (a sample generously supplied by the Koppers Co.), redistilled, was added dropwise over a period of three hours with stirring to 1.3 liters (ca. 20 moles, slightly more than 100% excess) of concentrated nitric acid at 50-60°, using 2 g. of ammonium metavanadate as catalyst, in a 2-liter, three necked, standard-taper-equipped flask, fitted with dropping funnel, "trubore" half-moon stirrer and reflux condenser. The reaction maintained itself at this temperature even with some external cooling. The resultant solution was siphoned off and re-added dropwise through the dropping funnel, this time with the flask maintained at 100° on a steambath. Considerable further reaction took place, as evidenced by nitrogen dioxide fumes being evolved copiously. After this second addition was complete, the vessel was heated one hour more at 100°, although nitrogen dioxide was no longer evolved after ten minutes. On cooling, a fluffy white precipitate was noted. This was filtered off, and shown to be p-nitrobenzoic acid, formed by aromatization of the hydroaromatic ring, with simultaneous oxidation of the side chain and substitution. In all, 2-3 g. of this nitro acid was obtained, m.p. 232°, methyl ester, m.p. 94° (corr.).

The excess nitric acid was conveniently destroyed by addition of formic acid at from room temperature up to 50°. Carbon dioxide and nitrogen dioxide were evolved until the nitric acid was completely destroyed. The water was stripped off on the steambath under aspirator vacuum, the residue (a light-brown viscous oil), was dissolved in acetone and the solution was boiled with Norite. A clear green solution resulted, which after taking off acetone, gave a solid mass, crude yield, 84%. A single recrystallization resulted in white crystals, m.p. 115-21° from acetonitrile.

The crude triacid was converted to the trimethyl ester by successively dissolving in methanol containing hydrogen chloride, stripping off the methanol and the water formed and re-adding methanol-hydrogen chloride. This was done three times and then the product was distilled. There was obtained 145 g. (62.5%) of trimethyl ester, b.p. 116-7°/1 mm. as well as 14 g. of a forerun boiling at 50-3°/1 mm., probably dimethyl succinate or glutarate.

The ester, 116 g. (0.5 mole) was saponified in 50% ethanol, using 120 g. (3 moles) of sodium hydroxide and refluxing for three hours. The solution became dark-brown in color and a flocculent precipitate appeared. This apparently consisted of $V(OH)_3$ (VCl_x compounds are volatile and soluble in organic solvents). The ethanol was taken off on the steambath, with some foaming. The solution was acidified and was extracted once with ether; the ether extract was discarded. The water was then removed on the steambath under aspirator vacuum, occasionally filtering off the salts which separated. The combined salts were extracted with boiling acetone and the acetone stripped off, leaving a tan crystalline residue. On recrystallization from acetonitrile it gave a pure white triacid, m.p. 118-120° (48), yield, 89 g. (99% from triester).

Degradation of 1,2,4-tricarboxybutane to 1,2,4-tribromobutane:

The silver salt of tricarboxybutane was made exactly as in the preceding procedure for silver succinate. The dry silver salt, 53 g. (0.104 mole), using the apparatus previously described, was dropped into 50 g. (0.312 mole) of bromine in 200 ml. of dry reagent grade carbon tetrachloride maintained at reflux temperature over a period of about six and one-half hours. Carbon dioxide was vigorously evolved from the exothermic reaction. After the addition was completed, the mixture was refluxed for one-half hour additional. On cooling, filtering and washing with 10% bisulfite solution, it was found that 18% of the bromine was left unused, presumably because of ester formation in the usual side-reaction. After washing with bicarbonate and water, the organic layer was dried and distilled giving 1.8 g. (6%) of tribromobutane. A solid residue, presumably polyester, remained in the distillation flask. From this run and from a like run (which gave a 4% yield) 3.3 g. of tribromide was obtained, b.p. 54-6°/1 mm., n_D^{25} 1.5554; in addition, 1.5 g. of bromolactone resulted, b.p. 70-75°/1 mm., n_D^{25} 1.5101. Possibly, better yields of the tribromide could be obtained by running the reaction at lower temperatures (see degradation of halogen-containing acids).

1,2,4-Tribromobutane

I. Authentic material was synthesized following the method described by Pariselle (47). Dry, resublimed paraformaldehyde (28 g. 0.93 mole) and 24 g. (1.0 mole) of clean magnesium turnings were put into 200 ml. of dry (dried over sodium) ether in a three-necked, 500 ml., standard-taper-equipped flask fitted with "trubore" stirrer, dropping funnel and reflux condenser topped with a drying tube. A few crystals of iodine were added and then allyl bromide, Eastman Kodak Co. white label, freshly redistilled, was added dropwise. The reaction started after 2-3 ml. had been added and continued nicely over an addition period of six hours. The mixture was refluxed for two hours after the addition had been completed. Ice-water and then dilute sulfuric acid were added until all of the magnesium had dissolved. The product was extracted with ether (3 x 100 ml.) and the extracts were freed of solvent. Further distillation gave biallyl which was taken off up to 95°/760 mm. and buten-4-ol was collected at 112-116°, yield 15.4 g. (19%). Pariselle states that the residue is mostly the formal of this alcohol.

The butenol was used without further purification. It was dissolved in 100 ml. of dry reagent grade chloroform and 34.3 g. (0.214 mole) of Merck reagent bromine was added dropwise at 0° with stirring. The bromine-color persisted after about nine-tenths of the theory of bromine had been added. The reaction mixture was stirred for one hour at 25°, washed with 10% bisulfite solution and with water, dried with magnesium sulfate and distilled. There was collected 30.7 g. (61%) of 1,2-dibromo-4-hydroxybutane, b.p. 85°/1 mm.

Glacial acetic acid (200 ml.) was saturated with gaseous hydrogen bromide at 0°. The alcohol obtained above was added and the temperature was kept below 10° for one hour. The temperature was then raised slowly so that a temperature of 70° was reached in five hours and in sixteen hours, a temperature of 100°. During this time the reaction mixture became black. The acetic acid was stripped off at 32°/23 mm., and the residue was washed with water to remove excess hydrogen bromide. The cloudy water-phase was then extracted with ether and the combined organic phases dried and distilled. There was obtained 31.89 g. (82%) of 1,2,4-tribromobutane, b.p. 56-9°/1 mm., n_D^{25} 1.5588.

Von Braun (46) has reported that this tribromobutane, when treated with magnesium*, simultaneously loses halogen from the vicinal bromine-containing carbon atoms and forms an olefinic Grignard reagent (MgBr attached at carbon atom 4). This reaction proceeded

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*Attempts to dehalogenate using zinc led to ill-defined products.

exactly as described, the resulting Grignard reagent was carbonated to give allylacetic acid, and the p-bromophenacyl ester of this acid was made according to McElvain (51). The ester so obtained melted at 59.5-60.5 (corr.) and did not depress the m.p. of authentic p-bromophenacyl allylacetate, m.p. also 59.5-60.5° (corr.)

II. An attempt was made to synthesize 1,2,4-tribromobutane from 1,2,4-trihydroxybutane obtained by the action of lithium-aluminum hydride on malic ester. Difficulties due to solubility relationships were encountered during the reduction step.

III. An attempt was made to synthesize 1,2,4-tribromobutane by the reaction of 1,4-dibromobutene-2 and hydrogen bromide. This addition is reported to proceed very slowly at 100°. In 48 hours at 100°, using a saturated glacial acetic acid solution of hydrogen bromide, no product could be isolated and the starting material was recovered unchanged.

IV. Attempted syntheses of 1,2,4-tribromobutane are listed above under the degradation of γ, δ -dibromovaleric acid and of allylacetic acid.

V. The successful synthesis of 1,2,4-tribromobutane is described above under the section dealing with degradation of 1,2,4-tricarboxybutane.

VI. 1,2,4-Tribromobutane is a by-product of the degradation of cyclobutane carboxylic acid, see below.

Attempted Degradation of 1,2,3,4-Tetracarboxybutane to 1,2,3,4-Tetrabromobutane:

An attempt was made to carry out this reaction with the silver salt of 1,2,3,4-tetracarboxybutane (60), but with no success. The silver salt was prepared in the usual fashion, by adding the sodium salt of the acid to a slight excess of silver nitrate solution and washing with water, acetone and ether. It was dried to constant weight, yield 70.6 g. (97%) from 25.7 g. (0.11 mole) of recrystallized Eastman Kodak Co. yellow label 1,2,3,4-tetracarboxybutane, m.p. 188-90° (dec.) (60) from acetone.

The reaction was much like that of the 1,2,4-tricarboxybutane, described above. Dry silver salt (70.6 g., 0.105 mole) was added to 67.5 g. (0.420 mole) of dry bromine in 300 ml. of dry carbon tetrachloride during four hours. A vigorous reaction took place with carbon dioxide evolution. At the end, 20% of the bromine was left. On filtering, most of the organic product remained with the silver bromide precipitate and could not be washed out with carbon tetrachloride (although it is soluble in boiling ethanol). The carbon tetrachloride solution, on evaporation on the steam bath, left only 2-3 g. of brown, uncrystallizable oil, which was almost completely soluble in concentrated hydrobromic acid. No evidence for the presence of 1,2,3,4-tetrabromobutane was obtained.

1,4-Dibromobutene-2, upon boiling with bromine in carbon tetrachloride slowly added bromine to form authentic 1,2,3,4-tetrabromobutane, m.pl 115.5-116.7°, in quantitative yield. 1,2,3,4-Tetrabromobutane is a possible by-product in the degradation of cyclobutane-1,2-dicarboxylic acid; see below.

Cyclobutanecarboxylic Acid:

1,1-Dicarbethoxycyclobutane (200 g., 1.0 mole) (preparation described in the Experimental Procedures section of Part I of this Thesis) was poured with good stirring into a solution of 240 g. (ca. 4.0 moles) of potassium hydroxide in absolute ethanol at 50°. An exothermic reaction took place and in a few minutes the reaction mixture set to a semi-solid. This was filtered as dry as possible, washed with 500 ml. of absolute ethanol and with 500 ml. of ether. It was dissolved in the minimum amount of water, acidified with hydrochloric acid to pH 4 and the water removed by distillation at atmospheric pressure. Some decarboxylation occurred and the resulting monoacid steam-distilled and could be extracted from the distillate with ether. The solid mass of salts that resulted from taking off the water was heated by means of an oil bath at 200° under reflux for two hours. At the end of this time the pressure was reduced and impure cyclobutanecarboxylic acid, b.p. 85-105°/25 mm. was removed. This impure distillate was combined with the above ether extract and redistilled. The yield of cyclobutanecarboxylic acid, b.p. 98-100°/23 mm., n_D^{25} 1.4424, was 86 g. (86%).

Degradation of cyclobutanecarboxylic acid to cyclobutyl bromide (and other products):

It was discovered that the conditions under which this reaction is carried out determine the major product. When the silver salt was added to bromine at 10°, cyclobutyl bromide was formed predominantly. At reflux temperature, the major product was that produced by opening of the cyclobutane ring, i.e., 1,2,4-tribromobutane. At 25°, when the bromine was dropped into the carbon tetrachloride suspension of silver salt, the major product was ester formed by the reaction of cyclobutyl bromide with the excess of silver salt.

I. Cyclobutyl bromide: The silver salt was made as previously described, using a minimum of water because of the rather high solubility of silver cyclobutanecarboxylate. The yield of silver salt was 89.4%, and 8% of cyclobutanecarboxylic acid could be recovered after acidification of the solvents used for washing. The salt was dried for eight hours at 80° without visible decomposition.

The previously described apparatus was used, dry Merck reagent bromine (34.6 g., 0.215 mole) was dissolved in 250 ml. of dry reagent grade carbon tetrachloride and the mixture was cooled to 10°. The silver salt (44.7 g., 0.216 mole) was shaken in slowly over a two-hour period. The evolution of gas was somewhat slow at 10°, much more rapid at 12°. Cason (29) has run this same reaction at -25°; he describes a considerable induction period, followed by fairly rapid reaction. When the addition of silver salt was about three-quarters complete, additional bromine was added since the bromine color had disappeared. In all, 39.9 g. of bromine (0.25 mole) was required. After the addition had been completed, the mixture was stirred for one-half hour and the silver bromide was filtered off and washed with solvent. The filtrates were washed with bisulfite, then with bicarbonate, finally with water and dried. The carbon tetrachloride was carefully removed and the residue distilled. Three fractions were noted, the first of which was the desired product, cyclobutyl bromide, 13.43 g. (46.2%), b.p. 46-8°/100 mm., 106-8°/755 mm., n_D^{25} 1.4768, d_4^{25} 1.430. The second fraction was cyclobutyl cyclobutanecarboxylate, 3.94 g. (23.8%), b.p. 49-50°/1 mm., 196-8°/755 mm., n_D^{25} 1.4528, d_4^{25} 1.024. The third was 1,2,4-tribromobutane, 7.53 g. (12.2%), b.p. 56-8°/ca. 1 mm., 74-6°/1.5 mm., n_D^{25} 1.5683, d_4^{25} 2.205.

II. Cyclobutyl cyclobutanecarboxylate: Silver cyclobutanecarboxylate (46 g., 0.222 mole) was suspended in 250 ml. of dry carbon tetrachloride at 25°. Bromine (35.5 g., 0.222 mole) was dropped in with good stirring and with cooling to maintain the temperature at 25°. When 27.2 g. (0.17 mole) of bromine had been added carbon dioxide evolution ceased and the bromine color persisted. The reaction mixture was stirred for an additional hour, the silver bromide was filtered off and the organic layer was washed with bisulfite, bicarbonate and water in that order, dried and distilled. No cyclobutyl bromide was obtained. The principal product was cyclobutyl cyclobutanecarboxylate, 10.66 g., (62.2%), b.p. 57-9°/3 mm., n_D^{25} 1.4530. Tribromobutane, 3.84 g. (6%) was also produced. A third high boiling fraction was also found, b.p. 120-140°/1 mm., that probably represents brominated esters.

Cyclobutyl bromide (1.5 g., 0.011 mole) and 1.72 g., (0.011 mole) of silver cyclobutanecarboxylate were mixed in 10 ml. of dry carbon tetrachloride and allowed to stand for twelve days at 25° with occasional shaking. In three days the characteristic sweet odor of the ester could be detected. On distillation, 1.27 g., (75%) of material boiling at 196-200° was obtained, n_D^{25} 1.4496.

III. <u>1,2,4-Tribrombutane:</u> Dry silver cyclobutanecarboxylate (47 g., 0.227 mole) was added to 37 g. (0.227 mole) of bromine in refluxing carbon tetrachloride over a period of one and one-half hours. The reaction was extremely vigorous. About half way through the addition, 30 g. extra of bromine was added, since the reaction mixture had become completely decolorized. On working up the product in the usual way, 1.4 g. (8.4%) of cyclobutyl cyclobutanecarboxylate was obtained, b.p. 57°/2 mm., and 44.8 g. (64.6%) of 1,2,4-tribromobutane, b.p. (on redistillation) 72-4°/2 mm., n_D^{25} 1.5675, d_4^{25} 2.206, m.p. -20 to -15° (macro.).

The constitution of this material was determined by comparison of its physical properties with material prepared by two other methods (see above), that of Pariselle (47) and that of the silver salt degradation of 1,2,4-tricarboxybutane. The infra-red spectra were also compared. The reaction with magnesium as described by von Braun (46), with subsequent carbonation and ester formation, was used to make the p-bromophenacyl ester of allylacetic acid from this tribromide. The melting point, 59.5-60.5° (corr.) is the same as that found for the authentic material; the mixed m.p. showed no depression.

Degradation of cyclobutane-1,2-dicarboxylic acids to 1,2-dibromocyclobutane:

I. *Cis* 1,2-dicarboxycyclobutane (42 g., 0.3 mole) was converted to the silver salt, as already described, in 98% yield (103.5 g.). A portion of this silver salt(44.2 g., 0.125 mole) was added over a period of several hours to a solution of 40 g. (0.250 mole) of bromine in 125 ml. of refluxing carbon tetrachloride. The reaction was vigorous but some external heating was needed to maintain at reflux. About 1 g. additional of bromine was needed towards the end to maintain color in the reaction vessel. The products were worked up in the usual way. Distillation gave 10.25 g. (40.6%) of material boiling at 64-72°/12.5 mm. Redistillation gave a principal fraction, b.p. 72-4°/20 mm., n_D^{25} 1.5352, d_4^{25} 1.928, m.p. -1.5 to +0.5° (corr.). This material when mixed with authentic, presumably *trans* 1,2-dibromocyclobutane from bromination of cyclobutene, melted at 2.5-4.5° (corr.). This sample of authentic *trans* dibromide melted at 4.75-5.75° (corr.).

II. The silver salt (52.4 g., 0.15 mole) of trans 1,2-dicarboxycyclobutane was treated in exactly the same way, except that no extra addition of bromine was required. The yield was 6.23 g. (39.4%) of material boiling at 73-6°/20 mm. This, on redistillation, gave dibromide as a major product, b.p. 72-4°/20 mm., n_D^{25} 1.5343, d_4^{25} 1.934, m.p. -1 to +1° (corr.). This material gave a mixed m.p. with authentic trans dibromide of 2.5-4.5° (corr.).

It was noticed that after standing several months the fractions boiling slightly higher than the dibromide, from these two experiments and another conducted with mixed cis and trans acids, contained some crystalline material, m.p. 54° (corr.), which later experiments indicated was 1,4-dibromobutene-2.

III. Merck reagent bromine (23.8 g.) was placed in a 50 ml. Claisen flask, fitted with mercury-sealed stirrer, connected on one side a tube to an ampoule containing 8.03 g. (0.149 mole) cyclobutene (see below for source), and on the other to a water manometer. With continued stirring, the cyclobutene was allowed to boil into the flask over the period of an hour while it was maintained at 0° and a pressure very slightly above atmospheric. The bromine was just decolorized. After the reaction was complete, the stirrer, manometer and ampoule were removed and the product distilled from the flask at 17 mm. pressure. There was obtained 27.92 g. (87.8%) of trans 1,2-dibromocyclobutane, b.p. 57.50-58.25°/17 mm., n_D^{25} 1.5362, m.p. 4.5-5.0° (corr.). A small residue, m.p. 115.5-116.75°, was left, evidently 1,2,3,4-tetrabromobutane (from some butadiene in the cyclobutene) since it did not depress the m.p. of authentic 1,2,3,4-tetrabromobutane.

Cyclobutene:

Reformatsky zinc dust (44 g., 0.66 mole) was mixed with 30 ml. of absolute ethanol in a 300 ml., 3-necked standard-taper-equipped flask, fitted with a mercury-sealed Hershberg stirrer, dropping funnel and reflux condenser topped with a calcium chloride tube leading to a glass tube, in turn leading into an ampoule in a Dry Ice trap. 1,2-Dibromobutane (42.8 g., 0.20 mole) was added dropwise over a period of two hours to the refluxing ethanol-zinc dust suspension. Half way through, polymer had to be cleaned from the tube leading into the ampoule. Since cyclobutene does not easily polymerize, this was probably butadiene, formed by dehalogenation of brominated straight chain impurities in the starting dibromide. These might arise as a consequence of ring cleavage during the silver salt degradation (see also degradation of cyclobutane carboxylic acid, above). After addition was complete the reaction mixture was refluxed for one hour while sweeping gently with dry nitrogen. The material that had collected in the trap was fractionated through a column at low temperatures. At complete reflux the temperature at the top of the column was 1.5°; 8.03 g. (74.5%) of the material boiled between 2.0 and 2.15° and was collected as cyclobutene.

Summary:

1. Silver salt degradations using a modification of the Hunsdiecker technique have been attempted on α-, β-, γ-, and δ-bromoacids. The α-bromoacid and β-bromoacid give reasonable yields of dibromoalkanes. The silver salts of the -bromoacid and of the γ-, δ-dibromoacid decomposed at 25°, presumably to give lactones.

2. Succinic acid has been degraded to ethylene bromide in 37% yield; ethylmalonic acid gave 28% of 1,1-dibromopropane and 25% of 1,1,1-tribromopropane.

3. The Hunsdiecker technique has been successfully applied to cyclobutanecarboxylic acids. Cyclobutanecarboxylic acid, cyclobutane-1,2-dicarboxylic acids, and spiro(3,3)heptane-2-carboxylic acid have been converted to the corresponding bromides.

Literature Cited.

1. Schutzenberger, *J. Chem. Soc.*, 13 , 248 (1862).
2. Zappi and Bonso, *Anal. Assoc. Química Argentine*, **35**, 137 (1947).
3. Hunsdiecker, Hunsdiecker and Vogt, German Patent 695,062; French Patent 803,941; British Patent 456,565 (1937).
4. Hunsdiecker, and Hunsdiecker, *Ber.*, **75**, 291 (1942).
5. Peligot, *Compt. rend.*, **3**, 9 (1836).
6. Kekulé, *Ann.*, **117**, 120 (1861).
7. Borodine, *Ann.*, **119**, 123 (1861).
8. Simonini, *Monatsh.*, **13**, 320 (1892); **14**, 81 (1893).
9. Birnbaum and Gaier, *Ber.*, **13**, 1270 (1880).
10. Birnbaum and Reinberg, *Ber.*, **15**, 456 (1892).
11. Kleinberg, *Chem. Reviews*, **40**, 381 (1947).
12. Wieland and Fisher, *Ann.*, **446**, 49 (1926).
13. Oldham and Ubbelohde, *J. Chem. Soc.*, **1941**, 368.
14. Windaus and Klänhardt, *Ber*, **54**, 581 (1921); **55**, 3981 (1922).
15. Birckenbach, Goubeau and Berninger, *Ber.*, **65**, 1339 (1932).
16. Birckenbach and Kolb, *Ber.*, **67**, 1729 (1934).
17. Prevost, *Compt. rend.*, **196**, 1129 (1933); **197**, 1661 (1933); **200**, 942 (1935).
18. Prevost et al., *Compt. rend.*, **198**, 2264 (1934);**204**, 700 989 (1937).
19. Bockemüller and Hoffmann, *Ann.*, **519**, 165, 189 (1935).
20. Hunsdiecker, Hunsdiecker and Vogt, U.S. Patent 2,176,181 (1939).
21. Hunsdiecker, Hunsdiecker and Vogt, German Patent 730,410 (1942).
22. Hunsdiecker, Hunsdiecker and Vogt, German Patent 722,464 (1942).
23. Arcus, Campbell and Kenyon, *Nature*, **163**, 287 (1949).

24. Arcus, Campbell and Kenyon, *J. Chem. Soc.*, *1949*, 1510.

25. Arnold and Morgan, *J. Am. Chem. Soc.*, *70*, 4248 (1948).

26. Bell and Smyth, *J. Chem. Soc.*, *1949*, 2372.

27. Doering and Farber, *J. Am. Chem. Soc.*, *71*, 1514 (1949).

28. Prelog and Seiwerth, *Ber.*, *74*, 1769 (1941).

29. Cason and Way, *J. Org. Chem.*, *14*, 31 (1949).

30. Price, *Mechanisms of Reactions at the Carbon-Carbon Double Bond*, Interscience Publishers, New York, N.Y., 1946, page 55.

31. Ziegler, Schenck and Krockow, *Naturwiss.* *29*, 390 (1941).

32. Willstätter and v. Schmaedel, *Ber.*, *38*, 1995 (1905).

33. Willstätter and Bruce, *Ber.*, *40*, 3985 (1907).

34. Buchman, et al.,to be published.

35. Goldschmidt and Gråfinger, *Ber.*, *68*, 279 (1935).

36. v. Braun, et al., *Ber*, *38*, 2340 (1905); *55*, 3576 (1922).

37. Freund, *Ber.*, *17*, 780 (1884).

38. Dice and Bowden, *J. Am. Chem. Soc.*, *71*, 3107 (1949).

39. Kirrman, *Bull. Soc. chim.*, (4), *41*, 318 (1927).

40. Gresham, Jansen, and Shaver, *J. Am. Chem. Soc.*, *70*, 998 (1948).

41. Conrad and Bischoff, *Ann.*, *204*, 168 (1880).

42. Merchant, Wickert, and Marvel, *J. Am. Chem. Soc.*, *49*, 1828 (1927).

43. Fittig and Messerschmidt, *Ann.*, *208*, 100 (1881).

44. Kharash, Engelmann, and Mayo, *J. Org. Chem.*, *2*, 288, (1937).

45. Lebedev and Skavronskaya, *J. Russ. Phys.-chim. Soc.*, *43*, 1124, (1912).

46. v. Braun and Lemke, *Ber.*, *55*, 3545 (1922).

47. Pariselle, *Ann. chim.*, *24*, (8), 317 (1911).

48. Roberts, Jeydel, and Armstrong, J. Am. Chem. Soc., 71, 3248 (1949).

49. Cason and Allen, J. Org. Chem., 14, 1036 (1949).

50. Demjanow and Dojarenko, Ber., 40, 2594 (1907).

51. v. Braun and Deutsch, Ber., 44, 3702 (1911).

52. Fuson and Kao, J. Am. Chem. Soc., 51, 1536 (1929).

53. Buchman et al., J. Am. Chem. Soc., 64, 2696 (1942).

54. Allen and Wilson, "Organic Syntheses," John Wiley and Sons, Inc., New York, N.Y., Vol. 26, 52 (1946).

55. McElvain, "The Characterization of Organic Compounds," The MacMillan Co., New York, N.Y., 1945, page 199.

56. Wohlgemuth, Compt. rend., 158, 1577 (1914).

57. McElvain, op. cit., page 185.

58. Ellis, "Organic Syntheses," John Wiley and Sons, Inc., New York, N.Y., Collective Vol. I, page 18 (1947).

59. I. G. Farbenindustrie, British Patent 510,638 (1939); Chem. Abstr., 34, 5093 (1939).

60. Farmer, J. Chem. Soc., 1929, 897.

Propositions

1. It should be possible to use the Hunsdiecker degradation to advantage in the synthesis of otherwise difficultly accessible ketones (through the disubstituted malonic acid), and neopentyl halides; it is the only good route to 1,1,1-tribromoalkanes, from which orthoesters, etc., can be readily made.

2. It is suggested that the Hunsdiecker reaction cannot be adequately explained by either the displacement mechanism suggested by Arcus, Campbell and Kenyon; or by the simple loss of carbon dioxide from a acyl hypobromite, with subsequent attack by Br^+ or $Br^\cdot$.

(1) Arcus, Campbell and Kenyon, Nature, 163 , 287 (1949).

3. A very interesting and unusual group of organic compounds ought to be made available by an extension of the Hunsdiecker degradation to reactions of silver alkylcarboxylates with compounds containing two radicals of the type of N_3, CN, NO, NO_2, SO, SO_2, SCl, SCN, NCO, Cl, Br, and I. The products from a given reaction may be predicted on the basis of the solubility in the reaction solvent of the silver salts formed, the electronegativity of the two groups, and the relative tendency of the radical involved to exist transiently as a positive ion.

4. Since it has been predicted that cyclobutadiene will be unstable in respect to its rearrangement products, it is proposed that the best routes for its preparation are those involving the mildest conditions. Removal of halogen from 1,2-dihalocyclobutene-3,

or from 1,2,3,4-tetrahalocyclobutanes by the action of zinc or magnesium, or by reaction with iodine, is suggested as a gentle method. The 1,2,3,4-tetrasubstituted cyclobutanes may be made from cyclooctatetraene(2 methods), diazoacetic acid, or even from truxillic acid.

(2) Wheland, J. Am. Chem. Soc., 63, 2025 (1941).

(3) Buchman, ibid., 64, 2701 (1942).

(4) Fiat **Final** Report 967 (1947).

(5) Owen and Simonsen, J. Chem. Soc., 1933, 1225.

(6) Buchner and Geronimus, Ber., 36, 3782 (1903).

5. It is now known that previous attempts to prepare cyclobutane-1,3-dicarboxylic acid were probably unsuccessful. It is proposed that it be synthesized by the reaction of 2,2-dibromomethyl-1,3-dihydroxypropane (readily available from pentaerythritol) with sodiomalonic ester, followed by oxidation of carbinol groups.

It is further proposed that the first product above, 1,1-dicarbethoxy-3,3-dimethylolcyclobutane, can also be used for the synthesis of polyspiranes by methods outlined in this thesis.

(7) Mooradian and Cloke, J. Am. Chem. Soc., 67, 942 (1945).

6. Cross-linking of acrylate polymers to give commercially usable rubbers is difficult to accomplish by conventional curing methods. It is suggested that this can be accomplished by the use of the appropriate acrylate ester in small amounts. Esters suggested are furfuryl, amino and glycolic acid. Addition of suitable

reagents upon milling (oxidants or acidic materials, a quaternary base, and zinc oxide, respectively), will cause cross-links to be established during curing.

(8) Mast and Fisher, Ind. and Eng. Chem., 40, 107-12 (1948).

7. 1-Methyl-3-aminoisoquinoline should be a compound well suited for diazo-copying use. Its synthesis can be readily accomplished, and because of several contributing factors it should show a considerable sensitivity towards light, with a good stability towards thermal and oxidative decomposition.

(9) Saunders, "The Aromatic Diazo-Compounds . . . ."
E. Arnold and Co., London., (1936), page 164 ff.

8. It is proposed that solid compounds containing uninegative rhenium might be obtained by the action of the alkali metals on rhenium metal or rhenium compounds in liquid ammonia.

(10) Lingane, J. Am. Chem. Soc., 64, 2182 (1942).

(11) Pauling, Chem. and Eng. News, 25, 2970 (1947).

9. Preliminary genetic studies involving the use of P^{32} indicate that its action cannot be wholly explained by ionizations caused by beta emissions, but may be due in part to transmutation of the phosphorous to sulfur. It is suggested that C^{14}, because of its low recoil velocity and bond-breaking power, may give greater information about this kind of mutagenic activity. It may be that new types of mutants involving substitution of nitrogen for carbon will be found, following ingestion of appropriate tracer compounds.

(12) Libby, J. Am. Chem. Soc., 69, 2523 (1947).

(13) Rubin, Genetics, 35, 133 (1950).

(14) King, Genetics, 35, 118 (1950).

10. While biochemical genetics has made many contributions to our understanding of metabolism and physiology, it now appears that the original appearance of one-to-one correlation in gene and enzyme action was in part an accidental result of the method by which the genes studies were selected. Possibly the results obtained in biochemical genetics have not brought us closer to a real understanding of the gene than have the methods of classical genetics.

11. It is suggested that the first year graduate curriculum at the California Institute should include advanced general courses in physical, inorganic and organic chemistry. These courses should cover extensively the more important aspects of the entire field, rather than intensively study a few particular aspects.