I. THE SYNTHESIS OF METHYLENECYCLOBUTANE FROM PENTAERYTHRITYL CHLORIDE

II. THE ATTEMPTED SYNTHESIS OF CYCLOBUTANONE

III. A REINVESTIGATION OF THE SYNTHESIS OF SPIROHEPTANEDICARBOXYLIC ACID

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ABSTRACT

I. THE SYNTHESIS OF METHYLENECYCLOBUTANE FROM PENTAERYTHRITYL CHLORIDE

A new method for preparing methylenecyclobutane is described in which the starting material is pentaerythrityl tetrachloride. Pentaerythrityl chloride is dechlorinated by zinc dust in the presence of sodium iodide and sodium carbonate, using as solvent either diethylene glycol or acetamide. Reasonable yields are obtained.

II. THE ATTEMPTED SYNTHESIS OF CYCLOBUTANONE

A synthesis of cyclobutanone through treatment of the methylenecyclobutane-nitrogen trioxide addition compound, with alcoholic potassium hydroxide is not successful.

The oxidation of methylenecyclobutane dibromide with potassium permanganate does not yield cyclobutanone.

III. A REINVESTIGATION OF THE SYNTHESIS OF SPIROHEPTANEDICARBOXYLIC ACID

An experiment is described in which two mols of malonic ester are condensed with one mol of pentaerythrityl chloride to form spiroheptanetetracarboxylic acid ester. The tetra acid is decarboxylated by heat to afford the dicarboxylic acid. The procedure is a modification of that described in the literature, whereby spiroheptanedicarboxylic acid is prepared from pentaerythrityl bromide.

A parallel experiment in which pentaerythrityl bromide is condensed with malonic ester is also described.

The yields are low in each case.

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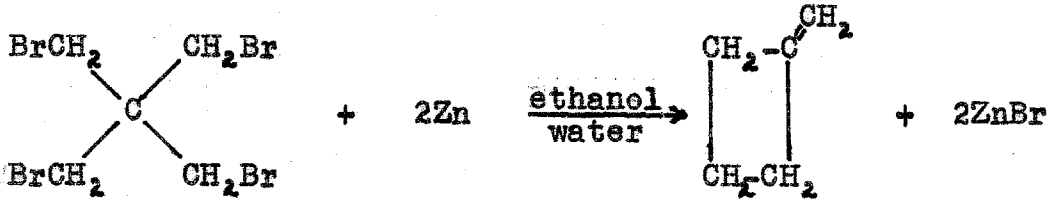
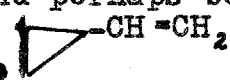
PART I

THE SYNTHESIS OF METHYLENECYCLOBUTANE FROM PENTAERYTHRITYL CHLORIDE

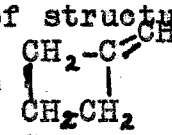
At the California Institute of Technology there is a broad research project in progress, under the direction of Dr. E. R. Buchman, which is directed toward an ultimate synthesis of cyclobutadiene. It was found advantageous to use methylenecyclobutane as a model for experiments involving four-membered ring compounds, since it is readily obtainable by the action of zinc dust on pentaerythrityl bromide, according to the reaction:



Methylenecyclobutane was first obtained by Gustavson (1) in 1896 by the action of zinc dust on pentaerythrityl bromide in 40-60% aqueous-alcoholic solution. The product consisted mainly of methylenecyclobutane,  ; however Gustavson first announced it as "vinyltrimethylene,"  sequent removal of hydriodic acid, it could be converted into "ethylidenetrimethylene,"  be 1-methylcyclobutene, ). He also formed a dibromide by addition of bromine, and an alcohol by addition of hydri-

odic acid and subsequent hydrolysis by warm water. Later Gustavson (2) announced that "vinyltrimethylene dibromide" was converted to cyclopentanone by the action of lead oxide (PbO_2) and water at 135°. He pointed out that the formula $CH_2-C=CH_2$ / CH_2-CH_2, methylenecyclobutane, would explain the reactions of his compound as well as, and perhaps better than the vinyltrimethylene formulation, 

Fecht (3), in 1907, proposed the spiropentane structure for Gustavson's hydrocarbon, basing his conclusion on the method of formation of the supposed spiropentane, and on the synthesis of an acid, α,α ethyleneglutaric acid, which he claimed was identical with an acid obtained from "vinyltrimethylene dibromide" through the dicyano derivative.

Demjanow (4), in 1908, prepared a new derivative of "vinyltrimethylene," a nitrosite, which gave succinic acid when oxidized with nitric acid, and on reduction with tin and hydrochloric acid gave a diamine, and also cyclobutanone, which was identified by comparison with cyclobutanone prepared by a method indicative of structure. On this evidence Demjanow favored the structure  . In 1913, Demjanow and Dojarenko (5) investigated Gustavson's alcohol from "vinyltrimethylene," finding that the iodide formed from it could be reduced with zinc and acetic acid to give a saturated hydrocarbon, which could also be obtained from "vinyltrimethylene" by reduction with hydrogen and platimum black. The physical constants of the alcohol indicated that it was 1-methylcyclobutanol-1, rather than a cyclopropane derivative.

Zelinsky (6), in 1913, stated that all the reactions of "vinyltrimethylene" could be explained on the basis of a spiropentane structure, and performed a catalytic reduction of "vinyltrimethylene" with hydrogen and nickel at low temperatures. It was completely reduced to gaseous hydrocarbons at 100°, therefore he concluded a four-membered ring was ruled out, as a cyclobutane ring would not be opened under these conditions. Further, with Krawetz (6), starting from pentaerythrityl, he synthesized a compound by stepwise ring closures, which he assumed was spiropentane. The physical constants of this compound, and its properties, agreed closely with those of Gustavson's "vinyltrimethylene." In experiments with selective catalytic reduction of his "spirocyclane," with Schtscherbak (6), he found it was reduced to "ethyltrimethylene" which has the same constants as the products obtained by Demjanow and Dojarenko (7), and by Philipow (8), in the reduction of "vinyltrimethylene."

Then Mereschkowski (9), in 1914, repeated the work of Fecht, finding that Fecht's results were unreliable; the acid which he synthesized was not α,α-ethyleneglutaric acid, but a combination of condensation products.

Philipow (10) stated in 1914 that "vinyltrimethylene" was a mixture of methylenecyclobutane, bp. 42°, and 1-methylcyclobutane, bp. 37.5°, in ratio of about 2 to 1, and that Gustavson's alcohol was 1-methylcyclobutanol-1. Because of difficulty in synthesizing the C_5H_8 compounds themselves, Philipow synthesized ethylcyclopropane and methylcyclobutane and compared them with the reduction product of "vinyltrimethy-

lene." He found it to be identical with methylcyclobutane. As further proof, he stated that the hydrogenated "vinyltrimethylene" was not isomerized by passage over Al_2O_3 at 326°, whereas a cyclopropane ring would be opened. He also found that the debromination of pentaerythrityl bromide carried out with small amounts of alcohol would give almost pure methylenecyclobutane, and further, that methylenecyclobutane could be isomerized to 1-methylcyclobutene by heating with zinc bromide in ethanol.

Faworski and Batalin (11), in the same year, came to the same conclusion when they oxidized "ethylidenetrimethylene," and obtained primarily laevulic acid. This indicated that "ethylidenetrimethylene" was 1-methylcyclobutene.

In 1916 Philipow (12) announced the results of oxidation studies on both of his C_5H_8 components, using as oxidizing agent potassium permanganate followed by chromic acid. The higher boiling fraction gave succinic, formic, acetic, and glutaric acids, with traces of oxalic acid and cyclobutanone. The formation of glutaric acid was explained as the result of isomerization of 1-formylcyclobutanol-1,  to 2-hydroxycyclopentanone,  which was then oxidized to glutaric acid. It has been previously noted that the four-ring could isomerize to a five-ring in the presence of acids. (13). The main reaction was the formation of succinic acid through cyclobutanone. The lower boiling fraction gave laevulic and succinic acids. Philipow also oxidized Gustavson's alcohol, obtaining formic, acetic, succinic, and malonic acids.

Then Demjanow and Dojarenko (13), (14) began work which led, in 1922, to the synthesis of methylenecyclobutane, itself, and the true vinyltrimethylene. Vinyltrimethylene was prepared by the Hoffmann degradation of an appropriate cyclopropane derivative, while methylenecyclobutane was prepared in low yield from the Hoffmann degradation of the quaternary base,  . This methylenecyclobutane was identical with Gustavson's hydrocarbon.

Ingold (15) then showed, by an oxidation which produced laevulic acid, that the C_5H_8 compound synthesized by Zelinsky was not spiropentane but principally 1-methylcyclobutene.

However, in spite of this evidence, in 1939, Rogowski (16) recalled the work of Fecht and Zelinsky and, basing his conclusion on electron diffraction studies, claimed that the Gustavson hydrocarbon was really spiropentane. His calculations showed C-C bond angles of 60°.

Bauer and Beach (17) repeated the work and found bond angles of 90°, supporting the four-ring structure. Also Shand, Schomaker and Fischer (18) verified the structure of methylenecyclobutane and 1-methylcyclobutene by electron diffraction studies. Their results agreed with those of Bauer and Beach and confirmed the structures of the two compounds as chemically established.

It is of interest to note that neither Whitmore and Williams (19), who prepared the methylenecyclobutane for the work of Bauer and Beach, nor Fischer (20), who prepared it for the California Institute group, found 1-methylcyclobu-

tene among the products. Whitmore and Williams prepared their product by debromination in 50% aqueous methanol solution, and found among the products only methylenecyclobutane and 2-methyl—1-butene. These were both identified by ozonolysis. Fischer, who carried out his hydrocarbon synthesis in aqueous ethanol (2:1), also reported that there was no constant boiling fraction at 37.5°, the boiling point of 1-methylcyclobutene. Nor is 1-methylcyclobutene reported by Murray and Stevenson (21), or Slabey (22), the most recent workers.

In 1944, Murray and Stevenson (21), (23) found that Raman spectra data indicated a component in the mixture resulting from debromination of pentaerythrityl bromide with zinc in the presence of methanol, which was not any known compound. They isolated some of this component, and after observing some chemical properties, together with their Raman spectra evidence, concluded it was spiropentane. The structure of spiropentane was independently confirmed by electron diffraction studies carried out by Donohue, Humphrey & Schomaker (24) at the California Institute.

Under the above conditions, Murray and Stevenson found three components in the reaction mixture: methylenecyclobutane, 2-methyl—1-butene, and the spiropentane, which occurred in very small yield. However, by using different conditions, namely acetamide as solvent, and sodium iodide and sodium carbonate as catalysts, according to the procedure of Hass and McBee (25), they obtained spiropentane as a major component, 40% of the total hydrocarbons. Methylene-

cyclobutane and 2-methyl—1-butene were also formed.

Slabey (22), in 1936, found that pentaerythrityl bromide could be debrominated with zinc in the presence of ethanol and water, in proportion of 3:1, if the Hass and McBee catalysts, sodium iodide and sodium carbonate, were present, giving a total hydrocarbon yield of 78-89%, of which 24-28% was spiropentane. Methylenecyclobutane was again the major component, with 2-methyl—1-butene, and a trace of 1,1-dimethylcyclopropane also present. He checked the work of Murray and Stevenson with the acetamide solvent reaction and found 47-60% of the total yield was spiropentane, while the total hydrocarbon yield was only 37-38%.

As previously stated, methylenecyclobutane was of interest to us as a readily available four-membered ring compound. However, because of the low cost of pentaerythrityl chloride as compared to the bromide, it was thought advisable to test the behavior of the chloride in a reaction with zinc dust analogous to the debromination of pentaerythrityl bromide.

$$C(CH_2Cl)_4 + 2Zn \longrightarrow \begin{matrix} CH_2 - CH_2 \\ | \quad\quad | \\ CH_2 - C \end{matrix} = CH_2 + ZnCl_2$$

Pentaerythrityl chloride was first prepared by Fecht (26), in 1907, by the action of hydrochloric acid on pentaerythritol. He obtained the tetrachloride only in small yield.

Orthner (27), in 1928, found that thionyl chloride with pentaerythritol gave a cyclic sulfite ester compound

obtained earlier by Bougault (28) with impure sulfur monochloride and pentaerythritol.

Govaert and Hansens (29), in 1940, reported that pentaerythrityl chloride could not be formed by the action of thionyl chloride on pentaerythritol in the presence of an organic base; that only the bi-sulfite ester compound would form. However, Mooradian and Cloke (30), in 1945, used thionyl chloride in the presence of pyridine and obtained a 76% yield of the tetrachloride. They purified it by reduced pressure distillation.

Pentaerythrityl tetrachloride was prepared by us with an average yield of 74% by the method of Mooradian and Cloke.

$$C(CH_2OH)_4 + SOCl_2 \longrightarrow C(CH_2Cl)_4 + SO_2 + HCl$$

The reaction goes smoothly and technical grade reactants are suitable. The products can be easily purified by reduced pressure distillation or by recrystallization from ethanol. The reduced pressure distillation was found to give a higher yield of purer pentaerythrityl chloride, and is therefore superior as a method of purification.

It was found that crude pentaerythrityl chloride can be dechlorinated with zinc without interference from the impurities. However, the presence of impurities, and especially water, was found to have a marked effect on the percentage composition of the resultant hydrocarbons.

The first attempt to prepare methylenecyclobutane from pentaerythrityl chloride was made according to the procedure for debrominating the bromo compound as developed by Fischer (20), using ethanol and water in a 1:2 ratio as the solvent. However, it was found that the reaction took place very slowly at the boiling point of ethanol, and after two hours at this temperature the major portion of the pentaerythrityl chloride could be recovered unchanged.

The next step was to try catalyzing the reaction with sodium iodide and sodium carbonate. The amounts of the catalysts were those suggested by the work of Hass and co-workers (25); the ethanol-water ratio was 3:1. The result was a slight improvement over that obtained from the uncatalyzed reaction mixture, but still too slow to be of practical value.

Since some olefin was evolved at the boiling point of ethanol, an investigation of the reaction at higher temperatures was considered worth while. The higher boiling solvent chosen was diethylene glycol. It was found that when heated to 140° the reaction proceeded spontaneously with evolution of considerable heat, however it is not as violent as the debromination of pentaerythrityl bromide in ethanol-water solution. The yield increased with the size of the run, presumably because of smaller mechanical losses. One mol of pentaerythrityl chloride gave crude hydrocarbons in a yield of 62%. Sixty-one per cent (61%) of the olefins boiled in the range 38.5°-41.5°, 22% from 30°-38.5°, of which nearly all boiled between 31° and 34°, with a very small

amount boiling below 30°. The remainder was a higher boiling material. Its constitution was not determined. The fraction boiling from 38.5°-41.5°, is presumably mostly methylenecyclobutane, and the lower boiling fraction, 2-methyl--1-butene. All of the materials remaining in the reaction flask at the end of the reaction were found to be soluble in water and hydrochloric acid, therefore there was no pentaerythrityl chloride unreacted. The overall yield of methylenecyclobutane based on pentaerythrityl chloride was 33%.

The method has two major disadvantages. One is the fact that the total hydrocarbon yield is not particularly high compared to the 85% obtainable from pentaerythrityl bromide; the other is the comparatively large amount of high boiling material left as a residue after fractionation. This residue constituted approximately 15% of the crude product.

In view of these difficulties, and the success which others had obtained using acetamide as a solvent in this type of reaction, it was suggested that acetamide might be more satisfactory than diethylene glycol. However, it was also realized that there was a strong possibility that spiropentane might be formed as a major component, since it was formed in the debromination of pentaerythrityl bromide in acetamide solution to the extent of 40-60% of the total hydrocarbons.

With dry molten acetamide at 180°, containing zinc

dust and sodium iodide and anhydrous sodium carbonate, it was found that purified pentaerythrityl chloride could be dechlorinated to give a mixture of hydrocarbons, 56% of the theoretical. The reaction would go at temperatures as low as 135°. Fractionation of the product, however, revealed a fraction, 56% of the total, boiling between 37° and 40°, mostly at 39.5°, which could not be separated with the fractionating apparatus available. The lower boiling fraction, bp. 28.5°-33°, constituted 23% of the total hydrocarbons, and an intermediate fraction, bp. 33°-37°, represented 6% of the total. The yield of products boiling above 37° was 31% based on pentaerythrityl chloride.

When the reaction was repeated using crude pentaerythrityl chloride which contained about 10% of water, it was found that the reaction took place spontaneously when heated to 130°, and would continue without further addition of heat at a temperature of 135°. The yield of hydrocarbons based on pure pentaerythrityl chloride was 62%. Tests on the reaction mixture revealed that all products were water soluble, hence the reaction had gone to completion.

Fractionation of the product revealed 49% in the boiling range 40.0°-40.5°, 21% from 37°-40°, 20% from 28°-37°, and 10% of higher boiling residue. The overall yield of the fraction 40.0°-40.5° based on pure pentaerythrityl chloride was 23%. The yield of materials boiling between 37.0° and 40.5° was 32%, based on pure pentaerythrityl chloride.

It appears that the presence of water and impurities results in the formation of more of the methylenecyclobutane, at least there was a large amount of material which boiled above 40°, which was not the case in the earlier experiment using dry acetamide and the purified tetrachloride.

The use of acetamide as the solvent also had disadvantages. While the high boiling residue was smaller, the acetamide was carried up through the apparatus by the gases liberated, where it condensed, clogging condensers and contaminating the product. When water was present there was further interference due to hydrolysis of the acetamide. The ammonia which was constantly evolving, together with the presence of acetamide in the condensers made it difficult to tell when the dechlorination of pentaerythrityl chloride was complete.

Because of this difficulty with acetamide, a liquid amide was tried. Formamide, it was thought, should not present such a problem. However, the only reaction which took place in this case was the hydrolysis of formamide itself. There was no evidence that the desired hydrocarbons had been formed.

Diphenyl ether had been used in zinc dust debrominations to form cyclopropane (25). Therefore, an experiment was run to see how it would serve in this reaction. The sodium iodide and sodium carbonate catalysts were used, however, no reaction took place, even at the boiling point of diphenyl ether, 249°.

Our results show a yield of methylenecyclobutane, boiling range 38.5°-41.5°, of 33% based on pure pentaerythrityl chloride, from the reaction of diethylene glycol, and 32% from the reaction in acetamide. This latter figure includes all hydrocarbons in the boiling range 37.0°-40.5°, It seems probable that there is a considerable percentage of spiropentane in this product, in view of the products obtained by Murray and Stevenson (21) and Slabey (22).

A reaction using unpurified, wet pentaerythrityl chloride and diethylene glycol was not tried. Possibly that would result in a higher percentage of methylenecyclobutane. Other workers have observed a difference in the composition of the products depending on the amount of water present in the reaction mixture (10).

Also, it appears that the catalysts, sodium iodide and sodium carbonate, favor the formation of spiropentane (20), (21). Since the catalysts gave little improvement in the rate of dechlorination of pentaerythrityl chloride in an ethanol-water solvent, it is a possibility that an uncatalyzed reaction would procede at higher temperatures just as well, and might result in a product containing a greater percentage of methylenecyclobutane.

At present, while the chloro compound yields a little more than half as much methylenecyclobutane from a given amount of pentaerythritol as the brom compound, the cost of converting a given amount of pentaerythritol into methylenecyclobutane via the bromide is more than twice as much. Furthermore, the reaction using pentaerythrityl chloride is

much more easily controlled and much less dangerous, with either diethylene glycol or acetamide, than the ethanol-water and zinc debromination of pentaerythrityl bromide.

Experimental

Preparation of Pentaerythrityl Chloride

To 362g. (2.66 mols) of pentaerythritol (Heyden Pentek) in a 3 liter 3 necked round bottomed flask equipped with a 250 cc. dropping funnel, a water cooled Allihn condenser, and a glass stirrer, was added 842g. (10.7 mols) of pyridine (Barrett's refined). The mixture was cooled in an ice bath, then technical thionyl chloride (Hooker's 95%) was added dropwise, with stirring, at a rate slow enough that the white fumes which formed did not rise in the condenser. The speed of addition was gradually increased, until three-fourths of the thionyl chloride had been added, after which time the remainder could be run in rapidly. 1278g. (10.7 mols) thionyl chloride was added.

When the addition of thionyl chloride was complete (addition time one and one-half hours) the ice bath was replaced with an oil bath and the temperature was raised to the boiling point of thionyl chloride. The bath temperature was gradually increased to 180° over a two-hour period, during which time large quantities of sulfur dioxide were evolved. The pentaerythrityl chloride was carried up into the condenser and had to be pushed out from time to time to prevent clogging the condenser. After two and one-half hours of

heating the sulfur dioxide had been removed from the reaction mixture, whereupon the reaction mixture was allowed to cool.

The cooled reaction mixture, at this point a solid dark cake, was removed from the flask by melting, and was poured into 6 liters of cold water with vigorous stirring. The product separated immediately as a crystalline solid. The water layer, dark red in color, was decanted and the product washed with warm water until the washings were clear. About 30 liters of warm water was necessary. The product was then filtered with suction on an 11" Buchner funnel and air dried. At this point it was a dirty white solid consisting of flaky crystals.

The partially dried product was separated in two equal parts, I and II. Part I was purified by recrystallization from 600 cc. of 95% ethanol. Two crops of crystals were obtained, light tan in color. The yield based on pentaerythritol was 69%. Part II was purified by reduced pressure distillation in a 500 cc. Claissen flask attached through an air condenser to a 500 cc. round bottomed flask, in turn attached to the vacuum line. The product distilled at 100.5° at 13 mm. pressure, and condensed in the receiver as a snow white solid. Yield based on pentaerythritol, 71%.

Preparation of Methylenecyclobutane in Diethylene Glycol Solvent

The apparatus for dechlorination consisted of a 2

liter 3 necked round bottomed flask fitted with a thermometer, a mercury-seal, variac controlled stirrer, and a 20 mm. column, 4 ft. long, topped by a downward ice-water cooled condenser; leading to a spiral downward condenser, also ice-water cooled, which led to a 125 cc. Erlenmeyer flask in a dry ice-acetone bath. The ice water was circulated by a centrifugal pump. The stirring rod was iron, as glass is not strong enough to stir the zinc dust slush.

In the 2 liter flask was placed an intimate mixture of 105 g. (one-half mol) of pentaerythrityl chloride purified by reduced pressure distillation, 131 g. (2 mols) of zinc dust (Braun), 106 g. (1 mol) of anhydrous sodium carbonate (Baker's analyzed), and 25 g. (one-sixth mol) of sodium iodide (Baker's analyzed). To this was added 200 cc. of diethylene glycol (Mefford's).

The reaction mixture was warmed by means of a Glascol heater, with stirring, to 135°, when a slight frothing was noted. The heating was discontinued and the reaction was allowed to run until the temperature began to fall-about five minutes later. The mixture was again heated until the reaction just began, then allowed to proceed spontaneously, until the temperature began to fall. Proceeding in this way the temperature was gradually raised to 220°, then heating was discontinued, since no more distillate could be seen passing through the condensers, and the reaction mixture was no longer evolving gases. The reaction time was two and one-half hours, however the reaction was virtually

complete at the end of one hour, with the temperature at 180°.

The reaction can be very nicely controlled through cautious heating, but if the reaction mixture is heated initially to a temperature as high as 150° it becomes very violent, and the temperature will immediately rise well above 200°. To prevent this a pan of water was kept available to substitute for the Glascol heater if the reaction should become too violent.

Investigation of the residue in the reaction flask showed that it was all soluble in hydrochloric acid and water, therefore no pentaerythrityl chloride remained unreacted.

The crude product was washed with 100 cc. of ice water and dried over calcium chloride. The washed and dried product weighed 19.7 g., yield 58% of the theoretical.

Fractionation of Crude Hydrocarbons:

The above mentioned 20 g.were fractionated together with 40 g. obtained by the same process (yield--62%).

The apparatus consisted of a 100 cc. boiling flask fitted with a 3 foot 20 mm. helice packed, asbestos wrapped fractionating column, topped by an air-cooled upright condenser 4" long, carrying a thermometer at the top and with a side arm condenser leading downward to a spiral downward condenser, leading in turn to a 125 cc. Erlenmeyer flask in an acetone-dry ice bath. The boiling flask was warmed in a dibutyl phthalate bath. A stream of air was

passed through the air condenser to maintain a rate of distillation of 6 drops refluxed to 1 drop distilled, except when the temperature of the vapors was not changing, when a faster distillation was permitted.

The fractionation gave 15.0 g. boiling from 30.0-38.5°, and 25.5 g. boiling from 38.5-40.7°. A residue of 14.5 g. remained. This fractionation apparatus had a large holdup, and a subsequent refractionation of the residue indicated it still contained approximately 5.5 g. of methylenecyclobutane bp. 39.0-41.5°. Also, since the fractionating column next described proved more efficient than the one used here, the lower boiling component was refractionated through that column giving an additional 3 g. of material in the boiling range of the higher boiling fraction. Thus the higher boiling fraction constitutes approximately 61% of the total product.

Preparation of Methylenecyclobutane in the Presence of Acetamide

The apparatus for dechlorination was the same as the one previously described. The same quantities and the same grades of zinc dust, sodium iodide, and sodium carbonate were used. The pentaerythrityl chloride was the crude product, direct from the reaction mixture, washed with large amounts of water, but not further refined. It contained 8% of water. One hundred five (105) g. of crude pentaerythrityl chloride (.42 mol of pure C $(CH_2Cl)_4$) was used, and 250 g. technical acetamide (Paragon practical) was added. The

reaction flask was warmed to 130°, where hydrocarbons began to evolve, after which the reaction was maintained by cautious heating. The temperature was gradually raised to 170° in the course of one hour, after which no more distillate was condensing, however frothing in the reaction flask was still apparent. The odor of ammonia was noted issuing from the receiver. Acetamide was being carried up into the condensers. The reaction flask was allowed to cool after an additional hour at 165°.

The crude product contained crystals of ice and acetamide, which were removed by washing with cold water. The products were then dried with calcium chloride and weighed. The yield was 17.8 g., 62% of theory based on pure pentaerythrityl chloride.

Fractionation of the Product

The fractionating apparatus consisted of a 25 ml. boiling flask carrying a 4½ foot fractionating column which contained a wire spiral inside a vacuum jacket. This was topped by a total reflux, variable takeoff head. The receiver was a 20 ml. graduated centrifuge tube in ice water. Vapors which did not condense were caught in a dry ice trap. The boiling flask was heated on a dibutyl phthalate bath.

The total product from the above reaction was fractionated. The first fraction boiled from 27.8 to 37.0°, weight 2.6 g. The second fraction boiled from 37.0 to 40.0°, weight 2.7 g. The third fraction boiled from 40.0 to 40.5°, weight 6.5 g. There was a residue of 1.4 g. The higher

boiling volatile fraction was 49% of the total hydrocarbons. The two higher boiling fractions constituted 70% of the total hydrocarbons.

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PART II

THE ATTEMPTED SYNTHESIS OF CYCLOBUTANONE

Cyclobutanone was first prepared by Kishner (1) in 1904, by the action of bromine and alkali on 1-bromocyclobutane-carboxamide. Some 1,1-dibromocyclobutane was also formed in the reaction and this was converted into cyclobutanone by heating with lead oxide (PbO_2) and water (2).

Demjanow (3) reduced the nitrosite of methylenecyclobutane with tin and hydrochloric acid, and obtained cyclobutanone along with the diamine. Demjanow and Dojarenko (4) also obtained a small amount of cyclobutanone by chromic acid oxidation of cyclobutanol.

Philipow (5) obtained a small amount of cyclobutanone from the oxidation of methylenecyclobutane with permanganate, followed by chromic acid.

Curtius (6) found, in 1917, that the diazide of tetramethylene-1,1-dicarboxylic acid would give cyclobutanone if boiled with absolute alcohol.

Demjanow and Dojarenko (7) found that 1-bromocyclobutane-carboxamide could be converted by heating with potassium carbonate to the 1-hydroxy acid and its anhydrides, which could be further converted by heat to cyclobutanone in 15% yield. Damjanow (8) also obtained some cyclobutanone

by the electrolysis of cyclobutane carboxylic acid. In later work, on the oxidation of cyclobutyl amines, he found, with Shuikina (9), that cyclobutylamine would give 18.7 and 25% yields of cyclobutanone, on catalytic oxidation with copper and with osmium oxide, respectively. With Telnov (10), he found that aminocyclobutane-1-carboxylic acid, when oxidized with sodium hypochlorite, gave yields up to 75% of cyclobutanone.

The most convenient preparation of cyclobutanone at present is that discovered by Lipp (11), in which ketene is passed into diazomethane at room temperature. Nitrogen is evolved, and the main product is cyclobutanone.

Buchman, Riems, and Schlatter (12) identified cyclobutanone among the products resulting from the Hoffmann degradation of the quaternary base derived from trans-1,2-diaminocyclobutane.

Derfer, Greenlee, and Boord (13) reported that ethylidenecyclobutane on ozonolysis gave acetic acid and probably cyclobutanone. The ethylidenecyclobutane was obtained by zinc dust debromination of ethyl-tri-(bromomethyl)-methane in acetamide solution.

The above references indicate the work which has been done on the preparation of cyclobutanone, and reactions whereby more or less cyclobutanone is formed.

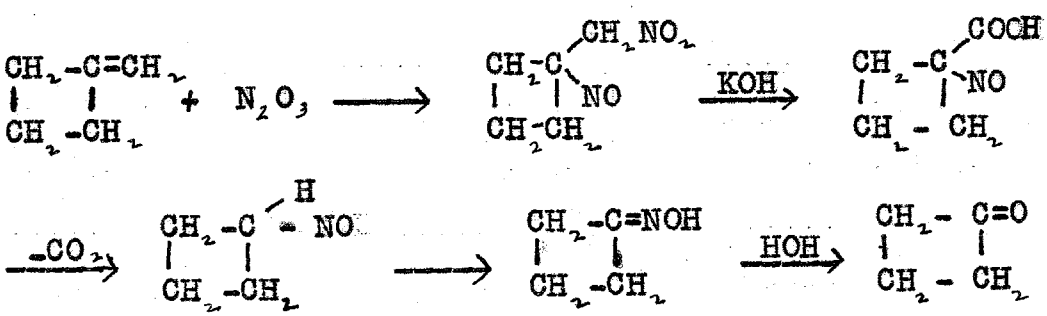
It was of interest in connection with the general research program at the California Institute on four-membered ring compounds to see if cyclobutanone could be obtained in

good yield from methylenecyclobutane or its derivatives.

Oxidation of a methylene side chain to give a cyclic ketone has been described in the literature. Camphenilone was prepared in this way from camphene by Jagelki (14), in 1889. Camphene in ligroin was treated with nitrous acid fumes, and the resulting materials, a green oil, and a crystalline material, were converted into camphenilone by the action of either permanganate or potassium hydroxide. Aschan (15) and Lipp (16) both reported the preparation of camphenilone from camphene by reactions in which the nitrosite was an intermediate. Blaise and Blanc (17) treated camphene with nitrogen dioxide and heated the entire reaction mixture with 30% potassium hydroxide to obtain camphenilone.

As stated above, the nitrosite of methylenecyclobutane has been prepared by Demjanow (3). The olefin was treated with the nitrogen oxide fumes from arsenious acid and nitric acid. Some cyclobutanone was formed on reduction of the product. It seemed possible that this nitrosite might behave like that of camphene, in which case, cyclobutanone should form when the nitrosite was heated with potassium hydroxide.

A possible course for the reaction is that given below:



Accordingly, an attempt was made to form cyclobutanone by a reaction through the nitronitroso compound (nitrosite) according to the procedure which Jagelki used to obtain camphenilone.

Methylenecyclobutane was dissolved in ligroin as an upper layer over a saturated solution of aqueous sodium nitrite. The mixture was cooled in an ice bath, and glacial acetic acid was added dropwise. As the fumes of nitrous acid passed through the upper layer it gradually became blue green in color, and a crystalline material formed slowly. After three days, the water and ligroin layers were separated, and the products in the organic layer, a green oil and crystalline material, were refluxed with aqueous alcoholic potassium hydroxide. The products were then steam distilled and the distillate tested with semicarbazide hydrochloride and sodium acetate for the presence of carbonyl compounds. No semicarbazone was formed.

Another reaction which was of interest in this connection was the oxidation of methylenecyclobutane dibromide. This substance is known to decolorize permanganate readily (18). The dibromide was first prepared by Gustavson (19), who observed that it was converted to cyclopentanone when heated with lead oxide and water. Demjanow and Dojarenko (7) found that methylenecyclobutane dibromide would give cyclopentanone in boiling water, or on long standing with water. Under the proper conditions, however, cyclobutanone might be formed according to a reaction similar to the following:

+ $2MnO_2$ + H_2O

The effect of permanganate on methylenecyclobutane dibromide was examined: 0.8 cc. of dibromide was dissolved in glacial acetic acid and treated with aqueous 2% potassium permanganate. When the color of permanganate was no longer discharged the acetic acid was neutralized with aqueous sodium hydroxide and the basic solution was distilled. The distillate was tested as before for the presence of carbonyl compounds.

In the first experiment of this type a trace of semicarbazone was formed. The yield was about 5 mg. from 2 g. of dibromide. The semicarbazone was recrystallized from water and dried, melting point 199.3-201.2° with decomposition.

Other similar experiments were run varying the temperature and concentration of permanganate. The reaction was also tried in alkaline medium, and with no solvent. However, we were unable to obtain any increase in the yield and in most cases no semicarbazone was formed at all.

Presumably the condition of the oxidation are too vigorous to allow formation of cyclobutanone as a final product. In view of the work of Gustavson (19) and Demjanow (7), it is probable the semicarbazone obtained was that of cyclopentanone. The melting point of cyclopentanone semicarbazone is 205°, that of cyclobutanone semicarbazone 212°.

The action of permanganate on methylenecyclobutane itself in glacial acetic acid was also tested. The reaction was carried out at room temperature with both the olefin and the permanganate dissolved in glacial acetic acid. A distillable carbonyl compound was formed, again in very small yield, which was detected as semicarbazone. In view of the work of Philipow (5), this may be the semicarbazone of cyclobutanone.

Experimental

Preparation of Methylenecyclubutane Nitrosite and Its Reaction with Potassium Hydroxide

Eighty-three (83) g. (1.2 mols) of sodium nitrite dissolved in 130 cc. of water was mixed with a solution of 13.3 g. (0.2 mol) of methylenecyclobutane in 60 cc. of ligroin (60-70) at 1°. The mixture was kept in an ice bath while 72 grams (1.2 mols) of glacial acetic acid was added dropwise with stirring. As the addition progressed and bubbles of nitrogen trioxide passed through the upper layer its color changed to a bright green. After one and one-half hours the addition was complete, and the ligroin layer was bright green while the phase interface was fuzzy in appearance.

Since the odor of methylenecyclobutane was still strong in the reaction flask, the mixture was stoppered and placed in the cold room at a temperature of 4° for three days. At the end of this time the ligroin layer was only a

pale green, and a large amount of white crystals had collected at the interface.

The phases were separated, the crystalline material remaining with the water phase. The ligroin was removed by evaporation on a steam bath leaving about 1 cc. of a green oil, which was immiscible with and lighter than water. The water was drained from the crystalline material, which was then dissolved in hot alcohol to remove it from the separatory funnel, whereupon it changed in color to a deep bright green.

The green oil and the green alcoholic solution were placed in a 1 liter flask and refluxed with an aqueous solution of 10% potassium hydroxide.

After two and one-half hours, during which time the mixture became dark brown in color, the reaction mixture was allowed to distill, and three 5 cc. portions of distillate which came over first were tested with semicarbazide hydrochloride and sodium acetate for the presence of carbonyl compounds. The distillate was boiled in the presence of semicarbazide to remove alcohol and allow separation of the semicarbazone on cooling. No crystals were formed.

Oxidation of Methylenecyclobutane Dibromide with Potassium Permanganate

0.8 cc. (1.45 g.) of methylenecyclobutane dibromide (furnished by Dr. D. R. Howton) was placed in a centrifuge tube and dissolved in 6 cc. of glacial acetic acid. 2% potassium permanganate was then added in small portions,

which was rapidly decolorized. When 6 cc. of permanganate had been added the dibromide had separated from solution; therefore the aqueous solution was poured off, the dibromide redissolved in glacial acetic, and treated with more potassium permanganate. In this way about 20 cc. of permanganate was added, until no more was decolorized. The solution was allowed to stand with a slight excess of permanganate present for two hours.

The solution was made basic with sodium hydroxide, with cooling, and transferred to a 1 liter round bottomed flask fitted with a still head. The basic solution was then boiled to steam distill any cyclobutanone. The first 15 cc. of distillate was collected in 5 cc. portions, each of which was tested with semicarbazide hydrochloride and sodium acetate for the presence of carbonyl compounds. The first 5 cc. fraction contained some heavy oil which did not react with semicarbazide, however the aqueous phase gave some colorless crystals immediately upon treating with semicarbazide hydrochloride and sodium acetate. The formation of semicarbazone was also prompt in the second 5 cc. fraction, while the third gave no semicarbazone.

The semicarbazone was recrystallized once from ethanol water solution and dried - mp. 196-203°. It was recrystallized three times from water - mps. 190-196°, 199.5-200.5°, and 199.3-201.2° corrected. The yield of semicarbazone was about 5 to 10 mg.

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PART III

A REINVESTIGATION OF THE SYNTHESIS OF SPIROHEPTANEDICARBOXYLIC ACID

A compound, isolated from the products of the action of zinc on pentaerythrityl bromide (1), (2), has proved to be the simplest spirocyclic compound (1), (2), (3), spiropentane. It is presumed that this hydrocarbon will be further studied for the purpose of shedding additional light on the relationship of structure to certain physical and chemical properties. For example, data from a determination of the heat of combustion would serve to indicate the amount of strain in the spiropentane molecule.

Furthermore, it should be interesting to prepare the next member of the spirocyclic series, spiroheptane, which is still unknown; to study its properties, and to correlate these with the findings on the other members of the series.

Spiroheptanedicarboxylic acid may be considered the logical starting point of any projected synthesis of spiroheptane. The acid, a known compound, has already served as the starting material for various other spiroheptane derivatives, such as the 2,6-diamine (4), (5), the 2,6-dibromoacid (6), the 2,6-diphenylmethylene derivative (7), and others (7). It is presumed therefore that it can be made available in the desired amounts. Furthermore it is conceivable that the

acid could be decarboxylated to the parent hydrocarbon, for instance, by reactions similar to those which have been utilized to prepare adamantane from adamantanedicarboxylic acid.*

Spiroheptanedicarboxylic acid was first prepared by Fecht (9), through the reaction of pentaerythrityl bromide with sodio malonic ester. Essentially the same reaction was developed by Backer and Schurink (10) to yield 80% of the theoretical. This improved procedure was used by Janson and Pope (4), (5) in preparing their spiroheptanedicarboxylic acid, and also by Lowry and Baldwin (6).

Fecht (9) also tried the reaction with pentaerythrityl iodide and chloride. He reported that the iodide was "no better" than the bromide, and that the chloride did not react.

We ran parallel reactions using equimolar amounts of pentaerythrityl chloride and bromide. The procedure was essentially that of Backer and Schurink (10), with certain alterations calculated to save time.

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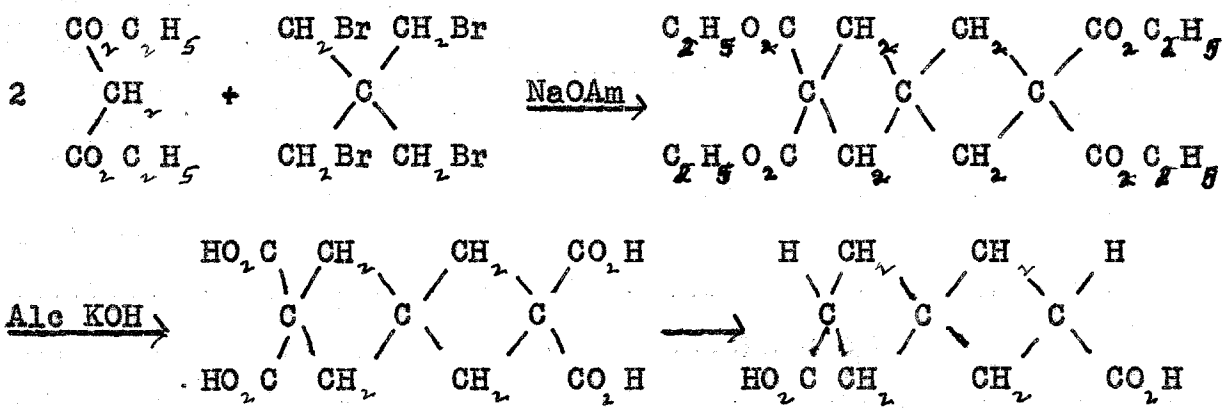
*Prelog and Seiwerth (8) were able to convert adamantanedicarboxylic acid to adamantane by three different paths: Direct decarboxylation gave, as might be expected, only small yields of hydrocarbon. The acid amide, via the Hoffmann reaction with sodium hypobromite and subsequent benzoylation, gave the dibenzoylamino compound, which with phosphorus pentabromide according to Von Braun yielded dibromoadamantane. Catalytic reduction with Raney nickel in the presence of alkali converted the latter to adamantane. In a third synthesis, the above mentioned dibromide was obtained through the action of bromine on the silver salt of adamantanedicarboxylic acid.

The reaction was the following:



Sodium was dissolved in pure amyl alcohol and malonic ester, and the bromide, or chloride, was added. The ethanol which forms was distilled off, and an equal volume of pure amyl alcohol was added. The reaction was allowed to run at the reflux temperature, 134°, for forty-seven hours in the case of pentaerythrityl bromide, and one hundred and sixteen hours in the case of the chloride.

At the end of this period, the ester from the tetrabromide experiment was saponified by alcoholic potassium hydroxide, and the product acidified to precipitate the acid. The mixture was next evaporated to dryness and extracted with glacial acetic acid; finally the acetic acid soluble portion was decarboxylated by heat. The resultant dark mass was extracted with ether in a continuous extraction apparatus. The ether extractable material thus separated was crystallized from ethyl acetate, with a final recrystallization from water. Its melting point was 209.5-210.4°, in accordance with that reported by Backer and Schurink. The yield was low.

The reaction using the chloride was worked up in the same manner. After the saponification, as the last traces of

alcohol were being removed with steam, it was found that unreacted pentaerythrityl chloride came over with the steam. The acidification of the organic acid salts gave a large amount of a viscous oily component. After the decarboxylation and continuous extraction with ether, it was found that the ether layer contained only a very small amount of spiroheptanedicarboxylic acid.

Experimental

Two hundred and fifty milliliters of amyl alcohol, bp. 134-136°, which had been purified by distillation over sodium, and 11.5 g. (0.5 mol) of sodium were placed in a 3 liter 3 necked flask. To this was added 80 g. (0.5 mol) of malonic ester, and 21 g. (0.1 mol) of distilled pentaerythrityl chloride. The mixture was brought to the boiling point of amyl alcohol, by distilling off all material which boiled below 134°. A volume of purified amyl alcohol equal to that distilled off was added, and the whole was refluxed for one hundred and sixteen hours. The reflux condenser was topped by a calcium chloride-soda lime drying tube to prevent decomposition of the sodiomalonic ester by water or carbon dioxide.

After the period of refluxing, the reflux condenser was exchanged for a takeoff condenser and most of the alcohol was distilled off. Seven hundred fifty milliliters of ethanol containing 90 g. of potassium hydroxide was then added and the whole was refluxed twenty-four hours to saponify the ester and produce the tetracarboxylic acid salt. At the

end of this period the ethanol and the remaining amyl alcohol were distilled off; the last traces being removed by addition of 200 ml. of water and steam distillation. At this point it was noted that unreacted pentaerythrityl chloride was coming over into the distillate. Altogether about 10 g. of pentaerythrityl chloride was recovered. When no more organic distillable material remained in the flask, the solution was transferred to a 6" evaporating dish, acidified with concentrated hydrochloric acid, whereupon the organic acid and the inorganic salts precipitated. At this point about 10 cc. of a black oil separated on top of the aqueous phase. The odor of the mixture was very strong and goatlike.

The acid mixture was evaporated to dryness on a steam cone. The dried acids and inorganic salts were then extracted with 600 cc. of hot glacial acetic acid, in several successive extractions. The acetic acid was distilled off, the last traces being removed at 125° under reduced pressure. When all of the acetic acid had been removed, the temperature was raised by means of an oil bath to 225° to decarboxylate the tetracarboxylic acid. At a temperature of 205° some oil began to distill from the mixture. The acid was held at 225° for fifteen minutes, then allowed to cool. The residue in the flask was a mass of solid, charred material.

Two hundred milliliters of water was then added to the flask, and the mixture was brought to a boil. The phase of dark oil over the water layer was separated at this point. The aqueous phase was boiled with a small amount of charcoal

(Nuchar), and filtered. The filtrate retained an appreciable amount of color, so it was boiled again with more Nuchar. The color was still not completely removed.

The aqueous phase was then concentrated and chilled to precipitate the acid. This was without result. The solution was then evaporated to dryness and the solid material, which was mostly inorganic salts, was extracted continuously with ether for four days. At the end of this period the ether was dried with anhydrous sodium sulfate and distilled off. The product, about 0.1 g. was recrystallized from alcohol, then ethyl acetate, and finally from water. The melting point of the product was 205.2-210.0° corrected.

The workup of the product from the reaction of malonic ester and pentaerythrityl bromide was the same as the one described above. The reaction time was forty-seven hours, however the yield, less than one gram, indicated that the reaction had not gone to completion.

A few experiments on the oily component mentioned above indicate that it is acid in nature. It is miscible with sodium hydroxide, and separates again on acidification. The oil is lighter than water; presumably its chlorine content is not high. It was not further investigated.

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