I. DERIVATIVES OF SPIRO(3,3)HEPTANETETRACARBOXYLIC ACID

II. ATTEMPTED NEW SYNTHESIS OF CIS-2-BUTENE-1,4-DIOL

Thesis by

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Emmett P. Monroe
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ABSTRACT

I. DERIVATIVES OF SPIRO(3,3)HEPTANETETRACARBOXYLIC ACID

The isolation of the isoamyl ester of spiroheptanetetracarboxylic acid, prepared by the condensation of sodiomalonic ester with pentaerythrityl tetrabromide in isoamyl alcohol is reported. The synthetic method is that of Fecht as modified by Backer and Schurink. Pentaerythrityl benzenesulfonate is substituted for the bromide in the reaction with the malonic ester, but the yield is found to be much poorer. Attempts to prepare the ethyl ester of spiroheptanetetracarboxylic acid by using pentaerythrityl benzenesulfonate in ethyl alcohol solvent, and pentaerythrityl bromide in excess malonate and xylene solvents are described. These experiments did not produce a practical synthesis of the ethyl ester.

The unsuccessful attempt to reduce the isoamyl ester of spiroheptanetetracarboxylic acid with lithium aluminum hydride is described.

II. ATTEMPTED NEW SYNTHESIS OF CIS-2-BUTENE-1,4-DIOL

A synthesis of cis-2-butene-1,4-diol by the reduction of maleic anhydride with lithium aluminum hydride is attempted. Two experiments are described, one of which employs an aqueous system in the isolation of the product, the other a non-aqueous system. No amount of any consequence of the diol was obtained. A discussion of lithium aluminum hydride as a reducing agent is included.

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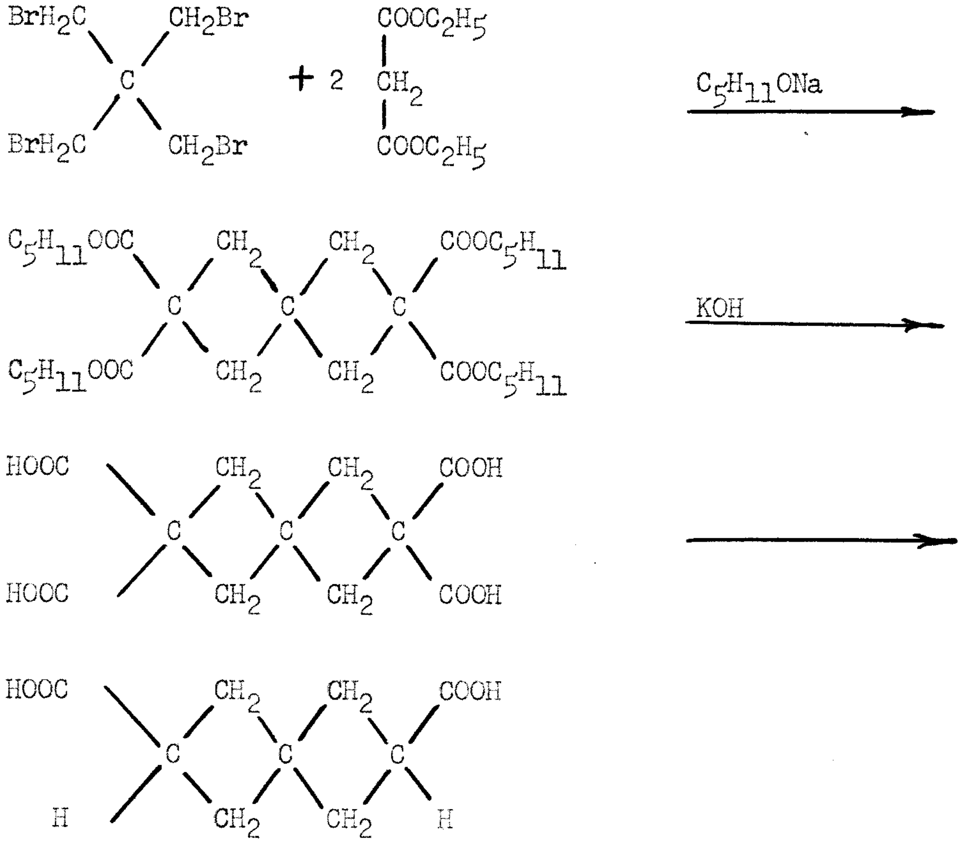
PART I

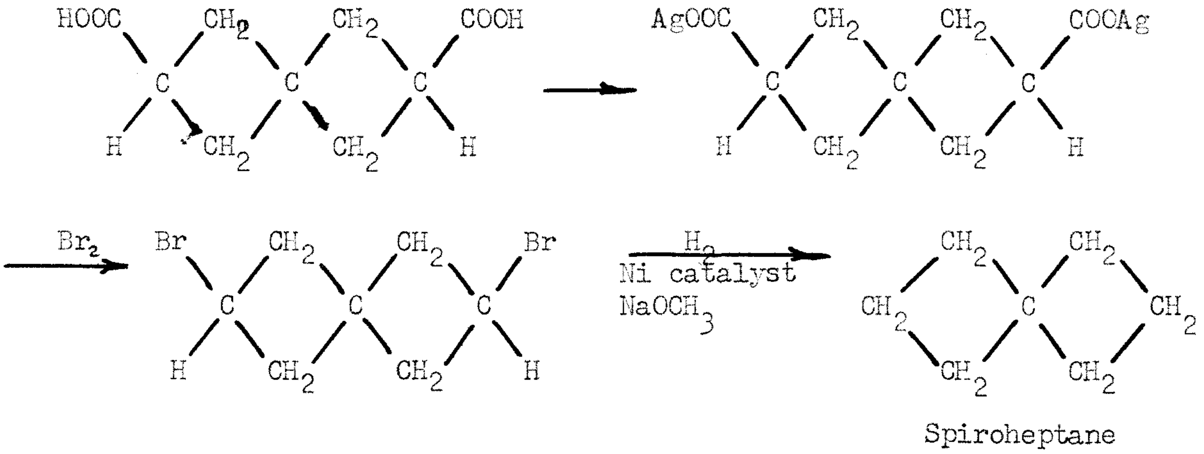
DERIVATIVES OF SPIRO(3,3)HEPTANETETRACARBOXYLIC ACID

The synthesis of compounds of the type containing the spiroheptane nucleus was first accomplished in 1907 by Fecht (1) who reported the condensation of two equivalents of sodiomalonic ester with one of pentaerythrityl tetrabromide. The product of this reaction, presumably the ester of spiroheptanetetracarboxylic acid, was soaponified with potassium hydroxide solution at room temperature yielding a mixture of the dicarboxylic acid and the unstable tetracarboxylic acid. When heated to 200°-220°, the tetracarboxylic acid was decarboxylated to the diacid which had a melting point of 210°. The yield of the dicarboxylic acid obtained by this method was 15 to 20% of the theoretical amount. Pentaerythrityl iodide and pentaerythrityl chloride were also tried in this type of reaction and it was found that the reaction involving the iodide gave no better result than that with the bromide, and no product at all was obtained when the chloride was used.

Some modifications in procedure were made by Backer and Schurink (2) which enabled them to realize a yield of up to 80% of the spiroheptanedicarboxylic acid. These revisions were: The monosodium derivative of malonic ester was used instead of the disodium derivative that Fecht used; the ethyl ester of malonic acid was used rather than the methyl ester. Isoamyl alcohol was used as solvent; in the system ethyl malonate-amyl alcohol, a replacement occurs which results in the production of amylmalonate and ethyl alcohol; the ethyl alcohol is then distilled off and the reaction takes place at the boiling point of amyl alcohol. The Dutch authors found that the reaction using pentaerythrityl iodide was not as efficient as that with the bromide. Both the dicarboxylic acid and tetracarboxylic acid were isolated; the respective melting points were given as 212°, and 219° with decomposition. The experimental procedure used in this thesis for carrying out the reaction of pentaerythrityl tetrabromide with malonic ester is that of Backer and Schurink.



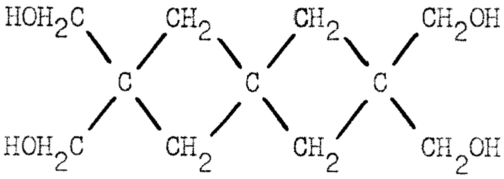
Several compounds with the spiroheptane nucleus have been prepared through spiroheptanedicarboxylic acid, such as the diamine (3,4), the dibromacid (5), the diethyl ester (6), and the parent hydrocarbon, spiroheptane (7). The synthesis of spiroheptane proceeded as follows:



Spiroheptane

The experiments that are described in Part I of this thesis were undertaken to study the preparation and isolation of the ester that results from the malonic ester condensation as described above. The pure spiroheptanetetracarboxylic acid ester has not been isolated before as such, and it was thought that it would be of interest to do so as well as study some other possible reactions, similar in nature, that might result in homologous esters. This was carried out as a part of the broader program of research that is being carried on in this laboratory under the leadership of Dr. E. R. Buchman and which is directed toward the study of syntheses of compounds containing four-carbon rings, particularly those of the spirane type. These present investigations might provide new intermediates of interest for further synthetic operations, might aid in the future syntheses of related compounds, and finally a contribution might be made through the determination of physical constants of the compounds involved.

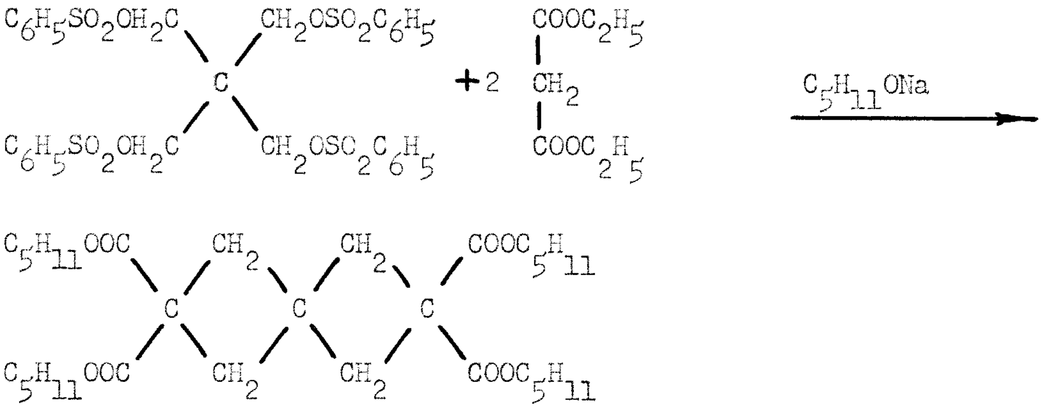
The availability of spiroheptanetetracarboxylic acid ester opens up possible routes to polyspirane types in which the cyclobutane ring is repeated, not twice as in the spiroheptanes, but many times. Pentaerythritol may be converted to the tetrabromide, which may be condensed to yield spiroheptanetetracarboxylic acid ester as indicated above. If this product could then be reduced to the corresponding compound with four hydroxyl groups,



then a compound would have been reached which is homologous to the starting material, pentaerythritol, but with the spiroheptane nucleus having been built up, which theoretically permits the passing on to new, more complex spirane systems through a repetition of the operations carried out with pentaerythritol. The last experiment of Part I, treatment of the tetracarboxylic acid ester with lithium aluminum hydride, is an attempt at a start along these lines.

The malonic ester synthesis used to obtain the isoamyl ester of spiroheptanetetracarboxylic acid was carried out using isoamyl alcohol as a solvent. The amount of sodium required for the monosodium derivative of malonic ester was dissolved in an excess of isoamyl alcohol; diethyl malonate was then added, the mixture refluxed for an hour, and pentaerythrityl tetrabromide introduced. Ethyl alcohol which formed by replacement by the amyl alcohol solvent of the ethyl rest in the malonic ester was distilled off until the reflux temperature of isoamyl alcohol was reached. The mixture was then refluxed for 46 hours. The ester was recovered by taking off most of the isoamyl alcohol solvent, neutralizing with hydrochloric acid and distilling out the ester at reduced pressure. The ester is a light yellow, viscous oil boiling at 226°-228° at about one millimeter pressure. It is apparently a stable molecule as there was relatively little decomposition at the high temperatures necessary for the distillation. There was evidence of some decomposition taking place, however, but it was not extensive. The product is believed to be the pure ester on the basis of the chemical analysis for carbon and hydrogen*, and the constancy of the boiling point and index of refraction on a second redistillation. The index of refraction at 25° was found to be 1.455. The yield of the final pure product was 37% of the theoretical amount. It is believed that there was a more than negligible amount of the ester in the forerun in the distillation, and there was some loss due to decomposition at the high temperatures. The forerun from the distillation was not fractionated further.

Reactions with pentaerythrityl halides, other than the bromide, were not attempted as earlier workers (1,2,8) have consistantly reported them to be no better than the bromide. However, the benzenesulfonate of pentaerythritol was prepared by a method similar to that outlined in Organic Syntheses (9), and a reaction was carried out using the sulfonate in place of pentaerythrityl bromide. The proposed reaction was as follows:



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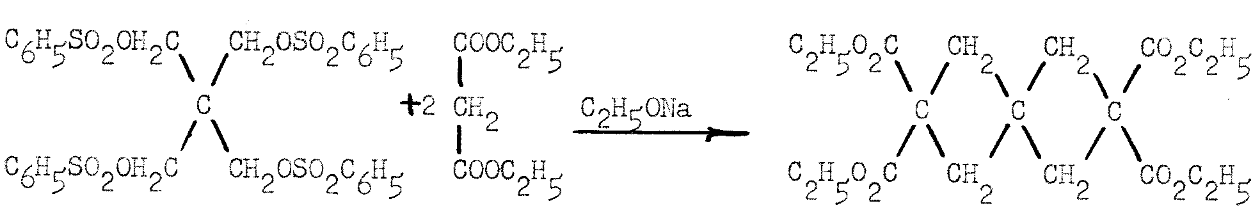
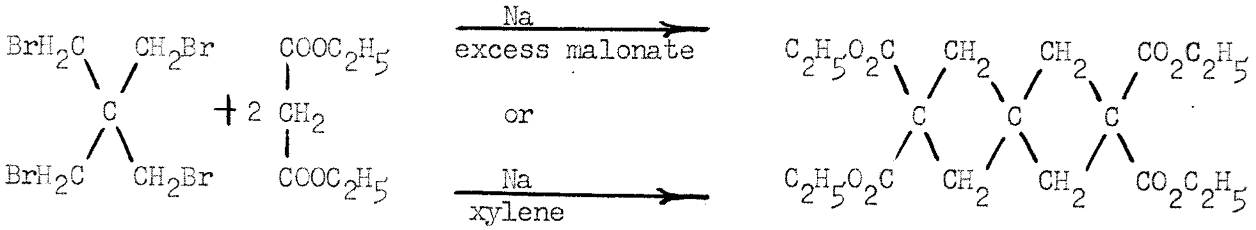
* For data see experimental section. The analysis was carried out by Eleck Microanalytical Laboratory, Los Angeles.

The reaction was carried out in a manner similar to that with the bromide yielding a small amount of yellow oil boiling from 225° to 235° at about one millimeter pressure. This represented a yield of less than 5% of theoretical even if the product was the pure ester. This study was not pursued further and the further identification of the product not carried out. It was concluded that the reaction with the sulfonate was not practical and not as good as that with the bromide.

Isoamyl alcohol has been used as the solvent for this reaction in order that the reflux temperature (128°) might be high enough for the reaction with the bromide to proceed. However, in the isolation of the ester formed there does arise the disadvantage of the high boiling point (226°/1mm.) of a molecule of such high molecular weight. It would be desirable if an ester of lower molecular weight, and consequently lower boiling point than the amyl ester, were prepared, especially if the case of a longer spiro-chain of four-carbon rings were to be realized. Three experiments along the line of preparing the ethyl ester of spiroheptanetetracarboxylic acid were undertaken; one was using the above-mentioned sulfonate of pentaerythritol in ethyl alcohol solvent and in the other two pentaerythrityl bromide was tried in two high boiling solvents, excess malonic ester and xylene.





The experiments using ethyl alcohol and excess malonic ester as solvents were carried out using a procedure similar to the previous runs; the procedure in the case of the experiment using xylene solvent was a modification of that described in Organic Syntheses for using sodium in xylene (10). None of the three attempts was successful. The yields of what could possibly be the ethyl ester were less than 10% in the case of the run in ethyl alcohol solvent, less than 5% for the run in xylene, and analysis of the product obtained from the run in excess malonate showed it not to be the ethyl ester. The products obtained were not identified in any of the three cases.

Lithium aluminum hydride has been used as a reducing agent for many types of compounds. Esters are among those which have been found to be affected by this reagent, reduction to the corresponding alcohol often taking place in good yield (11). A discussion of the use of this reagent will follow in Part II of this thesis. Buchman and Conly (12) were able to reduce 1,1-cyclobutanedicarboxylic acid ester, a compound somewhat similar to the isoamyl ester of spiroheptanetetracarboxylic acid mentioned above, to the corresponding glycol in good yield by treatment with lithium aluminum hydride. The reduction of spiroheptanetetracarboxylic ester with this compound was attempted here, but the attempt was unsuccessful and there was no product formed that could be identified as the corresponding alcohol.

Experimental

Reagents

Pentaerythrityl Tetrabromide

A three-liter, one-necked, round-bottomed flask was fitted with a glass connection permitting a dropping funnel to empty directly down into the flask and a water condenser to be installed on an arm of the fitting. The condenser was equipped with a calcium chloride drying tube. All fittings were standard taper ground glass joints.

Seven hundred and eighty (780) grams (5.73 f.w.) of pentaerythritol (Heyden Chemical Company, practical grade) were placed in the flask, heated with a steam bath, and 3120 g. (11. 5 f.w.) of phosphorous tribromide were added dropwise over a period of five hours. A considerable amount of gas was evolved. After the addition was completed, the flask was placed in an oil bath and the bath temperature was raised to 172° and maintained at 170°-180° for a period of 36 hours. The pentaerythrityl bromide was removed from the reaction flask and recrystalized by washing out with hot benzene which yielded 1660 g. of white crystals on cooling and spontaneous evaporation of the benzene. A red solid material which was insoluble in benzene remained in the reaction flask.

Pentaerythrityl Benzenesulfonate (9)

One hundred and thirty-six (136) grams (1 f.w.) of pentaerythritol and one liter of pyridine were placed in a five-liter, three-necked, round-bottomed flask equipped with a dropping funnel, thermometer, and stirrer. The reaction flask was open to the atmosphere, and the reaction was carried out in the hood. To the above, 741 g. (4.20 f.w.) of benzenesulfonyl chloride (Eastman practical grade) were added dropwise, with stirring, over a period of $1\frac{1}{2}$ hours, the temperature being maintained at 20° to 25° by external cooling. Stirring was continued for 2 hours after the final addition and the reaction mixture was left to stand overnight. Ten milliliters of water were added with stirring, and the reaction mixture then poured into a solution of 800 ml. of concentrated hydrochloric acid in one liter of water and ice. The resulting mixture was acid to litmus. The hardened mass that formed was broken up, washed with water, and air-dried, yielding 668 g. of the crude benzenesulfonate, which melted at 89°-95°. Before use, this was recrystalized from methanol and air dried, giving a product melting at 102°-103°.

Diethyl Malonate and Isoamyl Alcohol

The diethyl malonate (Lilly Company) that was to be used in these experiments was redistilled before use. The isoamyl alcohol was redistilled with 200 ml. of C.P. benzene to remove any moisture that might be present. The boiling point of the fraction used was 129° at 745 mm.

Procedure

Pentaerythrityl Bromide and Sodiomalonic Ester in Isoamyl Alcohol

To two liters of isoamyl alcohol in a five-liter, round-bottomed flask, 34.5 g. (1.5 g.a.) of sodium metal were added, the reaction taking place slowly. When all of the sodium was dissolved, 240 g. (1.5 f.w.) of diethyl malonate were added, and the mixture was refluxed for one hour. The reflux condenser was topped with a calcium chloride drying tube for protection from atmospheric moisture. After cooling, 120 g. (0.31 f.w.) of pentaerythrityl tetrabromide were added, and the ethyl alcohol distilled off until the boiling point of the solvent was reached (128°). Some boiling chips were added, and the reaction mixture was refluxed for 46 hours; the reflux condenser was again equipped with a calcium chloride drying tube. The solvent was removed by means of reduced pressure (aspirator) and a water bath with temperatures up to 85°. This procedure was discontinued when the rate of alcohol distilling over became very small. One liter of water was added, and hydrochloric acid was added until the mixture was neutral to litmus, a total of 10 ml. of 6N acid being used. The organic phase was separated from the aqueous phase, the aqueous phase extracted twice with about 200. ml. of ether each time, and the extracts combined with the organic phase which was then dried over anhydrous sodium sulfate. The ether was removed with an aspirator and water bath, the bath temperature reaching about 80°. The residue was a dark, viscous liquid which was distilled at a pressure of about one to two millimeters of mercury; the largest portion of the distillate came over between 215° and 245°. This fraction was redistilled and there was obtained 61 g. of a pale yellow, viscous oil which boiled at 226°-228° at about one millimeter pressure.

$n_D^{25} = 1.455$

Analysis: Calculated for spiroheptanetetracarboxylic acid isoamyl ester,

$C_{31}H_{52}O_8$: C = 67.36%, H = 9.47%

Found: C = 67.50%, H = 9.42%

Pentaerythrityl Benzenesulfonate and Sodiomalonic Ester in Ethyl Alcohol

In this experiment 21.7 g. (0.94 g.a.) of sodium were dissolved in 950 ml. of ethanol in the reaction flask in the same manner as indicated above. One hundred and fifty (150) grams (0.94 f.w.) of diethyl malonate were added and the whole was refluxed for one hour. To this mixture were added 131 g. (o.19 f.w.) of pentaerythrityl benzenesulfonate and the resulting mixture was refluxed for 120 hours with protection from atmospheric moisture afforded by a calcium chloride tube mounted on the reflux condenser. A solid precipitate appeared as the refluxing was carried on, and a color change going through light red to brown was noted. After the refluxing was discontinued, part of the ethyl alcohol was removed with a water pump. A liter of water was added in three portions, the aqueous phase being separated and removed each time. The solid precipitate was removed by the water. The aqueous portion was extracted with ether three times, and the extracts were combined with the organic phase, which was then washed with hydrochloric acid and dried over sodium sulfate. On distillation at reduced pressure, after stripping off the ether, about 20 ml. of liquid, boiling from 100° to 170° at about one millimeter, were obtained. That portion boiling below 100° at this pressure appeared to be diethyl malonate. Redistillation produced the following three fractions:

7.0 g. boiling at 108°-111° at about 1 mm.
6.8 g. boiling at 112°-160° at about 1 mm.
2.6 g. boiling at 160°-180° at about 1 mm.

Pentaerythrityl Benzensulfonate and Sodiomalonic Ester in Isoamyl Alcohol

The procedure was similar to that as described above in the reaction of the pentaerythrityl bromide. The quantities used were 23.0 g. (1 g.a.) of sodium in one liter of isoamyl alcohol, 160 g. (1 f.w.) of diethyl malonate, and 139 g. (0.20 f.w.) of pentaerythrityl benzenesulfonate. The time in reflux was 50 hours. Distillation of the organic phase, after separation from aqueous wash as before, yielded about 20 ml. of liquid boiling from 180°-240° at about 3 mm. pressure. When this was redistilled, there was obtained 4.3 g. of yellow oil boiling from 225° to 235° at about one millimeter pressure.

Pentaerythrityl Bromide and Diethyl Malonate in Excess Diethyl Malonate

The procedure in this experiment was different from that used previously in that no alcohol solvent was used, an excess of diethyl malonate being used in its place. Four hundred milliliters of diethyl malonate were placed in a one-liter, three-necked, round-bottomed flask and 11.5 g (0.5 g.a.) of sodium were dissolved therein. To this, 38.8 g. (0.1 f.w.) of pentaerythrityl tetrabromide were added. A stirrer, thermometer, and water condenser were installed and the reaction mixture was brought to 140° and was maintained between 125° and 140°, with stirring, for 24 hours. About 400 ml. of water were added to the cooled mixture, which was then brought to neutral to litmus with 10 ml. of 12N hydrochloric acid. The organic phase was separated from the aqueous phase and was washed three times with 200 ml. portions of water. The aqueous wash was extracted with 200 ml. of ether, which were added to the organic phase.

Drying over sodium sulfate, removal of the solvent, and distillation at reduced pressure yielded 4.6 g. of a liquid boiling at 178°-188° at about 2 mm. Ten and seven-tenths grams of the original bromide were recovered.

Pentaerythrityl Bromide and Diethyl Malonate in Xylene

In order to remove any water that might have been present, approximately 150 ml. were distilled off from one liter of xylene in a three-necked, two-liter, round-bottomed flask. Twenty-three grams (1 g.a.) of sodium were added and warmed until the sodium was melted, small balls of sodium being formed when stirred. To this, 165 g. (1.03 f.w.) of diethyl malonate were added, with stirring, over a period of one-half hour. The temperature was maintained at 110° with an oil bath, and the flask was equipped with a stirrer, dropping funnel, thermometer and air condenser. The stirring and temperature of 110° were maintained until the sodium was dissolved; 78 g. (0.20 f.w.) of pentaerythrityl tetrabromide were then added and the reaction mixture was refluxed for 49 hours ("glass coll" mantle; water reflux condenser topped with calcium chloride drying tube). After refluxing, most of the solvent was removed with an aspirator and water bath, the residue was combined with an equal amount of water and made neutral to litmus with concentrated hydrochloric acid, and the phases were separated; washing and combining of extracts with the organic phase were carried out as before, and finally the remaining organic material was dried over anhydrous sodium sulfate. The ether and most of the remaining xylene were taken off with an aspirator and hot water bath. After concentrating the residue, 48 g. of the original bromide were recovered and 4.2 g. of a liquid boiling 130°-200° at about 1 mm. were obtained.

Spiroheptanetetracarboxylic Acid Ester and Lithium Aluminum Hydride

One hundred and forty two (142) grams of C.P. ether, dried over sodium ribbon, were placed in a three-necked, 300 ml., round-bottomed flask and 3.40 g. (0.090 f.w.) of lithium aluminum hydride were dissolved in it. Care was exercised to keep to a minimum the exposure of the solvent ether and lithium aluminum hydride to the atmospheric moisture. The flask was then equipped with a stirrer, dropping funnel, and reflux condenser topped with a calcium chloride drying tube. Twenty grams (0.036 f.w.) of the isoamyl ester of spiroheptanetetracarboxylic acid, diluted with an equal volume of dry ether, were added dropwise, with stirring, over a period of about 1½ hours. External cooling was provided. A white precipitate formed as the addition proceeded, and the reaction mixture became progressively thicker. Stirring was continued for one hour after the final addition. The excess lithium aluminum hydride was decomposed by the addition of 20 ml. of water, dropwise and with caution at first as the reaction was quite vigorous. Evolution of hydrogen gas took place upon this addition of water. Ten more milliliters of water were added, and the ether layer was decanted off. The residue was made slightly acid with 10 ml. of 12N sulfuric acid, and was extracted a number of times with a total of about one liter of ether. The ether of the extract was distilled off, leaving 2.5 g. of a viscous liquid which boiled at about 200° at 2 mm. pressure.

Five grams of p-toluenesulfonyl chloride were dissolved in 2 ml. of pyridine, and one gram of the above product was added to this solution, with mixing. The resulting solution was allowed to stand for 48 hours. The reaction mixture was then poured into ice-water and the resulting precipitate washed with water and filtered. The precipitate was recrystalized from ethyl alcohol until a constant melting point (66°-67°) was reached. One and three-tenths grams of white crystals were obtained. This derivative was not identified.

Analysis: C = 45.46%; H = 4.23%; S = 17.28%

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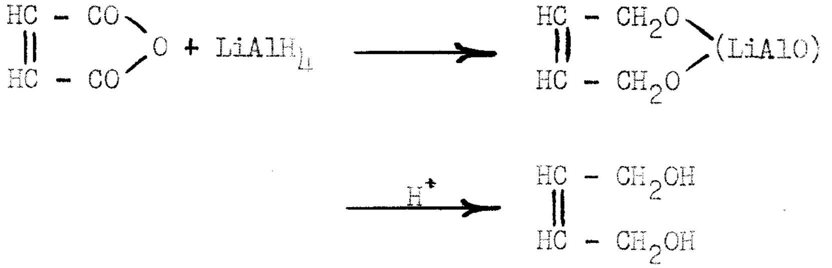
PART II

ATTEMPTED NEW SYNTHESIS OF CIS-2-BUTENE-1,4-DIOL

The recent discovery of lithium aluminum hydride (1) and its application to the reduction of organic compounds (2,3,4) suggests the possibility of a new synthesis of 2-butene-1,4-diol from maleic anhydride by a selective reduction of the acid anhydride group with lithium aluminum hydride, leaving the olefinic double bond unchanged.



$$\begin{array}{l} \mathrm{HC - CO} \\ \| \\ \mathrm{HC - CO} \end{array} \!\!> \mathrm{O} + \mathrm{LiAlH_4} \longrightarrow \begin{array}{l} \mathrm{HC - CH_2O} \\ \| \\ \mathrm{HC - CH_2O} \end{array} \!\!> \mathrm{(LiAlO)}$$

$$\xrightarrow{H^+} \begin{array}{l} \mathrm{HC - CH_2OH} \\ \| \\ \mathrm{HC - CH_2OH} \end{array}$$

cis-2-butene-1,4-diol

It was hoped that herein might lie a new laboratory synthesis of this compound which would be a one-step process, and presumably yielding only the cis stereo-isomer, free from contamination by the trans isomer. Reppe and Drossbach (5) reported performing the reverse process, oxidizing 2-butene-1,4-diol to maleic acid by means of oxygen and an oxidation catalyst, but the information is not available as to whether it was the cis or trans isomer, or both, that was used as the starting material.

The preparation of lithium aluminum hydride and its use as a reducing agent was first described by Finholt, Bond, and Schlesinger (1) in 1947, but the investigation of its potentialities in organic chemistry is being carried on by Nystrom and Brown working in the same laboratory. Their publications to date (2,3,4) are concerned with their experiments which are not intensive in nature but are designed to try a few representative compounds covering a large scope. Some of their findings, with generalities where possible, will be considered at this time.

Lithium aluminum hydride is a powerful reducing agent which works smoothly and rapidly at room temperature, usually with little side reaction and often with nearly quantitative yields. It is often possible to carry out reductions with this agent that in other cases were accomplished only by high pressures and temperatures and with poor yields. The action is often specific, as in case of the absence of action on olefinic double bonds which will be discussed later. Some other advantages that may be cited are: It is easily prepared on a laboratory or commercial scale (but is fairly expensive); it is stable at room temperature; it is ether soluble; the ratio of reducing capacity to mass is favorable, which to some extent compensates for the high cost; no unusual or special equipment is necessary to carry out the reductions. A disadvantage is that an active hydrogen may decompose the lithium aluminum hydride, with the evolution of hydrogen gas.

A wide range of compounds are reduced by this reagent and below are listed the main types that have been found to be affected:

a. aldehydes, ketones, acid chlorides, acid anhydrides and carboxylic acids are reduced to the corresponding alcohol.
b. alkyl halides are converted to hydrocarbons.
c. nitriles go to primary amines.
d. aromatic nitro and azoxy compounds go to azo compounds.
e. aliphatic nitro compounds are reduced to primary amines.

It has been noted that the experimental technique involved in the use of lithium aluminum hydride is very similar to that involving the Grignard Reagent; similar precautions must be taken to keep moisture from the reaction mixture, the substance to be reduced is usually diluted in ether before addition, and the metal alcoholate that is formed in the reaction is decomposed by acid hydrolysis. The analogy is seen to be carried even further in that many of the same types of compounds are attacked in each case, to such an extent that some reactions have been correctly predicted on that basis. Also the reaction products from lithium aluminum hydride treatments give a response to the Gilman-Schultz color test (6) which is considered characteristic for the carbon-metal bond. The lithium aluminum hydride reagent does differ from that of the Grignard, though, in that it is more reactive and the reaction is smoother and quicker for some types. An example of such analogous reactions is the reduction of carboxylic acids by lithium aluminum hydride, and the formation of a tertiary alcohol by the Grignard Reagent.

In the experiments that they have carried out, Nystrom and Brown have found that the olefinic double bond is usually left unaffected by lithium aluminum hydride reactions. Using crotonaldehyde, methyl oleate and sorbyl chloride they found that to be the case; also the olefinic double bond in sorbic acid and furoic acid is left unchanged by lithium aluminum hydride. However, in the case of cinnamic acid, the double bond was reduced, giving hydrocinnamyl alcohol as the product. They concluded from their experiences that it appears that the olefinic double bond is not affected unless it occurs as an ethylenic nucleus substituted on one side by a phenyl group and on the other by a reducible group, in which case the double bond is hydrogenated. They indicated that they were in the process of investigating this phase further and that in future publications they would have more to say on the subject. It may be noted that in the particular case with which we are concerned, that of maleic anhydride, there is essentially the ethylenic nucleus substituted on either side by a reducible group, which might or might not produce results similar to the above-mentioned case of substitution by a phenyl group and a reducible group.

In the work with the reduction of carboxylic acids (3), it was found that when dibasic acids were treated with an excess of lithium aluminum hydride, the diol was formed in good yield. When an amount of lithium aluminum hydride insufficient to reduce both acid groups was used, a mixture of the diol and unreacted diacid resulted, and in no case was it found that one carboxyl group was reduced and the other left unchanged.

Syntheses of 2-Butene-1,4-diol

From the literature it may be seen that there are two principal ways by which 2-butene-1,4-diol has been synthesized; by the partial hydrogenation of 2-butyne-1,4-diol and by the addition of a halogen to 1,3-butadiene with subsequent conversion of the product to the 2-butene-1,4-diol. Commercial synthetic methods for the production of 2-butyne-1,4-diol from acetylene and formaldahyde have been worked out by Reppe (7), and consequently this compound is available commercially or may be produced on the laboratory scale. From this starting material, syntheses of both the cis and trans isomers have been reported. Valette (8) describes the preparation of what he believes to be the pure cis-2-butene-1,4-diol by hydrogenation of 2-butyne-1,4-diol over Raney nickel in absolute ethanol at atmospheric pressure and room temperature. The yield is not stated, but one is led to believe that it is good. There is little difference in the boiling points or refractive indices of the two isomers; however, the trans does melt at 25° whereas crystals of the cis isomer have not been isolated. The identification of the product as the cis isomer was based on the following:

a. The Raman Spectrum was that which is characteristic of the cis-ethylenic structure.

b. Bromine addition to the product was trans.

c. When seeded with crystals of the trans isomer as prepared by Prevost (13), there was no crystallization of the product.

In 1946 Johnson (9) reported the syntheses in good yield of both the cis and trans isomer of 2-butene-1,4-diol from 2-butyne-1,4-diol. The trans isomer resulted from hydrogenation over Raney nickel at 150 atmospheres and room temperature. The yield was 92%. When the catalyst used was 0.5% palladium-calcium carbonate and the hydrogenation carried out at atmospheric pressure, cis-2-butene-1,4-diol was produced with 77% yield. The identification of this product was on the basis of the boiling point and refractive index, and using the melting point of the dibenzoate (69°-70°) as the means of distinguishing it from the trans isomer (m.p. of trans dibenzoate 101°, Prevost and Lutz (10)). In the patent literature are found two more cases in which the production of 2-butene-1,4-diol by hydrogenation of 2-butyne-1,4-diol is claimed. Reppe and Schnabel (11) used zinc dust and sodium hydroxide solution, obtaining a mixture of the cis and trans isomers. Schnabel, Schmidt, and Heintz (12) used high pressure catalytic hydrogenation, but it is not stated which isomer resulted.

The syntheses involving 1,3-butadiene as the starting material were carried out mainly by Prevost (13,14), with only the trans isomer reported by this method. Trans-1,4-dibromo-2-butene, which resulted from bromine addition to the butadiene, gave 98% yield of trans-2-butene-1,4-diol when treated with sodium acetate in ethyl alcohol and water, and the diacetate then saponified with barium hydroxide. A 45% yield of trans-2-butene-1,4-diol resulted from the treatment of the above dibromide with sodium bicarbonate in water at 80°. None of the cis isomer was found to be present in either case, which is explained on the basis that the addition of bromine to the butadiene is trans with none of the cis dibromide being formed.

There are some other publications which are of less importance from the standpoint of the synthesis of 2-butene-1,4-diol, but which reported the diol as a product. Prevost and Lutz (10) treated butadiene with silver iodobenzoate and the product was a syrup which, when hydrolized, gave 80% 3-butene-1,2-diol and 4% 2-butene-1,4-diol. Again the 2-butene-1,4-diol was the trans isomer. In an earlier paper (15) Prevost describes a cycle starting from erythritol which includes trans-2-butene-1,4-diol as a step in it, but the yield is small because of the number of steps involved. Another way of getting to the diol is given by Arbuzov and Zoroastrova (16) which consisted of treatment of butadiene with chlorine and sodium acetate to give 1-chloro-4-acetoxy-2-butene as one of the products which was then converted to 2-butene-1,4-diol. Information as to yield and stereochemistry is not available.

Results of This Attempted Synthesis

In the attempted synthesis of 2-butene-1,4-diol that was carried out here, two experiments were performed which differed in the treatment of the alcoholate that is formed by the reaction with lithium aluminum hydride, and the following working up of that product.

Maleic anhydride is somewhat soluble in ether, enough so that it was possible to use the usual method of adding dropwise an ether solution of the compound which is to be reduced, to an ether solution of lithium aluminum hydride. Ether which had been dried over sodium ribbon was used in each case, and the addition was carried out with constant stirring and external cooling. Precautions were exercised to prevent any moisture from being absorbed from the atmosphere; the similarity to the use of the Grignard Reagent in this respect was pointed out earlier. The reaction was quite vigorous at the start of the addition but as the addition of the anhydride continued, it became less so, and it was possible to proceed at a more rapid rate towards the end. A precipitate was formed when the reaction took place, and by the time the addition was finished it had become copious. The reaction mixture was stirred for a period after the addition was completed in order to allow any unreacted anhydride to come in contact with the lithium aluminum hydride. The procedure employed in the two experiments was the same thus far.

In the method that has been worked out by Nystrom and Brown (2), water is added at this time to decompose the excess lithium aluminum hydride, followed by sulfuric acid sufficient to release the free alcohol. This procedure was followed in the first experiment; however, the resulting mixture could not be left with an excess of sulfuric acid, if distillation from an aqueous solution was to follow, for dehydration of the diol would take place. Valette (8) included a discussion of the dehydration of cis-2-butene-1,4-diol by sulfuric acid in his paper. It was anticipated that 2-butene-1,4-diol would be much more soluble in water than in ether and consequently ether extraction would not be practical. A trial ether extraction of a small portion of the acidified aqueous solution of the reaction product tended to substantiate this opinion. Therefore it was from the aqueous solution that the distillation was carried out, after the solution had been made alkaline with sodium hydroxide and the precipitated lithium and aluminum hydroxides had been separated from the solution. A high-boiling product was obtained from this distillation, and redistillation of it produced a small amount of liquid boiling at 84°-86° at about one millimeter pressure. This represented about 10% of the amount of 2-butene-1,4-diol that was theoretically possible. In Figure 1 is shown the boiling points of cis-2-butene-1,4-diol as given by Valette (8) and Johnson (9). It may be seen that the boiling point of the above product lies on the extrapolation of the curve passing through the boiling points reported by these authors. However, the index of refraction at 25° of this product was 1.456, which does not compare favorably with $n_D^{20} = 1.478$ as given by Valette, and $n_D^{25} = 1.471$ as given by Johnson. Identification of the product was not carried out since, at best, the yield of diol was poor.

The procedure as outlined above had the undesirable feature that when the aqueous solution was made alkaline to avoid dehydration by the sulfuric acid, the hydroxides of aluminum and lithium were precipitated, giving a mixture which was very hard to separate cleanly into the liquid and solid phases. Consequently a method was devised to eliminate the handling of an aqueous system containing these hydroxides. In the second experiment the excess lithium aluminum hydride was decomposed with methyl alcohol, and water was added only in a quantity just sufficient to release the theoretical amount of free diol. In this manner the aqueous system and the addition of sulfuric acid were avoided, giving much cleaner separation of the hydroxide precipitates from the liquid phase (excess methyl alcohol used as solvent), and eliminating the sodium sulfate which was formed when the excess sulfuric acid was neutralized with sodium hydroxide in the first experiment. The sodium sulfate precipitated out as the water was distilled off in the concentration of the product in the first experiment. It was calculated that 55 ml. of methyl alcohol were required to decompose the excess lithium aluminum hydride, but 115 ml. were necessary before the point was reached when no more reaction could be observed on addition of the alcohol. This was taken as an indication that not all of the maleic anhydride had reacted. Two hundred and sixty milliliters was the amount of methanol that was calculated to be necessary if no reaction with the maleic anhydride had taken place and if all the lithium aluminum hydride remained unreacted. The first of the methanol that was added reacted very vigorously, as did the water in the previous cases where water was used to carry out the decomposition. After the hydroxides had been filtered off, the greater part of the methanol was evaporated, and the residue was distilled, yielding a liquid boiling at 88°-93° at 1 to 2 mm. This liquid was very similar in appearance to that from the aqueous run; the index of refraction at 25° was 1.455, as compared to 1.456 for the previous product; the boiling range also falls on the extrapolated curve in Figure 1; it seemed reasonable to assume that this was the same product that was obtained from the aqueous run, but it represented in weight only four per cent of the amount of 2-butene-1,4-diol that was theoretically possible. Chemical analysis for carbon and hydrogen showed it not to be pure 2-butene-1,4-diol. It was found to be 51.7% carbon and 10.2% hydrogen as contrasted to the calculated values for 2-butene-1,4-diol of 54.6% carbon and 9.11% hydrogen. The calculated composition of the saturated compound, butane-1,4-diol, which could conceivably be formed in this reaction, is 53.4% carbon and 11.1% hydrogen.

This attempted synthesis of cis-2-butene-1,4-diol was not succesful, and the method as carried out cannot be regarded as a practical method of preparation of this compound. The yields, if any, were less than 10% and less than 5% in the two cases, and the product was probably a mixture and not a pure substance. As was indicated earlier, it was thought that the reduction might take place leaving the double bond unaffected, or it might proceed as in the case of the ethylenic nucleus substituted with a phenyl group on one side and a reducible group on the other which results in hydrogenation of the double bond. If the latter were the case, butane-1,4-diol would be the product. Referring again to Figure 1, boiling points for the saturated diol have been plotted, and it may be seen that they lie very close to the curve for the unsaturated compound. Obviously, then, if any of the saturated compound had been formed, distillation would have given practically no separation. In agreement with a mixture of 2-butene-1,4-diol and butane-1,4-diol are the observed index of refraction and boiling point, but not the per cent of carbon found. It is possible that the product was a mixture of the saturated and unsaturated diols with some other impurity present (such as unreacted anhydride). A product obtained in such poor yield was deemed not worthy of further investigation, and consequently was not identified.

There are four possible areas of loss which might account for the absence of the desired product: Little reaction to start with, failure of the product to be freed from the precipitate, formation of a more volatile compound than the isolated material, and the remaining of a higher-boiling material in the residue from the distillation. The changes that were apparent on the addition of the anhydride were certainly indicative of a reaction of some sort, and there was very little residue after evaporating the ether that was separated from the aqueous phase right after the addition of water in the aqueous run. However, the amount of methyl alcohol needed to decompose the excess lithium aluminum hydride in the second run seemed to indicate that the reaction was not complete. It seems quite possible that some product or starting material could have been left in the precipitated hydroxides that were removed. When water is present the precipitate is especially sticky as it is hydrophilic. In his paper (8), Valette reported that cis-2-butene-1,4-diol was dehydrated to dihydrofuran and crotonaldehyde by sulfuric acid. This dehydration was quarded against and neither of these two products was detected as being present in foreruns, but the possibility of the formation of a volatile product, which was lost, is not excluded. The residues after distillation were not enough to account for much loss. That from the aqueous run consisted of a tarry material, some inorganic material, and some of what was possibly the same as the product obtained; that from the second run was mostly a tarry material.

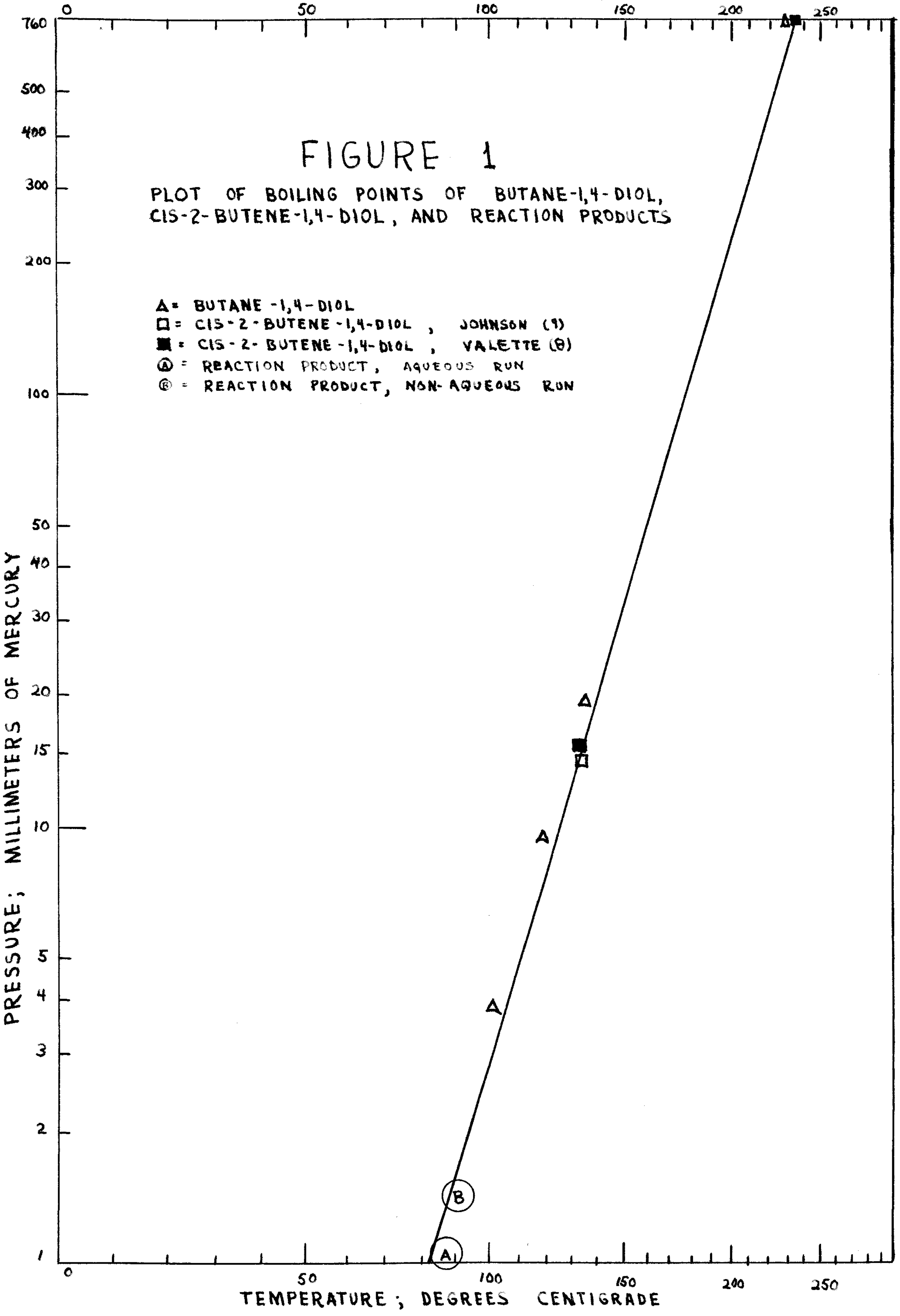


FIGURE 1

PLOT OF BOILING POINTS OF BUTANE-1,4-DIOL, CIS-2-BUTENE-1,4-DIOL, AND REACTION PRODUCTS

Experimental

Apparatus and Reagents

The apparatus used in these experiments consisted of a three-necked, round-bottomed flask of appropriate size, a Tru-bore stirrer, a dropping funnel topped with a calcium chloride drying tube, and a water condenser with a calcium chloride drying tube; provision was made for cooling externally with an ice bath. Connections and fittings were standard taper ground glass joints.

The ether used as solvent for the reactants was commercial anhydrous diethyl ether which was further dried over sodium ribbon. The maleic anyhdride was Eastman White Label and the lithium aluminum hydride was supplied by Metal Hydrides, inc., Beverly, Massachusetts.

Procedure

A. Forty-one grams (1.08 f.w.) of lithium aluminum hydride were dissolved in 1400 ml. of dry ether in a round-bottomed flask equipped with a stirrer and a condenser as described above. There was a little evolution of gas on addition of the lithium aluminum hydride, and stirring was maintained for one hour with external cooling to ice temperature towards the latter part of the hour.

Eighty grams (0.82 f.w.) of maleic anhydride were dissolved in 1050 ml. of dry ether and the resulting solution was added dropwise to the lithium aluminum hydride solution with stirring and external cooling over a period of about 2 hours. The reaction was vigorous at the start, but became less so as the addition proceeded. An insoluble precipitate formed and the reaction mixture became progressively thicker. The reaction mixture was stirred for one hour after the last addition, and left to stand overnight.

Up to this point, precautions were taken to exclude moisture and to keep exposure to the air at a minimum.

Three hundred milliliters of water were added dropwise with cooling and stirring, slowly at first as the reaction with the excess lithium aluminum hydride was quite vigorous with the evolution of gas. The ether layer was decanted off, and the remaining aqueous portion acidified with 200 ml. of 25% sulfuric acid. The solid material of the mixture was separated from the liquid portion by means of a centrifuge and filter. The filtrate was made alkaline with 80 ml. of 30% sodium hydroxide, and the precipitated material was removed as above. The residue was evaporated down to about 150 ml. on a steam bath.

Five hundred milliliters of methanol were added, and a solid precipitate, presumably sodium sulfate, was filtered off. The filtrate was again evaporated down to about 150 ml.; most of the remaining methanol was removed at reduced pressure with a water pump; the residue was distilled at reduced pressure giving a forerun, 7.3 g. of high-boiling liquid coming over at 93°-97° at 2 to 3 mm. (n_D^{25} = 1.450), 32 g. of residue which appeared to consist of some inorganic material, and a tarry material which possibly contained some of the high-boiling liquid which did not come over. The high-boiling liquid was redistilled, boiling at 84°-86° at about 1 mm.; n_D^{25} = 1.456

B. The reaction was carried out in the same manner as above, using 60 g. (1.58 f.w.) of lithium aluminum hydride in 2250 ml. of dry ether, 123 g. (1.25 f.w.) of maleic anhydride in 1250 ml. of dry ether, and a 5 liter flask. Stirring was maintained for 1½ hours after the final addition and again the reaction mixture was left to stand overnight.

Two hundred and ninety (290) milliliters of absolute methanol were added dropwise, 55 ml. being the theoretical amount required to react with the excess lithium aluminum hydride. The reaction was vigorous at the start, and the reaction had tapered off so as to be apparently over after about 115 ml. had been added, although the point of no more reaction is difficult to determine.

One hundred and fourteen (114) milliliters of water, the theoretical amount necessary to give the free diol, were added with stirring, followed by 3 g. of potassium hydroxide dissolved in 25 ml. of methanol; the mixture was stirred for 15 minutes. The solid material was easily filtered off, and was washed twice with a total of 800 ml. of methanol which were combined with the filtrate.

The filtrate was evaporated down to about 100-150 ml. with a water pump, and distilled, yielding a forerun, a high-boiling cut coming over at 90°-100° at about 2 mm., and 7 g. of tarry residue. The high-boiling fraction was redistilled giving 4.8 g. of liquid boiling at 88°-93° at about 1 to 2 mm., ($n_D^{25} = 1.455$). On redistillation, the product boiled at 87°-90° at about 1^+ mm.; there was no change in the index of refraction. Analysis: C - 51.73%; H - 10.18%.

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