[CONTRIBUTION FROM THE IPATIEFF HIGH-PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY, AND UNIVERSAL OIL PRODUCTS COMPANY]

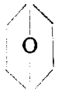
# The Dehydration of 1,4-Cyclohexanediol. Synthesis of 1,4-Epoxycyclohexane[1]

BY R. C. OLBERG, HERMAN PINES AND V. N. IPATIEFF

In the preparation of cyclohexadienes by the dehydration of a methanol solution of 1,4-cyclohexanediol with activated alumina as the catalyst, it was observed that, along with the desired products, some 3-cyclohexene-1-ol and a large amount (44%)[1a] of 1,4-epoxycyclohexane were formed. Since the presence of the epoxide as a dehydration product was not disclosed by previous investigators,[2-6] a study was made of the factors influencing its formation, such as solvent, temperature, geometric configuration and catalyst.

The use of solvents facilitated the carrying out of the reaction in a flow-type apparatus. In a series of experiments at 275 to 406°, with methanol as a solvent, it was found that the yield of 1,4-epoxycyclohexane based upon the reacted 1,4-cyclohexanediol decreased with increasing temperature from about 40 mole per cent. to 0.

At 350 and 400°, in addition to 3-cyclohexene-1-ol and cyclohexadienes, a complex mixture containing cyclohexene, methylcyclohexene, formaldehyde, methyl ether, and polymers of cyclohexadienes was obtained. The presence of cyclohexene was probably due to cleavage of epoxycyclohexane by hydrogenation to cyclohexanol with subsequent dehydration of the latter; the hydrogen required for this reaction was furnished by the dehydrogenation of methanol to formaldehyde.



$$+ CH_3OH \xrightarrow{Al_2O_3} \underset{\text{(Cyclohexanol)}}{C_6H_{10}OH} + HCHO \xrightarrow{-Al_2O_3} \underset{\text{(Cyclohexene)}}{C_6H_{10}} + H_2O$$

This type of hydrogen disproportionation, caused by catalysts which by themselves do not possess strong hydrogenation or dehydrogenation properties, is well known.[7,8,9] In order for the hydrogen transfer to occur, it is necessary that both a hydrogen acceptor and a hydrogen donor be present; molecular hydrogen under similar conditions might not cause the hydrogenation. When methanol alone was passed over alumina at 400°, only a trace of formaldehyde was detected. Benzene and cyclohexane were not present in the reaction product, a fact which indicated that cyclohexene could not have been formed by hydrogen disproportionation involving the cyclohexadienes. At 400° some uncondensable gas, consisting mainly of carbon monoxide and hydrogen, was formed. This gas probably resulted from the decomposition of formaldehyde.

The formation of the methylcyclohexene boiling fraction may have been due to (a) the interaction of 1,4-cyclohexadiene with formaldehyde or (b) the rearrangement of methoxycyclohexenol formed by the etherification of cyclohexanediol with methyl alcohol.

When the dehydration of 1,4-cyclohexanediol was carried out in an ethanol solution at 300°, the yield of 1,4-epoxycyclohexane was only 21.4%. At 340°, none of the epoxide was obtained, and the reaction product consisted to a larger extent of products resulting from hydrogen disproportionation, among which were found acetaldehyde, cyclohexene, and cyclohexanol. The yield of cyclohexadienes and cyclohexenol, which are normal products of dehydration, amounted to 36 per cent.

Since alcohols cause hydrogen disproportionation, it was of interest to carry out the dehydration in the presence of a solvent having no hydrogen donor properties. However, when acetone was used at 300°, the yield of 1,4-epoxycyclohexane was only 17%, while at 340° no epoxide was formed. The reaction product contained large amounts of isopropyl alcohol and cyclohexene. The isopropyl alcohol probably was formed by the transfer of hydrogen from 1,4-cyclohexanediol to acetone. (Such a redistribution of hydrogen in the absence of a hydrogenating catalyst, involving ketones and alcohols, had been previously observed in these Laboratories.) The cyclic ketones (A) formed may undergo condensation in the presence of alumina and yield polycyclic ketones. The isopropyl alcohol produced probably reacts with 1,4-epoxycyclohexane to form acetone and cyclohexanol, the latter may be converted to cyclohexene.

When the dehydration was carried out in the absence of a solvent, by refluxing the 1,4-cyclohexanediol over activated alumina and distilling off the dehydration product as formed, 48.6 mole per cent. of 1,4-epoxycyclohexane and 18.3 mole per cent. of 3-cyclohexene-1-ol were obtained. The reaction rate was low, requiring twenty-one hours to complete the dehydration. The substitution of iodine or potassium acid sulfate for alumina failed

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(1) This paper is based upon a thesis submitted to the faculty of the Department of Chemistry, Northwestern University, by R. C. Olberg in partial fulfillment of the requirements for the degree of Master of Science.

(1a) All yields are expressed in mole per cent. based on 1,4-cyclohexanediol charges.

(2) Willstätter and Lessing, *Ber.*, **34**, 506 (1901).

(3) Ipatieff, "Catalytic Reactions at High Pressures and Temperatures," The Macmillan Company, New York, N. Y., 1936, p. 106.

(4) Zelinskii and Titova, *Ber.*, **64**, 1399 (1931).

(5) Senderens, *Compt. rend.*, **180**, 790 (1925).

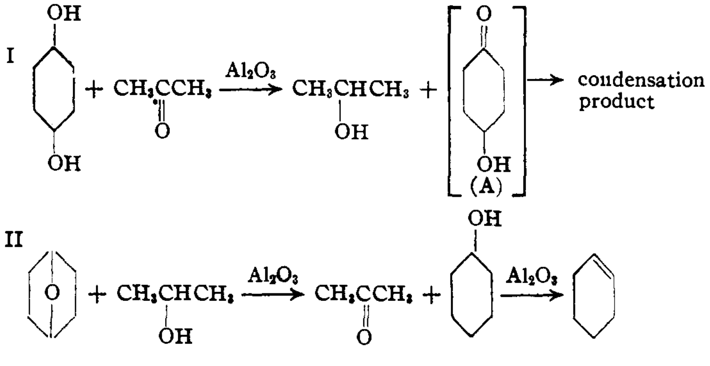
(6) Sabetay and Blager, *Bull. soc. chim.*, [4] **47**, 463 (1930).

(7) Ipatieff and Pines, *Ind. Eng. Chem.*, **27**, 1364 (1935).

(8) Ipatieff and Pines, *J. Org. Chem.*, **1**, 470 (1936).

(9) Pines and Ipatieff, *ibid.*, **6**, 242 (1941).

to give 1,4-epoxycyclohexane. Likewise, acid-type catalysts, such as sulfuric acid,[5] hydrobromic acid,[6] and bromine,[6] reported in the literature, failed to produce the epoxide.

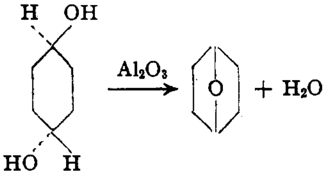


The effect of geometric configuration on the yield of 1,4-epoxycyclohexane was very marked. Table I summarizes the results obtained when methanol solutions of pure *cis*- and *trans*-1,4-cyclohexanediol were passed over alumina at 275°

TABLE I

| Products obtained based on cyclohexanediol treated | *Cis*-, mole % | *Trans*-mole % | Mixture mole % |
|---|---|---|---|
| 1,4-Epoxycyclohexane | 28.0 | 73.0 | 33.5 |
| 3-Cyclohexene-1-ol | 27.0 | 11.4 | 20.6 |
| Unreacted 1,4-cyclohexanediol | 16.0 | 10.0 | 17.0 |

The difference in the results obtained with the *trans*- and *cis*-isomers is in agreement with the work of Bartlett and his co-workers[10,11] with 1,2-dimethyl-1,2-cyclohexanediols and cyclopentanediols, and can be explained by assuming that a "backside approach" is responsible for the greater tendency of the *trans* isomer to form the epoxide.



The isomerization of part of the *cis* isomer to the *trans* isomer may account for the small yield of the epoxide obtained with the pure *cis* glycol.

***cis*- and *trans*-1,4-Cyclohexanediol.**—The methods described in the literature for the preparation of 1,4-cyclohexanediols consist of hydrogenation of quinone or hydroquinone in the presence of a nickel catalyst.[2,12,13,14] Some of the authors claim to have obtained the pure *cis*[12] isomer or predominantly the *cis*[13] isomer. The claims are based solely upon the melting points of their products. According to the melting point curve (Fig. 1,) it is evident that a mixture consisting of 38% *cis*- and 62% *trans*-1,4-cyclohexanediol has the same melting point as pure *cis*-isomer.

The separation of the *cis*- and *trans*-1,4-cyclohexanediol from the mixture was accomplished by the method of Baeyer,[15] which consisted of converting the glycols into the diacetates. The *trans* diacetate melted at 103°, while the *cis* diacetate, after fractional crystallization from dilute alcohol and hot acetone, melted at 33 to 34°.

An improvement was worked out in the procedure for the recovery of pure 1,4-cyclohexanediols after saponification with aqueous barium hydroxide. The aqueous solution was evaporated *in vacuo* to dryness, and the residue extracted with acetone. After drying *in vacuo* over phosphorus pentoxide the *cis*-1,4-cyclohexanediol melted at 107°, the *trans* at 142°. A melting point curve of a mixture of the two isomers is given in Fig. 1.

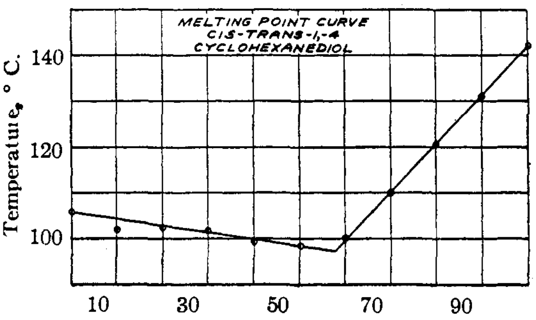


Fig. 1.

## Experimental Part

### A. Preparation of Materials

**Preparation of 1,4-Cyclohexanediols.**—Hydroquinone was hydrogenated 150° under 120 atmospheres initial hydrogen pressure and in the presence of an equal volume of methanol and 10% by weight of a nickel-kieselguhr catalyst. The product distilled at 172 to 175° at 42 mm. and melted at 98 to 99°; from 47 to 58% of it consisted of *trans*- and the remainder of *cis*-1,4-cyclohexanediol.

**Separation of *cis*- and *trans*-Cyclohexanediols.**—Four moles, 464 g., of the mixture of 1,4-cyclohexanediols was converted to the diacetates. The *trans*-diacetate, being less soluble in ether than the *cis*, was separated by filtration; and 302 g. of the crude *trans* compound was obtained, which on crystallization from hot absolute alcohol yielded 256 g. of *trans*-diacetate melting at 101 to 102°. The amount of crude liquid *cis*-diacetate recovered was 459 g. Two hundred grams of this product was dissolved in hot acetone, cooled to room temperature, seeded with a crystal of *trans*-acetate, and filtered. This procedure was repeated several times. One hundred seventeen grams of pure *cis*-diacetate melting at 33 to 34° was obtained along with 28 g. of *trans*-diacetate.

The pure *cis*- and *trans*-diacetates were each mixed with a 4:1 mole excess of barium hydroxide and refluxed for three hours. The water was removed by evaporation under reduced pressure, and the dry solid extracted with hot acetone. From 117 g. of *cis*-diacetate, 62 g., or a 95% yield, of the *cis*-1,4-cyclohexanediol was obtained, which melted

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(10) Bartlett and Pockel, THIS JOURNAL, **59**, 820 (1937).

(11) Bartlett and Bavley, *ibid.*, **60**, 2416 (1938).

(12) Adkins and Cramer, *ibid.*, **52**, 4349 (1930).

(13) Sabatier and Mailhe, *Compt. rend.*, **146**, 1194 (1908).

(14) Senderens and Aboulenc, *ibid.*, **173**, 1365 (1921).

(15) Baeyer, *Ann.*, **278**, 92 (1894).

TABLE II

EFFECT OF TEMPERATURE AND SOLVENT

| Experiment[a] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Conditions | | | | | | | | |
| Solvent | Methanol | | | | Ethanol | | Acetone | |
| Temperature, °C. | 275 | 300 | 350 | 400 | 300 | 340 | 300 | 340 |
| Rate, cc./hr. | 132 | 127 | 130 | 131 | 126 | 125 | 115 | 124 |
| Duration, hours | 2 | 3 | 3 | 2 | 2 | 2.75 | 2.1 | 1.75 |
| Product obtained by distillation | | | | | | | | |
| B. p., °C. | Mole %[b] | | | | | | | |
| 80–90 (cyclohexadienes) | 0 | 2.9 | 28.8 | 65.2 | 8.3 | 37 | 4.2 | 26 |
| 90–105 (methylcyclohexadienes) | | | 1.7 | 4.0 | | | | |
| 105–155 (1,4-epoxycyclohexane)[c] | 38.5 | 44.5 | 11.3 | 0 | 21.4 | 0 | 17.3 | 0 |
| 155–167 (cyclohexenol) | 9.8 | 15.5 | 14.7 | 3.6 | 27 | 16.3 | 23 | 23.5 |
| >190 (polymers) | | | 20.7 | 18.5 | 15.7 | 22.4 | 36.4 | 40.4 |
| 220–245 (unreacted diol) | 32.5 | 27.8 | | | | | | |
| Product derived from solvent[d] | | | | | | | | |
| | Mole % | | | | | | | |
| Methyl ether | | | 1.9 | 24 | | | | |
| Formaldehyde | | | | 2 | | | | |
| Acetaldehyde | | | | | 3.6 | 5.9 | | |
| Isopropyl alcohol | | | | | | | 7.8 | 5.7 |

[a] Three moles of solvent to 1 mole of 1,4-cyclohexanediol were passed over 120 cc. of activated alumina. [b] Calculated on the basis of mole % of cyclohexanediol passed. [c] Contains about 95% of 1,4-epoxycyclohexane. [d] Calculated on the basis of mole % of solvent passed.

at 107°. From 139 g. of the *trans*-diacetate, 65 g., a yield of 84.4%, of *trans*-1,4-cyclohexanediol was obtained, which had a melting point of 142°.

### B. Analytical Methods

The procedures below were adopted for determining the composition of some of the fractions obtained on distillation.

The degree of unsaturation of the various products was determined by means of selective hydrogenation. The reaction was carried out under mild experimental conditions in order not to hydrogenate the aromatic compounds that might be present. The hydrogenated product was usually tested for the presence of aromatic hydrocarbons. In order that cyclohexane in the presence of olefins might be determined, the latter were removed by alkylation, that is, by adding benzene to the product tested and treating the mixture with concentrated sulfuric acid. Under these conditions only alkylation of benzene by the olefins occurs.[16] The excess of benzene and higher-boiling aromatic hydrocarbons formed was removed with 15% fuming sulfuric acid. Sulfuric acid alone, in the absence of aromatic hydrocarbons, causes the formation of saturated hydrocarbons by conjunct polymerization.[8] The absence of a hydrocarbon layer after treatment with fuming sulfuric acid was evidence of the absence of cyclohexane.

The presence of cyclohexene and cyclohexadiene was determined by bromination and distillation. The dibromocyclohexane was a liquid, while the tetrabromocyclohexanes were solid.

**Hydrogen Number.**—About 8 g. of product, together with 10 cc. of pentane and 1 to 2 g. of nickel–kieselguhr catalyst,[17] was hydrogenated in a 125-cc. rotating autoclave at 50° and under 60 atmospheres of initial hydrogen pressure. The degree of unsaturation was determined from the pressure drop.

**Alkylation Method.**—About one part by volume of the cyclohexadiene fraction, mixed with three parts of benzene and cooled to 0°, was added to two parts of 96% sulfuric acid, also at 0°, and placed in a glass-stoppered graduated cylinder. The mixture was shaken at short intervals over a period of one hour. The upper layer was separated and treated with an equal volume of 15% fuming sulfuric acid at 0°.

**Cyclohexenol Fraction.**—The relative amounts of cyclohexenol and cyclohexanol were determined by means of hydrogen number as described above; the hydrogenation of the double bond was quantitative.

**Methylcyclohexadiene Fraction.**—The product, after being hydrogenated in order to determine the degree of unsaturation, was subjected to dehydrogenation with platinum alumina catalyst.[18] The toluene produced was identified by means of its dinitro derivative.

### C. Apparatus and Procedure

The apparatus used for continuous reaction consisted of a graduated cylinder connected to a Tropsch–Mattox[19] laboratory pump, a Pyrex glass reaction tube, a glass receiver, traps cooled with ice and dry-ice–acetone, and a gas-collecting bottle containing a saturated sodium chloride solution. The reaction tube was heated in a thermostatically controlled vertical furnace. The lower aqueous layer, when present, was separated and saturated with potassium carbonate to salt out the dissolved organic substances, which were added to the upper layer. The combined product was dried over anhydrous potassium carbonate, and then distilled. The great solubility of water in the reaction product made repeated distillations and removal of water sometimes necessary.

**Experiment 3.**—The cyclohexadiene fraction consisted of 33% cyclohexene and 67% cyclohexadiene.

**Experiment 6.**—The cyclohexadiene fraction was redistilled, and 8 g. of the portion boiling at 82 to 86°, $n^{20}\mathrm{D}$ 1.4600, was used for the determination of the hydrogen number. This fraction consisted of 80% cyclohexadiene and 20% cyclohexene; cyclohexane and benzene were absent.

The cyclohexenol fraction was redistilled, and 4 g. boiling at 161 to 165°, $n^{20}\mathrm{D}$ 1.4640, was taken for analysis. According to the hydrogen number the product consisted of 30% cyclohexanol and 70% 3-cyclohexene-1-ol. The presence of 3-cyclohexene-1-ol was determined by means of the phenylurethan derivative, m. p. 78 to 79°.

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(16) Ipatieff, Corson and Pines, THIS JOURNAL, **58**, 919 (1936).

(17) Ipatieff and Corson, *Ind. Eng. Chem.*, **30**, 1039 (1938).

(18) Pines and Ipatieff, THIS JOURNAL, **61**, 1076 (1939).

(19) Tropsch and Mattox, *Ind. Eng. Chem.*, **26**, 1338 (1934).

**Experiment 8.**—A portion (2.8 g.) of the redistilled cyclohexadiene fraction (b. p. 81 to 85°) was analyzed. It consisted of 33% cyclohexene and 67% cyclohexadienes.

**Dehydration of *cis*- and *trans*-1,4-Cyclohexanediol.**—Pure *cis*-, *trans*- and an equimolar mixture of *cis*- and *trans*-1,4-cyclohexanediol, dissolved in methanol in molal ratio 1:5, was passed over 36 cc. of alumina at a temperature of 275°; the experimental data are given in Table III.

The polymer fractions were composed of oxygen-containing high-boiling condensation products.

TABLE III

DEHYDRATION OF *cis*- AND *trans*-1,4-CYCLOHEXANEDIOL

| Experiment | | Rate, cc./hr. | Duration, hours | 1,4-Epoxycyclohexane | Cyclohexenol | Unreacted diol |
|---|---|---|---|---|---|---|
| *trans*- | 9 | 36 | 2.75 | 73 | 11.4 | 0 |
| *cis*- | 10 | 38 | 2 | 28 | 27 | 16 |
| Mixture | 11 | 36 | 2.75 | 33.5 | 20.6 | 17.0 |

**Dehydration of 1,4-Cyclohexanediol in the Absence of Solvent.**—Twenty-one grams of 1,4-cyclohexanediols and 15 g. of activated alumina were placed in a round-bottom flask connected to a distilling column and heated to a reflux temperature at 241 to 243° for twenty-one hours. The reaction product, which was distilled off as formed, consisted of 39 mole per cent. epoxycyclohexane, 18% cyclohexenol, and 23% high-boiling products.

**Properties of 1,4-Epoxycyclohexane.**—The boiling point of the epoxide determined by the Cottrell[20,21] method was 120.1° at 760 mm., $dt/dp$ (770–730 mm.) = 0.080°/mm., $d^{20}_{4}$ 0.9707, $dd/dt$ (20–30°) = 0.00092/°C.; $n^{20}_{\text{D}}$ 1.4477; $\text{M}^{20}_{\text{D}}$ 27.05 (Lorenz–Lorentz).

*Anal.*[22] Calcd. for $C_6H_{10}O$: C, 73.47; H, 10.20. Found: C, 74.19; H, 10.14.

1,4-Epoxycyclohexane is soluble in the usual organic solvents, such as methanol, ethanol, acetone, ether and benzene, and is partially soluble in water, with which it forms an azeotropic mixture boiling at 90°. The chemical properties of the 1,4-epoxycyclohexane are those of an ether. It may be dissolved in 40 to 60% sulfuric acid, and recovered unchanged on dilution with water. It does not react with ethylmagnesium bromide nor with metallic sodium.

**Hydrobromic Acid.**—A mixture of 5 g. of the epoxide and 15 cc. of 48% hydrobromic acid was refluxed for six hours. A lower layer was formed, which crystallized on standing. The material was cooled and filtered, and the solid was recrystallized from hot alcohol. This product melted at 112–113°, corresponding to *trans*-1,4-dibromocyclohexane.

*Anal.* Calcd. for $C_6H_{10}Br_2$: C, 29.75; H, 4.13. Found: C, 29.67; H, 4.07.

## Summary

The dehydration of 1,4-cyclohexanediol to 1,4-epoxycyclohexane was studied with reference to the effect of temperature, solvent, catalyst, and geometric configuration of the diol upon the yield of 1,4-epoxycyclohexane.

An improved method for the separation of the *cis*- and *trans*-1,4-cyclohexanediol was described, and a melting point curve of the mixture of the two isomers given.

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(20) Cottrell, THIS JOURNAL, **41**, 721 (1919).

(21) Bruun and Hicks-Brunn, *Bur. Standards J. Research*, **6**, 871 (1931).

(22) Analyses were made by Dr. T. S. Ma, University of Chicago.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# Introduction of the 3-Keto-Δ4-conjugated System in the Desoxycholic Acid Series

BY BYRON RIEGEL AND A. VERN MCINTOSH, JR.

The most physiologically active steroidal hormones from the adrenal cortex possess the same structure in ring A as found in testosterone and progesterone, namely, a 3-keto group and a carbon–carbon double bond at the 4,5-position. For the preparation of corticosterone and its derivatives from desoxycholic acid, the introduction of this conjugated system had to be studied.

In the preparation of methyl 3-keto-12-hydroxy-4-cholenate (XIII) and its *nor* (XIV), *bisnor* (XV), and *etio* (XVI) homologs from the corresponding methyl 3,12-dihydroxycholanates (I, II, III, IV), the 3-keto-12-hydroxy compounds (V, VI, VII, VIII) are necessary intermediates. The usual procedure for making these keto intermediates involves acetylation of both hydroxyl groups, then selective hydrolysis or alcoholysis of the 3-acetoxy group and oxidation of the resulting 3-hydroxyl compound to give the 3-keto derivative. These procedures are illustrated by the synthesis of methyl 3-keto-12-hydroxycholanate (V) by Yamasaki and Kyogoku[1] and methyl 3-keto-12-hydroxy-*etio*-cholanate (VIII) by Lardon and Reichstein.[2] Selective oxidation of the 3-hydroxyl group without protection of the 12-hydroxyl group would provide a simpler synthesis in this series. Gallagher[3] mentioned the preferential oxidation in the Oppenauer reaction of the 3-hydroxyl group in esters of cholic and desoxycholic acids. Ehrenstein and Stevens[4] found that the 3-keto derivative was obtained when 12-acetoxypregnan-3(α),7-diol-20-one was refluxed with cyclohexanone in the presence of aluminum isopropoxide. Recently Fuchs and Reichstein[5] reported the selective oxidation, by means of aluminum phenoxide in acetone, of the 3-hydroxyl group of 3,12-dihydroxy-21-acetoxypregnanone-20. Several examples have been reported where the 3-hydroxyl group has been selectively oxidized in compounds that also contain a 5,6-double bond. These are not considered

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(1) K. Yamasaki and K. Kyogoku, *Z. physiol. Chem.*, **233**, 29 (1939).

(2) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **26**, 607 (1943).

(3) T. F. Gallagher, *J. Biol. Chem.*, **133**, XXXVI, (1940).

(4) M. Ehrenstein and T. O. Stevens, *J. Org. Chem.*, **5**, 660 (1940).

(5) H. G. Fuchs and T. Reichstein, *Helv. Chim. Acta*, **26**, 511 (1943).