CIS-TRANS ISOMERISM IN THE POLYHYDROXY

CYCLOHEXANE SERIES

A Thesis

by

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TABLE OF CONTENTS

GENERAL INTRODUCTION	1
HISTORICAL INTRODUCTION	4
DISCUSSION OF RESULTS	24
EXPERIMENTAL PART	
Hydrogenation of Pyrogallol	49
Examination of a recorded procedure for separating the pyrogallitols	53
Attempted separation of the pyrogellitols by the isopropylidene acetal method	54
Synthesis of trans-1,2-cyclohexanediol and some of its derivatives	58
Condensation of trans-1,2-cyclohexanediol with acetone	61
Synthesis of 3-cyclohexenol acetate	6 6
Synthesis of the a- and β -pyrogallitols	69
Synthesis of isopropylidene-β- and δ- pyrogallitols	76
Preparation of the benzoates of isopropylidene- β- and δ- pyrogallitol	80
Synthesis of the monomethyl ethers of β - and δ -pyrogallitol	82
Oxidation of the monomethyl ethers of β - and V-pyrogallitol with lead tetrascetate	84
Preliminary Experiments in the 1,2,4-Cyclo- hexanetriol Series	84
SUMMARY	92
CLAIMS TO ORICINAL RESEARCH	95
BIBLIOGRAPHY	96

LIST OF TABLES

Table		Page
I	Physical Constants of the 1,2,3-Cyclo- hexanetriols and the 1,2-Cyclohexanediols	5
II	Yields of a-, β -, and δ -Pyrogallitols by the Hydrogenation of Pyrogallol	24
III	Oxidation of β- and δ-Pyrogallitol Monomethyl Ethers with Lead Tetraacetate	.85

LIST OF FIGURES

Figure

٠

I	Rate of oxidation of β - and V -Pyro-	
	gallitol Monomethyl Ethers with Lead	
	Tetraacetate	39

Chemistry

Charles Jennings Cogek

CIS-TRANS ISOMERISM IN THE POLYHYDROXY CYCLOHEXANE SERIES

The hydrogenation products of pyrogallol, <u>cis-cis-cis-, cis-cis-trans-</u> and <u>cis-trans-cis-1,2,3-</u> cyclohexanetricles, were of interest as starting materials in a war research. Since the latter two isomers were formed in low yield, the present research undertook to discover more productive ways of obtaining them.

The <u>cis-cis-trans-1,2,3-cyclohexanetriol</u> and the <u>cis-trans-cis-</u> isomer were accordingly synthesized in 23% and 1% yield respectively, by the hydroxylation of 3-cyclohexenol acetate. Isopropylidene-<u>cis-cis-cis-1,2,3-</u> cyclohexanetriol and the isopropylidene-<u>cis-cis-trans-1,2,3-</u> oyclohexanetriol and some of their derivatives were prepared and characterized.

The chemicals necessary for similar directed syntheses of the 1,2,4-cyclohexanetriols, i.e., 4-hydroxy cyclohexene and some of its derivatives, were synthesized from hydroquinone.

Isopropylidene-trans-1,2-cyclohexanediol was prepared and characterized. There are three position isomers of cyclohexanetriol, in which the hydroxyl groups occur at the 1, 2, 3; 1, 2, 4; and 1, 3, 5 positions, and each of these compounds may exist in a number of forms which are <u>cistrans</u> isomers. Although all of the position isomers are recorded in the literature, the different geometrical isomers have not been completely described, and some of them are not obtained readily by the recorded methods. The object of this research was to prepare certain of these alcohols and to study their chemistry.

The main interest of the present work was in the various isomeric forms of 1, 2, 3-cyclohexanetriol (pyrogallitol). This alcohol is closely analogous to glycerol, and a study of the properties of the nitrate esters of the cyclic triol might be expected to cast light on the behaviour of nitroglycerine as an explosive. A full documentation of this problem may be found in the thesis of W. R. Christian, from this laboratory (1).

Previous work indicated that the quickest approach to the 1, 2, 3-cyclohexanetriols was by the hydrogenation of pyrogallol. The three stereoisomers I, II, and III, were obtained by Christian, and each was assigned its proper configuration, but the a and β isomers, I and II, were isolated only in small amounts. Nevertheless, at the beginning of the present research, it was anticipated that a few hydrogenations, carried out on a large scale by Christian's methods, would yield all of these compounds in quantities sufficient for testing the explosive and chemical properties of the three trinitrates. When this hope was not realized, other ways of preparing the relatively inaccessible forms were sought.



Methods were examined for the oxidation of cyclohexene, XIII, to derivatives of 3-hydroxy cyclohexene, IV, such as the acetate, XV, or the methyl ether (cf. VI). The double bond was then hydroxylated by standard methods to yield mixtures of derivatives of the α - and β -pyrogallitols, I and II. Since the separation of the pyrogallitols by the previous technique (2), which involved the tribenzoates, was not entirely satisfactory, the possibility of a more efficient separation via the selective formation of isopropylidene derivatives was investigated.

The study of these ketals led to an examination of

(a) Dotted lines indicate a trans configuration. The nomenclature α , β , γ , is that employed by Lindemann and de Lange (2)

the condensation of acetone with <u>trans-1,2-cyclohexanediol</u>, XXII, and it was found that, contrary to statements in the literature (3), this glycol does react with acetone. Under suitable conditions, all three of the pyrogallitols condensed with acetone, and the structures of two of the derivatives formed were proven.

A relatively easy separation of β -pyrogallitol from synthetic mixtures of the α and β isomers was achieved by fractional crystallization from a mixed solvent composed of ethyl acetate and ethanol; however, in order to separate the relatively small amount of α triol present in these mixtures, the tribenzoate method mentioned above had to be used.

A brief study was made of the possible application of these new synthetic methods to the preparation of the isomeric 1,2,4-cyclohexanetriols, XXXIV - XXXVII, the synthesis of the starting material, 4-hydroxy cyclohexene, XXXIII, and some of its derivatives being carried out in collaboration with Mr. R. Y. Moir.

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- 3 -

HISTORICAL INTRODUCTION

As the name implies, the pyrogallitols were first obtained by the hydrogenation of pyrogallol. Christian (1) and Lindemann and de Lange (2) carefully considered the earlier work in this field by Sabatier and Mailhe (4) and Senderens and Aboulenc (5), and a repetition of their reviews is omitted from the present discussion. It seems desirable, however, to summarize the results of Christian.

The latter author made a detailed study of the rates at which the three isomeric pyrogallitols were oxidized by lead tetra-acetate and periodic acid. Since these reagents were known to oxidize <u>cis</u> 1,2-glycol units much more rapidly than the <u>trans</u> isomers, the rate-plots enabled him to confirm the configuration previously suggested for each pyrogallitol (2). His final results are summarized in Table I, together with similar data for the <u>cis</u>- and trans-1,2-cyclohexanediols.

Christian also made a detailed study of the yields of the isomeric pyrogallitols obtained by hydrogenating pyrogallol with Raney nickel catalyst under various conditions of temperature, time, and pressure of hydrogen. The δ isomer, III, always preponderated in the mixture and crystallized readily from it. From the benzoylated residue, β pyrogallitol, II, was separated as the ethanol insoluble

- 4 -

tribenzoate, in rather poor yield. Separation of the a isomer, I, as the ethanol soluble tribenzoate, even in very poor yield, was difficult and uncertain at best. Moreover, this separation was complicated by the presence of molecular debris from unchanged pyrogallol, which had been removed from the original crude hydrogenation product by oxidation with air in the presence of ammonia. Debenzoylation of the two tribenzoates, and purification of the resulting a- and β -pyrogallitols, was also tedious and involved substantial loss.

TABLE I

AND THE 1,2-CYCLOHEXANEDIOLS m.p. °Ca velocity constants^D Structure m.p. of °Ca benzoates, $k \ge 10^3$ k x 10⁸ 142° I 108 1.0 0.12 - α 184° II - β 124 14 0.60 142° III - 8 142 36 1.20 63^d cis-1,2-cyclo-- 98 1.5 54 hexanediol 93^d trans-1,2-cyclo-104 2.7 0.22 hexanediol

PHYSICAL CONSTANTS OF THE 1,2,3-CYCLOHEXANETRIOLS

- (a) All of the m.p.'s are taken from the paper of Lindemann and de Lange (2)
- (b) Units of k are 1./mole/sec. The first column refers to oxidations with Pb(OAc), at 18.6°; the second wolumn refers to oxidations with HIO, at 20.0°. (1).
- (c) Tribenzoates.
- (d) Dibenzoates.

Five references to the synthetic preparation of the 1,2,3-cyclohexanetriols were found in the literature. These syntheses all involved the preparation of 3-hydroxy cyclohexene, IV, or a derivative of that alcohol, followed by the addition of two hydroxyl groups to the double bond. In order to interpret the previous work in this field, the latter reaction will be discussed briefly.

Boeseken (6) concluded that potassium permanganate introduced two hydroxyl groups exclusively, or almost exclusively, in the <u>cis</u> configuration, whereas the glycols formed as a result of the action of a peracid on an olefinic double bond were <u>trans</u>. An exception to the latter statement occurred when one of the double-bonded carbon atoms carried a phenyl group, in which case a mixture of the <u>cis</u> and <u>trans</u> glycol was obtained. This exception was proven true for only one olefin, phenyl-1-cyclohexene, V. It is pertinent to note here that the peracid - olefin reaction occurs via an intermediate possessing an ethylene oxide ring (e.g., IX) which is hydrated, in dilute acid solution, to the <u>trans</u> 1,2 glycol.



In the synthesis of the 1,2,3-cyclohexanetriols,

- 6 -

the addition of a pair of <u>cis</u> hydroxyl groups to 3-hydroxy cyclohexene, IV, would yield either the δ , III, or the β , II, isomers, and most likely a mixture of these two; the addition of a pair of hydroxyl groups in a <u>trans</u> configuration would be expected to yield a mixture of α , I, and β , II, cyclohexanetriols.

Brunel (7) added the elements of hypoiodous acid to the double bond of 3-ethoxy cyclohexene, VI. The addition presumably proceeded in both possible ways, and a mixture of VII and VIII was obtained; treatment of this product with solid potassium hydroxide in ether gave the oxide IX, which was hydrolyzed quantitatively with boiling water to give X. Since the hydroxyl group and the iodine atom were probably <u>trans</u> to each other (8), VII and VIII were actually each a mixture of two geometric isomers, one of each of which is shown; IX and X likewise consisted of two isomers, and one of each of these is shown.

Brunel separated the two triols by fractional crystallization of their benzoates or acetates, and stated that almost all of his triol mixture consisted of the α isomer, I.





The same author oxidized 3-ethoxy cyclohexene, VI, with dilute potassium permanganate and obtained XI, which, after removal of the ethyl group, yielded β -1,2,3cyclohexanetriol, II. Apparently the \Im isomer, III, which would be expected according to the discussion presented earlier, was not formed. The intermediate ethoxy cyclohexanediol, XI, was described as a syrup; this experiment was repeated several years later by Hofmann and Damm (9), who obtained a solid, m.p. 27 - 28°, probably identical with Brunel's product.



McRae and Moir (10) proposed to oxidize 3-methoxy cyclohexene with the appropriate reagents and isolate the two isomeric oxide intermediates (cf. IX). Hydration of both oxides by the usual methods and demethylation would give a mixture of the α - and β -pyrogallitols, I and II. Since II could also be synthesized by permanganate oxidation of the same olefin, this triol contained one <u>cis</u> pair of hydroxyl groups and also one <u>trans</u> pair. The α triol, I, therefore must possess the <u>trans-trans</u> configuration. By a process of elimination, the triol, III, was assigned the <u>cis-cis</u> structure.

Kotz and Richter (11) prepared, in very low yield, a 1,2,3-cyclohexanetriol, m.p. 108°, by oxidizing the double bond in 3-hydroxy cyclohexene, IV, with perbenzoic acid and hydrolyzing the intermediate XII with aqueous acetic acid.



The tribenzoate of this alcohol melted at 165°, and a comparison of these m.p.'s with the constants given in Table I indicated that the triol prepared was possibly a mixture of the α and the β isomers, I and II.

Farmer and Sundralingam (12), and Hock (13), oxidized cyclohexene, XIII, with oxygen under the influence of ultraviolet light, and then treated the hydroperoxide formed, XIV, with dilute sulfuric acid. The yield on the second step of this synthesis, 50%, was that reported by Hock (13); the English workers (12) obtained 1 g. of



what was evidently the pure β triol, II, m.p. 124°, from 4 g. of the hydroperoxide. The reason for this steric selectivity is obscure.

A consideration of possible methods for the synthesis of the somewhat inaccessible β , II, and the still less accessible α -pyrogallitol, I, suggested that the following processes were worthy of examination:

(1) oxidation of cyclohexene, XIII, to 3-hydroxy cyclohexene, IV, or a derivative of IV, followed by the <u>trans</u> addition of two hydroxyl groups to the double bond. Cyclohexene itself is easily prepared in quantity (14).

(2) inversion of the central hydroxyl group of -pyrogallitol, III, a supply of which is readily available from the hydrogenation of pyrogallol. Methods for effecting this inversion were devised, but since no experimental work was done on this phase of the problem, these methods are more appropriately considered in the discussion.

The oxidation of cyclohexene at the methylene

group alpha to the double bond is possible by the reaction conceived by Riley, Morley and Friend (15), and adapted by Guillemonat (16) to give 3-cyclohexenol acetate, XV, in 45% yield. Selenium dioxide, in a mixed solvent composed of acetic acid and acetic anhydride was used in this process, the convenience of the method compensating for the rather low yield.



XIII

Cyclohexene was also oxidized by Criegee (17) with lead tetraacetate to give 3-cyclohexenol acetate, XV, in 21% yield, together with other products. This reaction will be considered in greater detail subsequently. As already mentioned, oxidation of cyclohexene to the hydroperoxide XIV was carried out photochemically, and XIV could be reduced to 3-cyclohexenol, IV, in 85% yield with sodium sulphite (18). 3-Ethoxy cyclohexene, VI, could be prepared in 45% overall yield by the method of Hofmann and Damm (9) which involved the reaction of 1,2-dibromocyclohexane, prepared from the reaction of bromine and cyclohexene, with sodium ethoxide.

Attention was also directed to the reaction

reported by Ziegler, Spath, Schaaf, Schumann and Winkelmann (19) for the substitution of a bromine atom for a hydrogen atom in the active methylene group of olefins. In this reaction, N-bromosuccinimide, XVI, which was readily prepared, was heated under reflux with the olefin in carbon tetrachloride solution, and the 3-bromo derivative was isolated in high yield. No doubt, 3-bromocyclohexene, XVII, a compound containing a reactive halogen atom, could be hydrolyzed to the corresponding alcohol with ease. The availability of XVII may increase the scope of the synthetic possibilities in the triol series. Winstein and Henderson (20) showed that replacement of the halogen atom in trans-2-methoxy-cyclohexene-bromide, XVIII, occurred with predominant retention of configuration, and if XVII could be



hydroxylated without loss of the halogen atom, it seemed possible that the products could be utilized as a source of the α - and β - pyrogallitols, I and II.



XVIII

It was clear that the synthesis of 3-cyclohexenol, IV, presents no serious difficulties, and that the addition of two hydroxyl groups to the double bond would result in the probable formation of a mixture of two of Unfortunately, no generalizations the pyrogallitols. concerning the effect of a neighbouring group such as is present in IV on the course of the hydroxylation can be In this regard, the work of Brunel (7), Farmer and made. Sundralingam (12), and Hock (13) are especially worthy of A study of the publications by Winstein and collanote. borators (20) on the effects of neighbouring groups in replacement reactions indicated that this work will also be important in research in this field.

One of the best methods for the hydroxylation of a double bond appears to be that reported recently by Swern, Billen, Findley and Scanlan (21). In this process, which was a development of earlier work by these authors, by Meerwein, Schoeller, Schwenk and Borgwardt (22) and by Boeseken (6), the reagent was hydrogen peroxide in formic acid. The active agent, probably performic acid, oxidized ethylenic double bonds to glycol monoformates together with a small amount of the free glycol. The American authors used the reaction to hydroxylate a number of open-chain unsaturated fatty materials but the patent of the German investigators dealt with cyclic compounds, and only the <u>trans</u> glycol was isolated. The course of this reaction has already been discussed.

Hydrogen peroxide in organic solvents, with catalytic quantities of certain metallic oxides, has been extensively used as a hydroxylating agent. Osmic acid (23) is the most common catalyst; yields of 30-60% of glycol are obtained and both <u>cis</u> and <u>trans</u> products, where these are possible, have been reported (24). Seguin (25) oxidized cyclohexene with hydrogen peroxide using selenium dioxide as a catalyst, and obtained only <u>trans-1</u>,2-cyclohexanediol, XXII.

The reaction reported by Prevost (26), in which olefins were treated with silver benzoate and iodine in boiling benzene, gave the corresponding glycol dibenzoate, often in excellent yield. Prevost stated that where the possibility of <u>cis-trans</u> isomerism existed, the product was predominantly or exclusively the <u>trans</u> isomer. However, the experiments on which this conclusion was based were not described. No experiments with cyclohexene, perhaps the simplest olefin which yields two geometrically isomeric diols, were presented.

Mercuric acetate oxidizes some olefins (27) to glycols. The reaction with cyclohexene in methanol appeared to be an addition of the elements of methoxy mercuric acetate to the double bond to give XIX (28). No successful attempts to replace the -HgOAc group in the adduct by the hydroxyl

- 14 -



group have been reported.

The use of lead tetraacetate for the hydroxylation of double bonds was introduced by Criegee (17). In the reaction of this salt with cyclohexene in glacial acetic acid, Criegee isolated 3-cyclohexenol acetate, XV, in 21% yield, a mixture of cis- and trans-1,2-cyclohexanediol diacetates (7%) and an unidentified cyclohexenediol diacetate (1%). Although some "addition" of acetoxyl groups to 3-cyclohexenol acetate, XV, would be expected, no triol derivative was isolated. It is well known that the reagent used cleaves 1,2-glycols to two carbonyl units, and the major products in the above oxidation may have been deriva-Nor was any triol derivative tives of adipic dialdehyde. isolated from the action of lead tetraacetate on any of the other olefins employed by Criegee. These facts discouraged experiments which might have been designed to prepare the pyrogallitol triacetates from cyclohexene in a single oxida-An important factor favoring peracid oxidation of tion. the double bond is that the configuration of the diol is almost always predictable, but no similar generalization can be applied to oxidation with tetravalent salts of lead.

Another method for the preparation of a 1,2glycol from an olefin involved the bromination of the double bond to form a dibromide, followed by replacement of the halogen atoms with hydroxyl groups by a suitable reagent, such as silver acetate (this reagent actually yields an acetate ester which must be saponified to obtain the glycol). Since the mechanism of trans addition of bromine to an olefin is now accepted (29), replacement of the halogen atoms would necessarily have to proceed without inversion, or with an even number of inversions, in order to obtain a mixture of the a- and β -pyrogallitols, I and II, by this method. Winstein and Buckles (8) obtained a 70% yield of a product that was 98% trans-1.2-cyclohexanediol, XXII, after saponifying the initial product, XXI, obtained by the action of silver acetate in dry acetic acid on trans-1,2-dibromocyclohexane, XX. When the same authors used moist acetic acid,





the final product was almost entirely <u>cis</u>-1,2-cyclohexanediol, XXV. A mechanism explaining these results was presented in the papers referred to above.

The addition of hypohalous acids to the double bond to give halohydrins is well known. Winstein and Buckles (8) prepared <u>trans-2-bromocyclohexanol</u>, XXIII, from cyclohexene, XIII, and N-bromoacetamide, XXIV, in 79% yield. This product could be transformed into <u>trans-1,2-cyclohexanediol</u>, XXII, or to its <u>cis</u> isomer, XXV, in excellent yields by the method mentioned above. The application of this process to syntheses in the pyrogallitol series was obvious.

Earlier in this thesis, dissatisfaction with Lindemann and de Lange's method (2) for isolating the α pyrogallitol, I, and to a lesser extent the β -isomer, II, was mentioned. An investigation of the literature revealed



that a simple, efficient process (3) which had been used by several workers (30)(31)(1) to separate the two isomeric 1,2-cyclohexanediols, XXII and XXV, could probably be applied successfully in the pyrogallitol series. This method was based on the generalization that <u>cis</u>-1,2-diols, but not the isomeric <u>trans</u> compounds, condensed with acetone in the presence of an acid catalyst to yield acetals whose solubilities and other physical properties were quite different from those of the parent alcohols. A typical acetal of this type was that obtained from XXV and acetone, in the presence of



XXV

IXVI

hydrochloric acid, and a dehydrating agent such as anhydrous sodium sulfate to absorb the water formed in the reaction.

The acetal XXVI boiled some 50° below XXV and was much more soluble than XXV in organic solvents such as benzene or petroleum ether. After the condensation was complete, the acid catalyst was neutralized, and the acetal could be distilled, leaving any of the <u>trans-1,2-</u> cyclohexanediol, XXII, recoverable in good yield from the residues. Acetals of this type (e.g., XXVI) were hydrolyzed in excellent yield in acid media to regenerate the alcohol (e.g., XXV).

Only a single case of the condensation of a <u>trans</u> 1,2 glycol was known; <u>trans-1,2-cycloheptanediol yielded an</u> isopropylidene acetal when hydrochloric acid was used as a catalyst (3). Since, however, <u>trans-1,2-cyclohexanediol</u>, XXII, was inert toward acetone, there was a sound basis for the view that β -pyrogallitol, II, would condense with the ketone to give XXVII, whereas α -pyrogallitol, I, would not

- 18 -

react. Mixtures of I and XXVII could probably be separated as the two cyclohexanediols had been.



A complication which existed for the pyrogallitols was the possibility that acctone might condense with the 1,3-hydroxyl groups. Isopropylidene acetals of a few 1,3-glycols have been reported. Boeseken and Hermans (32) condensed acetone and trimethylene glycol successfully: Boeseken, Schaefer and Hermans (33) prepared both mono- and di-isopropylidene pentaerythritol; Haworth and Porter (34) proved that a six membered ring was present in acetone-xylose, and Reichstein and Grussner (35) proved that the same was true of sorbose; Hibbert and Morazain (36) cited the preparation by Carter of isopropylidene- β -methyl glycerol; Fischer, Taube and Baer (37) synthesized isopropylidene-1,3-dihydroxyacetone. All of these condensations are, however, exceptional.

No investigation of the reaction of the two 1,3 cyclohexanediols (resorcitols) with acetone has been made. Fischer and Dangschat (38) proved that acetone-quinide and isopropylidene-shikimic-acid-methyl-ester had the structures XXVIII and XXIX. This research, together with the other work just discussed, lent credence to the view that β -



pyrogallitol, II, would, under suitable conditions, react with acetone to form XXVII, and that α -pyrogallitol would not react.

A procedure for the preparation of isopropylidene glycerol, recently developed by Newman and Renoll (39), used p-toluenesulfonic acid as the catalyst, and described the removal of the water formed in the reaction by azeotropic distillation with petroleum ether of boiling point 30 too. Since this method avoided the acid concentrations employed by Derx (3) for the preparation of these acetals, it appeared to be entirely suitable for the reaction contemplated with the pyrogallitols.

In anticipation of the successful preparation of isopropylidene- β - and δ -pyrogallitols, for which XXVII and XXX appeared to be the probable formulae, methods for

determining the structure of these new compounds were sought. The free hydroxyl group in these acetals could probably be methylated, and the products would give,



after hydrolysis of the acetal bonds in mildly acidic media, XXXI from XXVII and XXXII from XXX.

The earlier work on the rate of oxidation of isomeric polyhydroxy glycols with lead tetraacetate and periodic acid was reviewed by Christian (1), who also reported data for the rate of oxidation of the two 1,2-cyclohexanediols, XXII and XXV, and the three isomeric pyrogallitols, I, II, and III, with these reagents. This work formed the basis for the determination of the structures of the β - and δ -isopropylidene pyrogallitols, which were probably XXVII and XXX, by oxidation of the methylated and hydrolyzed derivatives, probably XXXI and XXXII.

The 1,2,4-Cyclohexanetriols

Only two references to these alcohols were found in the literature. Senderens and Aboulenc (5) hydrogenated 1,2,4-trihydroxybenzene and obtained what was described as a vitreous mass, b.p. 260 - 280°. Zelinskii and Titova (40) synthesized a compound which softened at 104° and melted at 122° by the action of either potassium permanganate or perbenzoic acid on 4-hydroxy cyclohexene, XXXIII. The compound was very hygroscopic, was insoluble in benzene and ether, but soluble in ethanol and in water. In the light of the discussion presented earlier, the four possible <u>cis</u>trans isomers XXXIV - XXXVII would be anticipated from these



two reactions. Presumably all of these triols could be resolved into optical enantiomorphs.

The 1,3,5-Cyclohexanetriols

The 1,3,5-cyclohexanetriols exist in the <u>cis-cis</u>-<u>cis</u> form, XXXVIII, and the <u>cis-trans-cis</u> form, XXXIX, neither of which is capable of optical resolution.

Wislicenus (41) isolated 1 - 2 g. of a 1,3,5-cyclohexanetriol by the reduction of 10 g. of phloroglucinol with sodium amalgam. The crystalline triol melted at about 115°, resolidified, and melted again at 184 - 185°; it was insoluble in ether and benzene, and soluble in water and ethanol. The product formed a dihydrate, and crystallized in the form of needles, anhydrous, from ethyl acetate. No configuration was assigned to this compound



XXXVIII

XXXIX

Senderens and Aboulenc (5) hydrogenated phloroglucinol at 135 - 140°, under 40 kg. pressure of hydrogen. The cyclohexanetriols distilled at 245 - 260°, and combined with three moles of acetic acid.

Lindemann and Baumann (42) prepared two isomers, one melting as described by Wislicenus and the other melting at 145°, by the hydrogenation of phloroglucinol. The former was designated the a isomer, the latter the β isomer, but configurations were not assigned to these products. From 126 g. of the phenol, 25 g. of the a and about 14 g. of the β -phloroglucitols were obtained. The two compounds were separated by fractional crystallization from acetone in which the a isomer was much less soluble than the β form.

No further experimental work on the 1,3,5 cyclohexanetriols was found recorded

DISCUSSION OF RESULTS

A total of six hydrogenations of pyrogallol, the results of five of which are shown in Table II, were carried out. The products obtained from the five reductions tabulated were worked up by the same methods, but the crude pyrogallitol fraction obtained in the sixth reduction was used, (a) to test for the presence of the α - and the β -pyrogallitols, I and II, in the acetone insoluble (III) fraction; and (b) to examine the possibility of separating the α and the β isomers by the isopropylidene acetal method.

TABLE II

YIELDS OF α -, β -, and δ -PYROGALLITOLS BY

Pyrogallol Cyclohexanetriols						
g .	ö isomer m.p. 146-147°		δ isomer β-tribenzoate h.p. 146-147° m.p. 176-180°		a-tribenzoate m.p. 136-138°	
	g.	% ^a	8.	za	g.	% ^a
316 ^b	40.0	12.4	6.6	0.6	0.4	0.04
316 ^b	39.5	12.3	40.0	3.7	7.6	0.7
316 ^b	76°	24	3.1	0.3	none	
316 ^b	47.8	14.9	18.9	1.7	12.1	1.1
94.5 ^d	6.1	6.3	2.7	0.8	2.2	0.7

HYDROGENATION OF PYROGALLOL

(a) Percent of theory.

(b) With Raney Nickel catalyst.

(c) M.p. 130 - 137°. This would yield approx. 60 g., m.p.146 - 147°.

(d) With nickel on supercel catalyst (43).

In the first hydrogenation, unchanged pyrogallol was destroyed by the procedure of Christian (1), in which any phenols present in the crude, filtered reduction product were destroyed by oxidation with air in the presence of ammonia. The separation of pyrogallol from the triols by ether extraction was just as efficient, and avoided the oxidized products formed in Christian's pro-The ether extraction appeared to remove the cycedure. clohexanediols too (see, however, page 36), but a simple process for recovering these, and free pyrogallol from the ether extract, could doubtless be devised. In addition, the crude products from the hydrogenation were distilled after removing the Raney nickel catalyst, but before removal of the pyrogallol. This change in the procedure of Christian, who destroyed the pyrogallol in his crude filtered product. gave clean materials during the succeeding operations.

Since one of the objectives of this research was to find a convenient source of the β , II, and more especially, the α tricl, I, an examination of the hydrogenation process for possible defects which might be avoided was made, and other preparative schemes were also devised.

The conditions of the hydrogenation itself were adapted from the work of Christian (1), and were not further investigated. The separation of the δ -, III, from the α - and β -tricls, I and II, by means of acetone was examined carefully. This separation was fairly efficient, but not quantitative, and it was proven that some loss of the α and the β isomers occurred here. However, this proof involved several recrystallizations and the small yields of these two isomers did not justify the work necessary for their isolation.

Other work, discussed later in this thesis, indicated that acetone reacted with the pyrogallitols, and that its use as a solvent in the above separation introduced complications. Qualitative evidence for this reaction was obtained, for the products which had been in contact with this ketone frequently possessed the odor characteristic of the acetal. In addition, this solvent had no exclusive advantages; the separation of the V isomer occurred mainly because of its great predominance in the isomeric mixtures. As an alternative solvent, the use of ethyl acetate, mixed possibly with a small amount of ethanol to increase the solubility of the triols, is suggested. This solvent was not employed to separate the 5-pyrogallitol, but in view of its successful use in the separation of the β isomer from a synthetic mixture of the α - and β -pyrogallitols, and considering again the high percentage of the form obtained in the hydrogenation experiments, it appears worthy of trial for the purpose suggested.

The yields obtained in the benzoylation of the a-

- 26 -

and β -triol fraction were not always satisfactory. Whenever tricls whose purity was certain were benzoylated, the esters were isolated almost quantitatively. In those benzoylations in which only a 75% yield of the triester was obtained, the development of a brown color in the reaction mixture frequently occurred, but the nature of the impurities responsible for the discoloration remained unknown. Crude pyrogallol-free products from the hydrogenations behaved in this way, although the only impurity suspected was a small amount of 1,2-cyclohexanediols.

With the foregoing considerations in mind, the hydrogenation of pyrogallol was abandoned as a convenient source of the a- and β -pyrogallitols, and other synthetic methods were sought. The oxidation of cyclohexene using selenium dioxide in a mixture of acetic acid and acetic anhydride was a rapid means for the preparation of 3-cyclohexenol acetate, XV, although the yields reported by Guillemonat (16) could not be duplicated. In this connection, it may be noted that Bartlett and Woods (44) could not repeat the French author's preparation of 2-cyclohexenone by the same method, and Whitmore and Pedlow (45) devised another synthesis for the same ketone.

The hydroxylation of XV was preceded by an investigation of the same reaction with cyclohexene, XIII. Of the two methods of hydroxylation which appeared to be among the best available, that of Seguin (25) and that of Swern,

- 27 -

Billen, Findley and Scanlan (21), the contention of Seguin that the product obtained by his method was exclusively trans-1,2-cyclohexanediol was confirmed. The procedure of the American authors was carried out with cyclohexene for the first time. This reaction also yielded the pure trans diol, and none of the cis compound; further, it was shown that benzoylation of the free hydroxyl group in trans-1,2-cyclohexanediol monoformate, which was the main product in this reaction, occurred readily, and partial saponification of the diester to yield trans-1,2cyclohexanediol monobenzoate was also easily accomplished. The ease with which the formate esters are selectively hydrolyzed may prove useful in future work. No experiments were conducted to determine whether trans-1,2-cyclohexanediol monoformate (or monobenzoate) could be as readily transformed into a derivative of cis-1,2-cyclohexanediol as was the case with the monoacetate of the trans diol (20).

3-Cyclohexenol acetate, XV, was the only substituted olefin which was hydroxylated in this research, although qualitative experiments showed that the same reaction could be carried out with 3-cyclohexenol itself, and there is no doubt that the reaction with 3-alkyl ethers of the olefinic alcohol would occur successfully too. The use of ethers in this reaction was of particular interest because of the work of Brunel (7) and Hofmann and Damm (9) which indicated that the products obtained by these authors were

- 28 -

predominantly, and in one case exclusively, of a single configurational type. A disadvantage attending the use of the simple alkyl ethers is that drastic conditions are generally necessary to regenerate the alcohol, and the yields are often unsatisfactory. The use of the trityl ether, XL, which is easily hydrolyzed (46), and is conveniently analyzed (47), would circumvent this difficulty.



XL

The average yield in the hydroxylation of 3cyclohexenol acetate was 35% (crude product), which was somewhat disappointing in view of the much higher yields obtained in the same reaction with cyclohexene. In the case of the hydroxylation of 3-cyclohexenol acetate with the formic acid - hydrogen peroxide reagent, a second product containing a carbonyl group which reacted with 2,4-dinitrophenylhydrazine was isolated in fair yield. The same compound probably accounted for the low yield in the experiment in which hydrogen peroxide in glacial acetic acid was used. The structure of this substance was not determined.

There was no decisive advantage in any of the three methods employed in the hydroxylation, but for

convenience the use of hydrogen peroxide in formic acid (21) was preferred. Hydrolysis of the esters which were the initial products of the reaction by a small quantity of sulfuric acid in ethanol, and separation of as much of the β -pyrogallitol, II, as possible by repeated crystallization from a mixture of ethyl acetate and ethanol, were the most satisfactory methods of completing the synthesis. The hydroxylation of XV was a good source for β -pyrogallitol, but the α isomer was obtained in low yield, and the best means for preparing this isomer appears to be from the hydroxylation of ethers of 3-hydroxy cyclohexene, IV.

The search for a simple, convenient, quantitative method for the separation of the α - and β -pyrogallitols led to an investigation of the isopropylidene compounds of these triols. This research revealed some new and interesting facts.

The condensation of <u>trans-1,2-cyclohexanediol</u>, XXII, by the recently developed procedure of Newman and Renoll (39), in which p-toluenesulfonic acid was used as the catalyst and the water formed in the reaction was distilled azeotropically with petroleum ether of boiling point 30 - 60°, occurred readily, and yielded an oil, b.p. $77 - 78^{\circ}/20 \text{ mm., n}_{D}^{20}$ 1.4468, possessing all the properties of the acetal XLI. This result was surprising, since several experiments reported in the literature (3)(30)(31), indicated that the reaction did not take place. All of the authors referred to,

- 30 -



XXII

XLI

however, used hydrochloric acid gas as the catalyst, and anhydrous sodium sulfate to absorb the water formed in the reaction.

Some of the present experiments indicated how easily the <u>trans</u>-1,2-cyclohexanediol isopropylidene acetal, XLI, when prepared using hydrochloric acid as the catalyst, could be over-looked. When the <u>trans</u> diol was treated with acetone and dry hydrogen chloride of concentration 0.1% or 1% by weight, a small amount of the acetal XLI was isolated, and much of the unchanged diol could generally, though not always, be recovered. A 3% yield was a maximum value, obtained with the more dilute concentration of hydrogen chloride; when a 1% concentration was employed, the yield was even lower, not more than 1% of the acetal being isolated.

Derx (3) steam distilled the acetals, after sodium sulfate was removed by filtration and the acid catalyst was neutralized; a small amount of the <u>trans</u>-diol isopropylidene derivative might have been hydrolyzed in this operation, or

- 31 -
may have remained dissolved in the water phase in the subsequent extraction with ether. Subsequent workers (30) (31)(1) used Derx' method to separate mixtures of the two isomeric glycols, and the small amount of trans diol which may have gained entrance into the cis fraction as the isopropylidene compound, would probably be lost without notice in recrystallizing the cis diol. Also, it seems reasonable to presume that in mixtures of these two alcohols, the cis form would condense preferentially, perhaps to the exclusion of the trans isomer. Maan (48), using Derx' methods, examined the reaction of some substituted trans-1,2-cyclohexanediols, and noted the formation of small amounts of steam volatile fluids, but, without examining this material, concluded that it consisted of condensed products of the acetone itself.

Boeseken and his collaborators (48) devised the following methods for determining whether a 1,2 glycol possessed a <u>cis</u> or a <u>trans</u> configuration, where both possibilities existed:

(1) Boric acid solutions exhibited an enhanced conductivity in the presence of a <u>cis</u> but not a <u>trans</u> glycol. This hypothesis was valid in many cases, e.g., the 1,2-cyclopentanediols, but with the 1,2-cyclohexanediols the results were inconclusive (49)

(2) Cis-1,2-glycols formed acetone derivatives, whereas

the <u>trans</u> glycols did not. Boeseken and Derx (50) observed only a single exception to this rule, for both the <u>cis-</u> and <u>trans-1,2-</u>cycloheptanediols condensed with acetone. As far as has been discovered, this was the only exception observed up to the time of the present work.

From the study of a number of 1,2-glycols, Boeseken and his collaborators (51) concluded that boric acid and acetone condensed with adjacent hydroxyl groups which were in a single plane and whose proximity was favorable for the reaction. The products in the case of the boric acid reaction were borospirans (e.g. XLII), and the acetone condensation gave the usual five-membered ring (e.g. XXVI).



Derx (3) interpreted his results in the 1,2-cyclohexanediol series in the following manner. An examination of the space models of the two cyclohexanediols revealed that, in the <u>cis</u> diol the hydroxyl groups and the carbon atoms to which they were attached were in the same plane and these hydroxyl groups were also favorably spaced when the cyclohexane ring was in the "boat", but not in the "chair" form (52); in neither the "chair" nor the "boat" form of the <u>trans</u> diol, however, were the contiguous hydroxyl groups in the same plane as the carbon atoms carrying them, and the distance between these two groups was unfavorable for the acetone condensation. Derx concluded that the <u>cis-</u> 1,2-cyclohexanediol was fixed in the "boat" form, at least in part, under the conditions of the acetone condensation, and that probably much less of the <u>cis</u> glycol was in the same form under the conditions of the boric acid reaction.

The present work indicated that these views were not justified. Derx' observation that the two hydroxyl groups, and the two carbon atoms bearing them were not in the same plane in <u>trans-1,2-cyclohexanediol</u> was checked using Fisher-Hirschfelder-Taylor models, and found to be correct. Using these models, a form of the <u>trans</u> diol in which the proximity of the hydroxyl groups was such that only a slight strain would be incurred in the acetone condensation could be built.

The explanation of the superiority of the method of Newman and Renoll (39) for the condensation of <u>trans</u>-1,2cyclohexanediol with acetone remains obscure. The very slight acidity employed in this procedure, much less than when hydrogen chloride was the catalyst, may be an important factor. Although a large excess of the water-absorbing agent was employed in the experiments using hydrogen chloride,

- 34 -

the ineffectiveness of this agent in driving the reaction to completion was manifest. Nevertheless, the explanation of this anomaly may be more subtle than the fore-going statement suggests, for with the <u>cis</u> diol the same reaction does proceed to completion with the same dehydrating agent. Clarification of the whole problem demands more experimental work to determine the equilibrium constants and the role of the catalyst.

Winstein and Buckles (20) recently observed that <u>trans-1,2-cyclohexanediol condensed with ethyl orthoacetate</u>, XLIII, to form XLIV, an ortho-ester with a close structural resumblance to isopropypidene <u>trans-1,2-cyclohexanediol</u>, XLI. The procedure used was strikingly similar to that of Newman and Renoll (39), p-toluenesulfonic acid being the catalyst, and the ethanol formed being removed by fractional distillation of the reaction mixture. A yield of 60 - 70%



XXII

XLIV

of the pure ortho-ester, XLIV, was obtained. The condensation of optically active <u>trans-1,2-cyclohexanediol</u>, which is fairly easily prepared (53), and the isolation of an optically active cyclic acetal would constitute a confirmation of the course of the reaction.

XLIII

A crude pyrogallitol mixture obtained by the hydrogenation of pyrogallol, and from which most of the δ isomer, III, had been removed by the method of Lindemann and de Lange (2), was condensed with acetone according to the procedure of Newman and Renoll (39), and the acetals were fractionally distilled. The identification of isopropylidene trans-1,2-cyclohexanediol, XLI, led to the investigation discussed above. It was noteworthy that none of the corresponding acetal of <u>cis-1,2-cyclohexanediol</u> was found although some of the cis glycol was produced in the hydrogenation (1). By acid hydrolysis of the higher boiling acetal fraction. and separation and identification of the pyrogallitols obtained, it was proven that all three of the isomeric 1,2,3cyclohexanetriols condensed with acetone under the conditions From the residue left after all of the acetals employed. were distilled, a-1,2,3-cyclohexanetriol, I, and only I, was These facts were tentatively explained by asrecovered. suming that a-pyrogallitol condensed with acetone at a much slower rate than did the β isomer, II, which predominated in the crude triol fraction, and probably very much more slowly than the disomer, III. The amount of the latter in the mixture acetonated was about the same as that of the a form, I. If further rate data on the condensation are accumulated, a partial separation of the α -pyrogallitol from the β and the forms by acetonation may be possible.

Several experiments were carried out on isopropylidene-

- 36 -

 β - and - δ -pyrogallitols, XXVII and XXX, which were prepared from the pure triols, II and III, and acetone, with both hydrogen chloride and p-toluenesulfonic acid as the condensation catalysts. The structures referred to anticipate the discussion which follows.

The β accetal was isolated in a pure, crystalline state, m.p. 50.2 - 51°, b.p. 130 - 132°/18 mm., but the accetal was not crystallized and was probably not absolutely pure. The latter substance was very readily hydrolyzed, and reverted fairly rapidly to the parent pyrogallitol, even when the distilled product was kept in a tightly stoppered flask. The stability, of course, might have been greater if the substance had been obtained in a rigorously pure condition.

Both XXVII and XXX were converted into monobenzoates and monomethyl ethers by standard reactions. The ethers were prepared from samples of the acetals synthesized with both of the catalysts mentioned, but were not isolated, since some hydrolysis of the acetal bonds during the methylation with silver oxide and methyl iodide was anticipated. The crude methylated acetals were therefore hydrolyzed to the corresponding monomethoxy cyclohexanediols, XXXI and XXXII.

The identity of the δ -pyrogallitol monomethyl ethers, XXXII, prepared using the two catalysts was proved by a mixed m.p.; both ethers melted at 69.5 - 71°, and no



depression of the mixed m.p. was observed. The β -monomethyl ethers, XXXI, were both extremely hygroscopic solids, m.p. 35.5 - 37°, and a mixture of the two samples melted at the same temperature. These facts proved that the acetonation of β - and δ -pyrogallitols with either catalyst gave acetals of the same ring structure.

In order to determine their ring sizes, compounds XXXI and XXXII were oxidized with lead tetraacetate under the conditions outlined by Hockett and McClenahan (54) for the selective cleavage of 1,2 glycols. The results (Fig. 1 and Table III) confirm the fact that the two samples of XXXI were identical; the slight discrepancy in the corresponding plots was attributed to the circumstance that one of these ethers (plot 2) was slightly less pure, m.p. 35.5 - 37°, than the other (plot 3), m.p. 36 - 37°. Figure 1 also shows that both XXXI and XXXII were 1,2-glycols, since nearly one mole of the oxidant was rapidly used up, in circumstances where the consumption by a 2-methoxy-1,3-cyclohexanediol would have been negligible. Moreover, the rate plots for the β -pyrogallitol monomethyl ether are almost superimposable on that of

- 38 -





the δ isomer, in which the exposed 1,2 glycol unit is certainly <u>cis</u>. It follows that the pair of hydroxyl groups in the former case is also <u>cis</u>, and that the β isomer is XXXI, and not XLV. If the reverse had been the case, the rate of oxidation of the β isomer would have been close to those of <u>trans-1</u>,2-cyclohexanediol or of a-pyrogallitol, I, in which the pairs of adjacent hydroxyl groups are all <u>trans</u> to each other. Christian's (1) data for a comparable oxidation of the latter substance are reproduced in Figure 1.

These syntheses and oxidations confirm the structures of the β - and δ -pyrogallitols as proven by Christian (1). It is unfortunate that Christian continued his lead tetraacetate oxidations for only about eight hours, at the rather unusual temperature of 18.6°. Because of lack of material, the structure of isopropylidene-a-pyrogallitol was not determined.

Some comment on the benzoates of the isopropylidene- β - and δ -pyrogallitols is necessary. From the work on the methyl ethers of the same acetals, the two benzoates would be expected to have the structures XLVI and XLVII.



- 40 -

16

Although good analyses were obtained for both of these compounds, and the melting point of XLVI was sharp at 102 - 103.5°, repeated recrystallization and sublimation failed to yield a constant value for XLVII, the observed values being 72.7 - 73.7°, 71.5 - 73.1°, 72 -75.5°, 71.5 - 76°. The cause of this behaviour is not known. It was originally intended not to isolate these compounds but to hydrolyze them directly to the corresponding triol monobenzoates. For this reason, both XLVI and XLVII were heated under gentle reflux with dilute hydrochloric acid, and the fact that there were two phases present during the reaction presumably accounts for the absence of hydrolysis. The experiment should therefore be repeated, omitting the acid treatment entirely.

As was noted earlier in this thesis, another possible route to the inaccessible a-pyrogallitol, I, consisted of inverting the configuration of the central hydroxyl group in the readily available δ -pyrogallitol, III. The most promising method for effecting such a transformation appears to be based on a reaction discovered by Winstein and Buckles (20), who observed that when <u>cis-1,2-cyclohexene-</u> ethyl-orthoacetate, XLVIII, was heated with acetic anhydride

XLVIII

for ten hours, and the product fractionally distilled, the distillate consisted of <u>trans</u>-1,2-cyclohexanediol diacetate, the amount corresponding to a 43% yield. A further small amount of <u>trans</u>-1,2-cyclohexanediol, XXII, equivalent to 11% of XLVIII was recovered from the residue. Similar results were accomplished by heating XLVIII in a mixture of acetic anhydride and acetic acid with dry hydrogen chloride and lithium chloride. The product, isolated in 63% yield, was the <u>trans</u>-1-acetoxy-2-chlorocyclohexane, which was converted in 36% yield to <u>trans</u>-1,2-cyclohexanediol. The other product of this reaction, isolated in 29% yield (total yield, 92%) was <u>cis</u>-1,2-cyclohexanediol diacetate.

On the basis of this work, the following synthesis might be feasible:



This reaction, by analogy with the corresponding one with cis- (or trans-) 1,2-cyclohexanediol, should proceed in 60 - 70% yield. The product should undergo partial inversion by the methods outlined above to yield a mixture of all three pyrogallitols. It seems advisable to prove that the oxygen containing ring in XLIX is five, and not six membered, for both compounds are theoretically possible; it may also prove essential to block the free hydroxyl group (see page 37). The essay by Pacsu (55) is an excellent discussion of the carbohydrate orthoesters.

A second possible method for the inversion of the central hydroxyl group of δ -pyrogallitol, III, was based on the probable existence of L. Although no acetals of the 1,3-cyclohexanediols have been reported, Hann and Hudson (56) have shown that in the carbohydrate series, formaldehyde preferentially condenses with <u>cis</u>-1,3-glycol units to form six membered cyclic acetal rings. Even if a proportion of the five membered isomer were encountered, the separation of such mixtures is not generally difficult (57).



Assuming the availability of a compound of the type of L, the inversion of the free hydroxyl group might be carried out by oxidation to give LI, followed by reduction of the ketone to the alcohol. Similar epimerizations have been successful; for example, that of the hydroxyl

- 43 -

group in the third position of cholesterol, LII (58).



LI

In the projected transformation, however, the initial oxidation might encounter difficulty, for the hydroxyl



group appears to be effectively shielded by the acetal structure.

Although other methods for this inversion were devised, the work of Winstein and his collaborators (20) made the successful accomplishment of these schemes seem very unlikely, and further discussion of them has been omitted.

The 1,2,4-Cyclohexanetriols:

The successful hydroxylation of 3-cyclohexenol acetate to mixtures of the pyrogallitols suggested that similar hydroxylations of derivatives of 4-hydroxy cyclohexene, XXXIII, might yield mixtures of the isomeric 1,2,4-cyclohexanetriols. The preparation of the starting materials, XXXIII, LIII, and LIV encountered no difficulties



LIII

and requires little comment. Hydroquinone, or its monomethyl ether, was readily hydrogenated to 1,4-cyclohexanediol or the corresponding monomethyl ether. Dehydration by distillation with a little sulfuric acid introduced the double bond and yielded XXXIII and LIII, a new compound, b.p. 135.5° - 136.5°. Benzoylation of XXXIII gave LIV, b.p. 149 - 150°/12 mm., another new compound. Both LIII and LIV possessed the properties to be expected of substances of this type. The outstanding problem is the determination of the configuration of the four stereoisomers, XXXIV -XXXVII, and this will be discussed in detail. It is essential that both LV and LVI, which would be prepared



by the <u>trans</u> hydroxylation of LIV, be isolated in a pure state and in reasonably large quantities; the intermediate ethylene oxide might also be isolated (59), although this step is not absolutely necessary. The separation of LV and LVI would probably have to be accomplished by the technique of fractional crystallizations, and should not prove impossible. The trityl ethers, which have several advantages (46), and which were used to separate the two isomeric resorcitols (42), might prove advantageous in the present case.

The second step in proving the structure of the 1,2,4-cyclohexanetriols would involve the mono-esterification of both LV and LVI, preferably, for reasons to be mentioned later, with p-toluenesulfonyl chloride. This reaction was accomplished successfully, and in good yield, with <u>trans-1,2-</u> cyclohexanediol, XXII, by Criegee and Stanger (60). From LV (or LVI) two pairs of compounds LVII and LVIII (and LIX and LX) would be obtained, and the separation of these mixtures by fractional crystallization is considered essential. If the monotrityl ethers of LV and LVI are available, a not unreasonable possibility, another route to



these compounds is available.

With the preparation of these diesters, preferably all four, the problem is largely completed. On oxidation, LVII should yield the ketone LXI, and the carbonyl group in this compound should be capable of elimination (e.g., by the Clemmensen method) to give LXII, a resorcitol derivative



whose structure can be related to authentic <u>trans</u> resorcitol by conventional methods. In a similar fashion LVIII would (a) Tsl = p-toluenesulfonyl yield a <u>cis</u> quinitol diester. The same operations could of course be carried out with LIX and LX, the cyclohexanediol derivatives which these two compounds would yield being clear. Only relative configurations could be assigned to the four 1,2,4-cyclohexanetriols on the basis of this work, since the absolute configurations of the quinitols is not known and the proof of the configuration of the resorcitols is not complete (42)(61).

Criegee and Stanger (60) and Winstein and Buckles (20) showed that trans-1,2-cyclohexanediol-monoparatoluenesulfonate-monoacetate could be inverted, in excellent yield, to a derivative of <u>cis</u>-1,2-cyclohexanediol. This reaction has been mentioned previously, and its application to the preparation of derivatives of XXXIV and XXXV seems practicable.

Perhaps a simpler approach to assigning the configurations would be to condense the pairs XXXIV - XXXV and XXXVI - XXXVII with formaldehyde. As already explained, the methylene acetals so formed would probably engage the 1,3 hydroxyl groups that were <u>cis</u> to each other, or, in other words, <u>six</u> membered cyclic acetals would form only with XXXIV and XXXVII. Such an observation, together with the confirmation of the <u>cis-trans</u> relationship of the adjacent hydroxyl groups by the lead tetraacetate method, would go far toward elucidating the stereo-chemistry of the four possible 1,2,4cyclohexanetriols.

EXPERIMENTAL

The following chemicals were prepared by the methods noted: cyclohexene (14); lead tetraacetate (62); Raney nickel catalyst (63); hydrogen peroxide in tertbutyl alcohol (64).

Stock acetone was purified by allowing it to stand over calcium chloride for twenty-four hours. The solvent was decanted, heated under reflux with a few crystals of potassium permanganate and distilled after any acids had been neutralized with an excess of anhydrous potassium carbonate.

Stock chloroform which had been washed with water repeatedly to remove any alcohol present was dried over calcium chloride for twenty-four hours, decanted, and stored in an amber colored bottle.

All melting points are uncorrected.

Hydrogenation of Pyrogallol (1)

The phenol, 316 g. (2.5 moles), was dissolved in ethanol (total volume of solution, 1,000 ml.), 50 g. of Raney nickel catalyst was added, and the mixture was hydrogenated in the usual apparatus for three hours at 140° under 3,000 pounds initial pressure of hydrogen. Over this period of time, 8.2 moles of gas were absorbed; the amount of gas necessary to saturate the ring alone was 7.5 moles.

The catalyst was removed by filtering, and ethanol was distilled from the filtrate; the residue distilled at 90 - 135°/0.05 mm. to give 290 g. of a clear, colorless, partially crystalline oil. This material was dissolved in water and the solution, volume 500 ml., was extracted continuously for forty-eight hours with ether. At the end of this time the extract gave no color when tested for phenolic substances with a solution of ferric chloride in By oxidation with standard sodium hypoiodite (1) methanol. it was found that theether had extracted 30 g. of unchanged After all solvent had been removed from the pyrogallol. aqueous phase, the yellowish gum remaining was distilled at 120 - 140°/0.02 mm., to give a white solid product weighing This corresponded to a yield of 33% of the mixed 90.7 g. 1,2,3-cyclohexanetriols. No fraction corresponding to cyclohexanediols, b.p. 85 - 100°/0.02 mm. (1) was isolated from the hydrogenated mixture, presumably because they had been extracted by the ether. There is no doubt, however, that some cyclohexanediols were in the "triol" fraction (see page 55)

The mixture of solid triols was heated under reflux for one-half hour with 200 ml. of acetone, cooled, and after standing over-night, the crystals were recovered. On recrystallization from a solution of 200 ml. of acetone and 25 ml. of water, 40.0 g. of δ -1,2,3-cyclohexanetriol, m.p. 145.5 -147° were obtained as white needles. A second recrystallization from ethanol afforded purer material, m.p. 147 - 148°. The mother liquor was worked up, and yielded an additional 2.0 g. of the same compound, m.p. $147 - 148^{\circ}$. These melting points are correct for the δ isomer.

On evaporation of the first acetone filtrate, 11.7 g. (0.085 moles, calc'd as pyrogallitol) of a brown This oil was dissolved in 200 ml. of oil remained. pyridine and 65 ml. of benzoyl chloride (0.56 moles) was added slowly. After the initial heat of reaction had subsided, the mixture was heated on a water bath at 60° for one-half hour. The solution, which darkened rather quickly to a deep red color, was poured into one litre of The brown semi-solid settled to the bottom of the water. beaker and the pale yellow supernatant liquid was decanted. The product was washed twice with 500 ml. portions of water, once with dilute sodium bicarbonate, then with 500 ml. of water containing a few ml. of sulfuric acid, and finally with water. The brown gummy solid was then warmed with 100 ml. of ethanol, and the mixture was cooled and filtered.

The tan-colored precipitate became pure white upon washing with 75 ml. of ethanol. After drying, this solid weighed 7.9 g., and melted at 174 - 180°. Three recrystallizations, each from 100 ml. of glacial acetic acid, yielded 6.0 g. of pure β -1,2,3-cyclohexanetriol tribenzoate, with the melting point of 182 - 183.5° (cf. Table I).

The ethanol mother liquors were evaporated to approx. 50 ml., and kept at -15°. On standing for a few days, a white solid crystallized, and was filtered. This product was recrystallized twice from 50 ml. of mothanol. On each recrystallization, a small amount of β -1,2,3-cyclohexanetriol tribenzoate, which was nearly insoluble in the boiling solvent, was removed by filtration before any of the a triester had crystallized. This separation was simplified by the fact that the β -pyrogallitol tribenzoate crystallized as very small shapeless crystals, while the a triester formed short needles. In this manner, 0.4 g. of a-pyrogallitol tribenzoate, m.p. 136 - 138° was obtained. Two more recrystallizations from methanol yielded the pure ester, m.p. 140 - 141° (Table I).

Preparation of 8-1,2,3-Cyclohexenetricl Tribenzoate

Two grams (0.015 mole) of the δ triol (m.p. 147 -148°) were dissolved in 60 ml. of pyridine. Benzoyl chloride, 12 ml. (0.10 mole) was added to the well-cooled solution. After the initial heat of reaction had subsided, the pale yellow solution was heated under reflux for one-half hour. The mixture was then poured into 300 ml. of water with stirring; the ester precipitated as a pale orange smorphous solid, which was filtered, and washed with hot water. After recrystallization from 60 ml. of ethanol, 6.1 g. of white crystals (needles), melting at 137 - 138.7° were obtained. The ester was recrystallized a second time from 85 ml. of ethanol; yield 5.6 g., (83.5%), m.p. 140 - 141°.

Demonstration of the Presence of the α and β Isomers in the Acetone Insoluble Pyrogallitol Fraction

A sample of a mixture of the three pyrogallitols, weighing 38.5 g., and prepared as described by the hydrogenation of pyrogallol, was carried through the procedure of Lindemann and de Lange (2), and an effort was made to make the process as quantitative as possible. The sample, b.p. 130 - $135^{\circ}/0.05$ mm. was very faintly yellow, but did not give a coloration with a solution of ferric chloride in methanol.

The sample was ground in a mortar with acetone, filtered, and the precipitate was washed with the same sol-The white insoluble solid, which weighed 28.4 g., vent. was recrystallized from 200 ml. of ethyl acetate and 100 ml. Yield, 18.2 g. of 8-pyrogallitol, m.p. 145 of ethanol. 147°, in the form of fine white needles. The mother liquor was evaporated to dryness, and the residue was recrystallized twice from an ethyl acetate-ethanol mixture. Yield, 4.5 g. of J-pyrogallitol, m.p. 147 - 148°. The mother liquors obtained in the last steps were combined and evaporated to dry-The residue distilled at 120 - 130°/0.04 mm., as a nezs. On the addition of 10 ml. of acetone, this proyellow gum. duct partially crystallized to form a white solid, weighing 1.3 g., m.p. 124 - 128°, and a solution, which on evaporation yielded 1.6 g. of a very pale yellow solid. The white solid was recrystallized from ethanol, and gave 1.0 g. of 8pyrogallitol, m.p. 147 - 148°.

The yellow solid was dissolved in pyridine and benzoylated in the usual way. The mixture of esters was fractionally crystallized in the manner described and the following fractions were isolated:

(1) β -pyrogallitol tribenzoate, m.p. 181 - 183°, 1.9 g. This m.p. indicated a slight impurity in the ester.

(2) a-pyrogallitol tribenzoate, m.p. 140 - 141°, 0.4 g. In admixture with authentic δ -pyrogallitol tribenzoate the m.p. was 121 - 137°, but a mixed m.p. with pure a-pyrogallitol tribenzoate of the same m.p. was not depressed. In isolating this ester, the use of methanol containing small amounts of water, about 5%, was advantageous in the recrystallizations.

Attempted Separation of the Components of the Acetone Soluble Pyrogallitol Fraction by the Isopropylidene Acetal Method

The acetone soluble material obtained in the above separation (page 53), and presumably containing all of the α and β -pyrogallitols, but little, if any, of the isomer, was made up to 150 ml. with acetone, and to the clear solution 150 ml. of petroleum ether (b.p. 30 - 60°) and a few crystals of p-toluenesulfonic acid monohydrate were added. The solution was set up in the apparatus for an azeotropic distillation described on page 62. This distillation was continued for forty-eight hours; during the final twelve hours of this period, the level of water in the trap did not change.

The yellow solution was neutralized with sodium acetate, solvents were evaporated, and the oily residue was then distilled. The following fractions were collected:

(a) b.p. 83 - 86°/23 mm., 2.4 g., a clear colorless oil with a strong peppermint odor.

(b) b.p. 128 - 133°/23 mm., 8.2 g., a clear colorless oil with a sweet smell. This fraction was redistilled twice, and the possibility that any of fraction (c) was carried over mechanically was negligible.

(c) b.p. 130 - 140°/0.05 mm., a yellow gum which crystallized slowly, weight 0.7 g.

Fraction (a) was dissolved in 50 ml. of ethanol, 3 ml. of concentrated hydrochloric acid was added, and the solution was heated on the steam bath for one hour. The solvents were then evaporated, and when a deep green color developed, the error in failing to neutralize the acid seemed evident. The dry residue, on recrystallization from ethyl acetate, yielded 0.3 g. of a white solid, m.p. 103 - 104.3°. This product was benzoylated according to the directions of Shriner and Fuson (65), and the benzoate was recrystallized three times from aqueous ethanol, when it melted at 92 - 93°. The melting point of <u>trans-1</u>,2-cyclohexanediol dibenzoate prepared from the pure <u>trans</u> glycol (see page 58) was 92.5 - 93.8°, and a mixed melting point of these two compounds was 92 - 93.8°.

No other product was isolated from this fraction. This result was the first indication that <u>trans-l,2</u> glycol units were condensing with acetone.

A portion of fraction (b) weighing 3.2 g. was hydrolyzed by refluxing a solution in 50 ml. of ethanol with 3 ml. of concentrated hydrochloric acid on the steam bath for one hour. The acid was neutralized with basic lead carbonate, the mixture was filtered, and the filtrate was evaporated to dryness. Yield, 1.5 g. of crude product, a white solid. This solid was dissolved in 25 ml. of hot ethyl acetate and allowed to crystallize. The crystals were distinctly heterogeneous, consisting of needles, and small, apparently spherical particles. The m.p. of this solid was 70 - 113°.

It was essential to establish the constitution of this solid, and this was accomplished by fractionally crystallizing the benzoates. The solid was dissolved in 25 ml. of pyridine, and 4.5 ml. of benzoyl chloride was added to the solution. The benzoates were isolated in the manner described previously. In the usual way, 1.1 g. of β -pyrogallitol tribenzoate, m.p. 182 - 183.5 was separated. The mother liquors yielded a solid which was recrystallized four times

- 56 -

from aqueous methanol containing approximately 10% of water. A white solid, in the form of needles which crystallized in clusters, was obtained; yield, 0.35 g., m.p. 137 - 139°. Further crystallization did not raise this melting point. In admixture with authentic δ -pyrogallitol tribenzoate, the melting point was 119 - 134°, but a mixed melting point with authentic a-pyrogallitol tribenzoate,was 137 - 139°. This product was therefore a-pyrogallitol tribenzoate, and it was evident that a-pyrogallitol was condensing with acetone under the conditions described above.

The methanol mother liquors were evaporated to dryness, and the solid residue was recrystallized three times from aqueous methanol; a substance crystallized in the form of short white needles, which did not cluster in the manner characteristic of the a-pyrogallitol tribenzoate. These crystals melted at 139 - 140°, and a mixed melting point with authentic **5**-pyrogallitol tribenzoate was not depressed, but in admixture with a-pyrogallitol tribenzoate the melting point was 122 - 136°. The yield of this compound, which was **5**pyrogallitol tribenzoate, was 0.3 g. It was clear that **5**-pyrogallitol condensed with acetone to form an isopropylidene acetal under the conditions of this experiment.

No further examination of this fraction was made. The recoveries reported above are far from quantitative but inevitable losses attended the process of fractional crystallization.

- 57 -

Fraction (c) was dissolved in 30 ml. of ethyl acetate, and the solution was allowed to crystallize in the cold room. The solid was recovered and recrystallized from 10 ml. of ethyl acetate; yield, 0.10 g., m.p. 109 - 110°. A mixed melting point with pure α -pyrogallitol of the same melting point was not depressed. The tribenzoate, prepared by the method of Shriner and Fuson (65) melted at 140 - 141°, and a mixed melting point with the same ester prepared synthetically was not changed.

Synthesis of trans-1,2-cyclohexanediol; XXII

(a) By the hydroxylation of cyclohexene with hydrogen peroxide using selenium dioxide as catalyst (25)

Cyclohexene, 25 g. (0.30 mole) was mixed with a solution of hydrogen peroxide in tert-butyl alcohol, 150 ml., containing 11.32 g. (0.33 mole) of the peroxide. Selenium dioxide, 1.33 g., was almost completely dissolved in the solution by shaking for a few minutes, and the mixture was then kept at 5 - 6° for sixty-five hours.

At the end of this time, the solvents were distilled in the vacuum of a water pump at room temperature. The red color of the solid residue indicated the presence of selenium from which the product was extracted with 75 ml. of ethanol. After distillation of the ethanol under reduced pressure, the yellow residue distilled at $107 - 122^{\circ}/14$ mm. to give a white crystalline solid. The distillate, m.p. 85 - 105°, weighed 19.1 g., corresponding to a 54% yield of the crude product.

When this solid was recrystallized twice from ethyl acetate, the melting point was not improved. Recrystallization from benzene (53) proved effective; using this solvent, 11.5 g. (33) of <u>trans</u>-1,2-cyclohexanediol, m.p. $103 - 104^{\circ}$ was recovered. In addition, 0.4 g. of somewhat less pure material, melting at 100 - 104° was obtained from the mother liquors. The melting point recorded in the literature is $103 - 104^{\circ}$ (31). No depression with <u>trans</u>-1,2-cyclohexanediol prepared by method (b) was observed.

No <u>cis-1,2-cyclohexanediol</u> was isolated in this experiment; if formed, this compound was present only in very small amounts.

(b) By the reaction of cyclohexene with hydrogen percyide in formic acid (21)

Superoxol, 116.2 g. (1.025 moles of hydrogen peroxide) was added over a period of twenty minutes to a mixture of 82 g. of cyclohexene (1 mole) and 300 ml. of formic acid (87%). The mixture was stirred continuously and maintained below 40° for three hours. At the end of this time, the temperature had ceased to increase spontaneously, and the solution, now homogeneous, was kept at 35° overnight. The solution then gave only a faintly positive test for peroxides with acidified potassium iodide. The solvents were removed <u>in vacuo</u>, and the main product was distilled at 100 - 120°/12 mm. This material was redistilled through a 20 inch Vigreux column, and gave 107.2 g. of a clear, colorless oil, b.p. 109 -111°/12 mm. On standing in the cold, the oil partially crystallized.

After recovery of the crystalline portion, two recrystallizations from benzene gave 10.5 g. of <u>trans-1,2-</u> cyclohexanediol, m.p. 103 - 104°. The dibenzoate of this glycol, prepared using a slight excess of benzoyl chloride in pyridine, melted at 92 - 93°, in agreement with the value reported in the literature (53).

Preparation of trans-1,2-cyclohexanediol monobenzoate from a product of this reaction

The liquid portion of the product had a saponification equivalent of 131, whereas the theoretical value for a cyclohexanediol monoformate is 144. The product probably contained a small amount of cyclohexanediol diformate.

A small sample, 5 g. of this liquid was treated with 5 g. of benzoyl chloride (1.02 moles, assuming that the starting material was pure 1,2-cyclohexanediol monoformate), in a solvent mixture composed of 15 ml. of pyridine and 15 ml. of chloroform. The solution was allowed to stand at room temperature for twenty-four hours, and was then washed successively with 100 ml. of water, 50 ml. of normal sulfuric acid, 50 ml. of a saturated solution of sodium bicarbonate, and finally with water. After the chloroform had been removed at the water pump, the residue was distilled, and 5.5 g. of a clear, colorless oil, b.p. 195 - 205°/18 mm. was collected. This fluid was redistilled twice, b.p. 199 - 202°/18 mm., and 117 - 119°/0.05 mm., but it did not crystallize. The small solid residue in the distillation flask was not examined.

Sulfuric acid, 0.7 ml. and water, 2 ml., were added to a solution of this product in 50 ml. of ethanol, and the solution was heated at $45 - 50^{\circ}$ for ninety minutes. The solution was neutralized with sodium bicarbonate, and when about four-fifths of the solvents had been evaporated the oil which separated crystallized. This solid was recovered, and after three recrystallizations from petroleum ether, it melted at $89.5 - 91.5^{\circ}$. A further recrystallization from 200 ml. of water and 50 ml. of ethanol gave 0.5 g. of crystals, fine white needles, melting 90 - 91°. <u>Trans</u>-1,2-cyclohexanediol monobenzoate melts at 91 - 92° (53).

Calc'd for C₁₃H₁₈O₃ : C 70.86% H 7.34% Found : C 70.32% H 7.61%

Condensation of trans-1,2-cyclohexanediol with acetone to give XLI

(a) by the method of Newman and Renoll (39)

In a 500 ml. round bottom flask was placed 7.0 g.

of <u>trans</u>-1,2-cyclohexanediol, m.p. 103 - 104, (0.06 moles), 150 ml. of acetone (119 g., 2.04 moles), 150 ml. of petroleum ether (b.p. 30 - 60°), and a few crystals of p-toluenesulfonic acid monohydrate. The acid catalyst was not weighed, but the amount added was certainly not more than 0.1 g.

The flask was fitted with a condenser, the jacket of which was partially (about one-half) filled with water. A water-trap of the ordinary type, carrying a second condenser in which a rapid flow of water was maintained, was attached at the top of the first condenser. The condenser attached to the flask returned acetone vapor to the flask effectively, but the petroleum ether vapors reached the second condenser.

The mixture was heated under gentle reflux for sixty hours, during which time it slowly turned yellow, and decreased in volume by about 75 ml., owing to a slow loss of vapors. Two phases formed in the water-trap, and the aqueous phase contained a small amount of acetone, evident from its odor.

Sodium acetate was added to neutralize any free p-toluenesulfonic acid, and the solvents were distilled under reduced pressure, at room temperature. The main product, a clear colorless oil possessing a strong peppermint odor, and weighing 5.5 g., distilled at $77 - 78^{\circ}/20$ mm. The residue in the distilling flask was extracted with 50 ml. of boiling benzene, and the insoluble material was discarded. On cooling, the benzene solution yielded 0.9 g. of white crystals, which, after two more recrystallizations from benzene, yielded 0.6 g. of <u>trans-1,2-</u> cyclohexanediol, m.p. 103 - 104.2°. A mixed m.p. with an authentic sample of the same compound showed no depression.

The yield of the acetal was 67% of the theoretical amount; the density was d_{20}^{20} , 0.98052, and the refractive index, n_D^{20} , 1.4468.

Calc'd	for	an	isopropylidene		ene cycl	cyclohexanediol, C.H160g:		
		C	69.18%	H	10.31%	Mol.	Refraction,	42.66
Found		С	69.55%	H	1033%	Mol.	Refraction,	42.57

The acetal was allowed to stand for several weeks at -15°, but it did not crystallize. The corresponding acetone derivative of <u>cis</u>-1,2-cyclohexanediol melts at -6.5° (3).

Hydrolysis of isopropylidene-trans-1,2-cyclohexanediol

A solution containing 1.0 g. of the acetal, 3 ml. of concentrated hydrochloric acid, and 50 ml. of ethanol was heated under reflux on the steam bath for one hour. At the end of this time, the acid was neutralized with basic lead carbonate and the precipitate was filtered and discarded. The filtrate was evaporated to dryness and recrystallized from - 64 -

15 ml. of benzene. The white solid product, in the form of short needles, melted at 103 - 104°, alone and in admixture with authentic <u>trans</u>-1,2-cyclohexanediol. Yield, 0.73 g., or 98% of theory.

(b) Using hydrochloric acid as catalyst

<u>Trans-1,2-cyclohexanediol, 5 g., m.p. 103 - 104</u>° (0.04 mole) was dissolved in 300 ml. of acetone, (238 g., 4.1 moles) through which dry hydrochloric acid gas had been bubbled until the acid concentration was 0.1% by weight. Anhydrous sodium sulfate, 3.0 g., was added to this solution and the mixture was mechanically shaken for five days.

At the end of this time the liquid was pale yellow, and the acid in solution was neutralized with basic white lead. The solids were removed by filtration, and the filtrate, which was still acid to litmus, was made alkaline with dry ammonia gas. The solvents were then distilled under reduced pressure and the yellow residue was extracted with 100 ml. of petroleum ether, b.p. $30 - 60^{\circ}$. The mixture was filtered, and after the solvents had been removed from the filtrate under reduced pressure, a clear colorless oil distilled at $76 - 78^{\circ}/23$ mm., weight 0.20 g. (3% of theory). This liquid possessed the strong peppermint odor characteristic of the isopropylidene acetal.

Since this liquid was obtained in such small

amount, it was identified only by hydrolysis. The entire product was dissolved in 15 ml. of ethanol and 1 ml. of concentrated hydrochloric acid, and the solution was heated on the steam bath for one hour. The acid was then neutralized with basic lead carbonate, the mixture was filtered, and the filtrate was evaporated to dryness. The white solid residue was recrystallized twice from 10 ml. of benzene. A yield of 0.108 g. (73%) of pure <u>trans-1,2-</u> cyclohexandiol, m.p. 103 - 104° was obtained. A mixed melting point of this material with authentic <u>trans-1,2-</u> cyclohexanediol was also 103 - 104°.

The petroleum ether insoluble material (see above) was recrystallized three times from benzene. The white solid product, which weighed 2.7 g., melted at $103 - 104^{\circ}$, and a mixture of this substance with authentic <u>trans-1,2-</u>cyclohexanediol melted at the same temperature.

A similar experiment, in which the acid concentration was 1.0%, was also carried out. This reaction mixture was shaken for only thirty hours, at the end of which time the liquid was bright yellow in color. The process employed for the recovery of the acetal and the unchanged glycol was the same as that described above.

The acetal-containing distillate boiled at $60 - 65^{\circ}/23$ mm., and weighed 0.80 g. The odor of the acetal in this fluid was distinct, but on hydrolysis according to the

procedure described above, only 35 mg. of pure <u>trans</u>-1,2cyclohexanediol, m.p. 103 - 104° unchanged on admixture with authentic <u>trans</u>-1,2-cyclohexanediol, was isolated. It is possible that some of this distillate consisted of a low boiling condensed derivative of acetone.

The yield of pure <u>trans-l,2-cyclohexanediol cor-</u> responded to a 0.7% yield of pure isopropylidene-<u>trans-l,2-</u> cyclohexanediol. The crude yellow residues, isolated in the manner described, weighed 4.0 g., but six recrystallizations from benzene gave material melting poorly, at 85 - 90°.

Synthesis of 3-cyclohexenol acetate, XV

(a) By the oxidation of cyclohexene with lead tetraacetate (17)

The procedure employed was that described by Criegee (17), and the details are therefore not presented here. A yield of 16.2% of the pure ester, b.p. 59 - 61°/ 10 mm. was obtained; Criegee's yield of the same compound was 21%

(b) By the oxidation of cyclohexene with selenium dioxide (16)

This experiment, which has been repeated three times, is described in detail because the yields obtained were very much lower than those reported (16).

The selenium dioxide used was a high grade

commercial product, kindly supplied by Canadian Copper Refineries, Montreal, Quebec.

Over a period of four to five hours, 389.5 g. (3.5 moles) of selenium dioxide was added to a solution of 820 g. (10 moles) of cyclohexene (b.p. 82 - 84°) in 500 g. of acetic acid and 300 g. of acetic anhydride. A three-necked flask equipped with a reflux condenser and a stirrer was used as the container. The mixture was maintained at 70 - 80° during this time; heating was required to reach this temperature, but the reaction was strongly exothermic and the temperature remained in the stated range without further application of heat during the gradual addition of the selenium dioxide. The dark red solution was refluxed for thirteen hours after addition of the oxide was complete.

In order to hydrolyze any remaining acetic anhydride, 70 ml. of water was added slowly to the black opaque mixture. Steam distillation of this mixture yielded 140 g. of cyclohexene, b.p. 82 - 84°, and 92.4 g. of 3-cyclohexenol acetate, b.p. 81 - 83°/25 mm.

Water was distilled from the residue under diminished pressure, and the heavy black gum which remained was pyrolyzed at 200° for several hours under a vacuum of 25 mm. A brown oil distilled very slowly. This oil was washed with water until the aqueous phase was neutral, and was then
distilled. A light yellow mixture of 3-cyclohexenol acetate and 2-cyclohexenone, b.p. 80 - 86°/26 mm., weight 171.0 g., was obtained. This liquid was shaken with 50 ml. of a 40% aqueous solution of sodium hydrogen sulphite for two hours, and the white precipitate was removed by filtration. The ester in the filtrate was separated, washed with water, and dsitilled. Yield, 132 g., b.p. 81 - 83°/25 mm., a clear colorless fluid which did not react with 2,4-dinitrophenylhydrazine.

The solid sodium bisulphite-ketone complex, weighing 6.7 g., was decomposed with dilute hydrochloric acid. The ketone was recovered by ether extraction and distillation; yield, 3.1 g. of 2-cyclohexenone, b.p. 65 - 67°/24 mm.

The boiling points recorded here are very close to those reported in the literature (16). The total yield of the ester was 224.4 g., or 19.3% of the theoretical amount, and the yield of ketone, 3.1 g., was 0.4% of theory, calculated on the basis of the amount of cyclohexene which reacted; Guillemonat's yields, calculated on the same basis, were 47% for the ester, and 10% for the ketone.

By careful treatment of the black residue from the final pyrolysis with concentrated nitric acid, almost all of the selenium dioxide was recoverable.

Saponification of 3-cyclohexenol acetate

The ester was saponified by shaking with an

equivalent amount of aqueous barium hydroxide for one hour. The unsaturated alcohol was extracted with benzene, and isolated in the usual way. Yield, 68% of the theoretical amount, b.p. 60 - 62°/12 mm. The boiling point recorded in the literature (16) was 67°/15 mm., but the yield was not reported.

Synthesis of a- and β -pyrogallitols from 3-cyclohexenol acetate, XV

(a) By the method of Seguin (25)

To 275 ml. of a solution of hydrogen peroxide in tert-butyl alcohol containing 0.58 moles of the peroxide was added 79.7 g. (0.57 moles) of the unsaturated ester, and 2.3 g. of selenium dioxide. After a few minutes' shaking, all of the oxide dissolved, and the solution was kept at 6° for six days. The amount of catalyst corresponded to 4.0 g. per mole of ester.

The solvent was distilled <u>in vacuo</u> (water pump) at room temperature; the temperature was then raised, and 22.7 g. of the unchanged ester, b.p. 82 - 85°/29 mm. was collected. The black residue was heated at 0.1 mm. pressure, and 31.3 g. of a light yellow gum, containing a trace of red selenium, distilled at 120 - 130°/0.05 mm. Yield, 44% calculated on the basis of the amount of ester which reacted, and assuming that the product was a mixture of aand β -1,2,3-cyclohexanetriol-1-acetates. The viscous black residue in the distilling flask gave evidence of the presence of carboxylic acids when tested with sodium bicarbonate solution, but it was not further examined.

The product was treated with 10.1 g. of potassium hydroxide dissolved in 125 ml, of methanol for one hour. The potassium chloride which precipitated on adding 15.1 ml. of concentrated hydrochloric acid was separated by filtration. Solvents were evaporated from the filtrate <u>in vacuo</u>. The residue, on distillation at 0.02 -0.03 mm, pressure, yielded a pale yellow semi-crystalline gum, b.p. 115 - 125°, weighing 24.8 g. This yield is practically quantitative.

Benzoyl chloride, 140 ml., (1.2 moles), was added to a cold solution of this product in 200 ml. of pyridine. The mixture of tribenzoates was worked up in the manner previously described. Yield, 57.2 g. of crude β -pyrogallitol tribenzoate, m.p., 174 - 181°; recrystallization from 400 ml. of glacial acetic acid afforded 45.4 g. of the same ester as a micro-crystalline powder, m.p. 180.5 - 182.5°. The mother liquors yielded 4.7 g. of an impure product, m.p. 130 - 160°. The yield of α -1,2,3-cyclohexanetriol, recrystallized twice from methanol, was 3.7 g., m.p. 138.5 - 140°, and the mother liquors yielded a further 0.4 g. of a slightly less pure product, m.p. 132 - 137°.

Total yield on the benzoylation was 63.0 g. of crude product (75.5%). The overall yield of the β isomer

calculated as the triol, was 24.6%, and of the α isomer, 2%.

(b) By the method of Meerwein, Schoeller, Schwenk and Borgwardt (22)

A solution containing 44.7 g. of hydrogen peroxide (30%, 0.395 moles), 44.7 g. of glacial acetic acid, and 4.6 g. of concentrated sulfuric acid was added, with stirring, to 50 g. of 3-cyclohexenol acetate (0.36 mole) over a period of one hour. After stirring for about five hours at 10 -15°, the mixture became homogeneous. The solution was maintained at this temperature for fifty-six hours, at the end of which time it was heated with stirring for three hours at 40 - 50°.

When the solution was neutralized with the calculated amount of concentrated sodium hydroxide, two layers appeared, and the upper layer was combined with a benzene extract of the lower aqueous phase. Water was distilled from the latter solution in vacuo, and the residue was extracted with acetone. The insoluble inorganic salts were discarded. The organic solutions were combined, and when the solvents had been removed, 3.1 g. of 3-cyclohexenol acetate, b.p. 75°/27 mm., was distilled. The dark brown residue, which contained a high percentage of inorganic matter, distilled in part at 120 - 127°/0.05 mm., to give 29.0 g. of This was a yield of 50%, assuming that a light yellow gum. the product was a monoacetate ester of 1,2,3-cyclohexanetriol. After standing for a period of about one month, this product partially crystallized, and had a saponification equivalent of 258. Since the theoretical value for the monoester is 174, it was concluded that some of the acetate groups had been hydrolyzed during the reaction. In the light of other work (see page 60), this conclusion appeared reasonable.

The mixture was saponified with 4.3 g. of potassium hydroxide (the theoretical amount, calculated on the basis of the above saponification equivalent) in 45 ml. of methanol for one hour at room temperature. The solution was acidified with concentrated hydrochloric acid, filtered, and solvents were distilled from the brown filtrate at the water pump. The residue distilled at 130 - 132°/0.08 mm., giving a distillate which weighed 13.7 g.

Separation of this triol mixture into the two isomers was accomplished by the usual crystallization of the tribenzoates. The benzoylation was carried out in a mixture of 125 ml. of chloroform and 125 ml. of pyridine with 50 ml. of benzoyl chloride (0.43 mole). At the end of twenty-four hours, the tribenzoates had precipitated. After filtration, the white precipitate was washed thoroughly with hot water.

By the usual methods, described previously in this thesis, 34.8 g. of β -1,2,3-cyclohexanetriol tribenzoate, m.p.

181.5 - 183°, was obtained from this precipitate.

The chloroform filtrate was evaporated, and the residue was combined with the ethanol extract (100 ml.) obtained from the separation of the β -triester. The solution was cooled for twenty-four hours in the refrigerator, and the resulting precipitate was recrystallized from methanol three times. In this manner, 0.8 g. of a-pyrogallitol tribenzoate, m.p. 139 - 140°, was obtained.

The crude tribenzoates obtained in this experiment weighed 42.0 g., a yield of 91%. The overall yield of the β isomer, calculated as the triol, was 22.9%, and of the a isomer, 0.5%.

(c) By the method of Swern, Billen, Findley and Scanlan (21)

(1) Hydrogen peroxide, 58.1 g. (30%, 0.502 moles), was added over a period of fifteen minutes to a mechanically stirred mixture of 70 g. of 3-cyclohexenol acetate (0.50 moles) and 150 ml. of formic acid (87%). The initial reaction was fairly exothermic, and the temperature was not allowed to rise above 55°. After two or three hours, external cooling was unnecessary, and the clear colorless solution was kept at 55° for a further sixteen hours.

At the end of this period, the preparation was brown in color and had deposited a small amount of dark resinous material. After the removal of solvents at 20 mm. pressure, the residue on vacuum distillation yielded a pale yellow oil, b.p. 120 - 135°/0.05 mm., weighing 53.2 g.

This product was heated under reflux with 100 ml. of water for one hour, and after cooling, the mixture was extracted with ether. During the heating, the waterinsoluble portion darkened considerably. The ether extract was set aside, but was not further examined. Water was distilled from the aqueous phase, and the light brown residue gave a very pale yellow gum, b.p. 130 - 133/0.05 mm., weighing 26.8 g., which deposited crystals slowly on standing. The saponification equivalent of this material was 389, indicating that most of the ester groups had been stripped off during the reaction or in the subsequent processing.

The remainder of the procedure employed in working up this mixture was identical with that outlined in section (b) above. A yield of 21.6 g. of triols (redistilled b.p. 125 - 130°/0.05 mm.) was obtained on complete saponification, and from this, 45.6 g. of β -pyrogallitol tribenzoate, m.p. 181.5 - 183°, and 2.5 g. of a-pyrogallitol tribenzoate, m.p. 139 - 140° were obtained. This corresponded to an overall yield of 20.0% for the β -isomer, and 1.1% for the a form. The yield of crude tribenzoates in this experiment was 55.0 g., or 55% of the theoretical amount.

(2) The following experiment is a duplicate of the one just described, but some of the methods employed in working up the reaction mixture were new and are therefore presented in detail. The quantities of reactants used were the same as before, but the reaction was permitted to continue for twenty-four hours at room temperature. At the end of this time, the solution was light yellow in color.

The solvents were distilled <u>in vacuo</u>, and the residue was dissolved in 150 ml. of ethanol and 25 ml. of water. Concentrated sulfuric acid, 3 ml., was added to the light brown solution, which was heated on the waterbath at $45 - 50^{\circ}$ for one and one-half hours. The solution was neutralized with sodium bicarbonate, filtered, and the solvents were distilled. The residue yielded a yellow gum, b.p. 120 - $135^{\circ}/0.02$ mm., weighing 36.3 g.

The mixture obtained after this gum was shaken mechanically with 100 ml. of ethyl acetate for one hour was filtered, and the white precipitate, weighing 18.6 g., melted at 107 - 115°. This solid was recrystallized five times, each time from a mixture consisting of 75 ml. of ethyl acetate and 15 ml. of absolute ethanol, and the m.p's after the successive recrystallizations were as follows: 118 - 123°, 121 - 123.5°, 122.5 - 124°, 124 - 125°, 124 - 125°. The final product, weighing 11.5 g., was pure β -pyrogallitol. These crystallizations occurred rapidly.

Further attempts to separate the two isomeric pyrogallitols in the mother liquors by crystallization from ethyl acetate were unsuccessful. All of the solutions were combined and evaporated to dryness. The yellow residues,

- 75 -

weighing 6.4 g., were dissolved in 50 ml. of pyridine and benzoylated with 21 ml. of benzoyl chloride (0.18 mole) according to the procedure of Shriner and Fuson (65). The yield of crude, slightly yellow product was 21.3 g., or 99% of the theoretical amount. This mixture of esters was separated in the manner already described, and yielded 17.4 g. of β -pyrogallitol tribenzoate, m.p. 181.5 - 183°, and 2.0 g. of a-pyrogallitol tribenzoate, m.p. 139 - 140°.

The solvent in the ethyl acetate solution (see above) was distilled, and the residue, distilled subsequently, yielded 17.5 g. of a yellow oil, b.p. 120 - 135°/ 0.15 mm., which did not crystallize. This oil was soluble in ethyl acetate, benzene, and ethanol, but was insoluble in water; with 2,4-dinitrophenylhydrazine, a bright red precipitate formed. This observation indicated that the oil contained a carbonyl group, but no further tests on this product were made.

The overall yield of the β -isomer, calculated as the triol, was 24.6% and of the a-isomer, 0.9%

Condensation of β - and δ -pyrogallitols with acetaone to give XXVII and XXX

(a) By the method of Newman and Renoll (39)

This experiment was carried out exactly as described previously for the condensation of <u>trans-1,2-cyclo-</u> hexanediol and acetone. In the case of δ -pyrogallitol, 5 g., (0.04 mole m.p. 147 - 148°) was used, and the other reagents were in the quantities employed previously (page 61). The triol dissolved completely after about fifteen hours, and the condensation was continued for two days in all. After neutralization and removal of solvents, the reaction mixture was extracted with benzene, the benzene was removed by distillation, and the acetal distilled at 113 - 115°/ 18 mm. The product was a clear colorless oil weighing 6.0 g. (92% of the theoretical amount).

β-Pyrogallitol, 4.2 g., (0.03 mole, m.p. 124-125°) was condensed with acetone according to the same procedure. Solution of the triol occurred within one hour, and the reaction was continued for a further twenty-nine hours. The mixture was then worked up in the usual way; when the solvents were distilled, the acetal crystallized completely. The crystalline mass was dissolved in 50 ml. of hot ethyl acetate, but crystallization of the solute did not occur. The ethyl acetate was evaporated, and the acetal was distilled. The product was a clear, colorless oil, b.p. 128 - 131°/19 mm., weighing 2.19 g., (53% of the theoretical amount).

(b) Using hydrochloric acid as catalyst

5-Pyrogallitol, 5 g., (0.04 mole, m.p. 147 - 148°), was condensed with acetone, 300 ml. (238 g., 4.1 moles), in the presence of dry hydrochloric acid gas, 1% by weight, and anhydrous sodium sulfate, 3 g. The reaction was carried out as described, with mechanical shaking for twenty-four hours, and the reaction mixture was worked up in the usual way (see page 64). The average yield of the acetal, obtained as a clear, colorless oil, was 69%, b.p. 111 - 114°/ 16 mm. Toward the end of the distillation white crystals, in the form of needles, appeared in the neck of the distilling flask. Probably these crystals were a small amount of the free triol, but this conjecture was not proven.

 β -Pyrogallitol, 5 g., (0.04 mole, m.p. 124 - 125°), was condensed with dry acetone, 200 ml., (158 g., 2.7 moles), in the presence of dry hydrochloric acid gas, 0.2% by weight, and anhydrous sodium sulfate, 3 g. The mixture was shaken for forty-two hours. The product was worked up as described (see page 64), and distilled at 130 - 132°/18 mm. The average yield of the acetal, obtained as a clear, colorless oil, was 71%. This oil was crystallized by dissolving it in petroleum ether (b.p. 30 - 60°), and cooling the solution below 0°. On recrystallization from the same solvent, there was obtained 2.9 g. (45%) of fine white needles, m.p. 50.2 -51°.

Calc'd	for	$C_{\bullet}H_{18}O_{s}$	•	C	62.76%	H	9.37%
Found			:	С	62.95%	H	9.51%

Both of these new compounds are soluble in benzene, acetone, methanol, ethanol, petroleum ether, and are practically insoluble in water.

- 78 -

The acetone compound of δ -pyrogallitol is unstable, and although several combustion analyses on this substance were attempted, closely checking results were never obtained, even though the sample was kept in a tightly stoppered container. The best analysis was the following:

Calc'd for C.H₁₆O₈ : C 62.76% H 9.37% Found : C 62.4% H 8.9%

A duplicate analysis on the same product, carried out immediately after the first analysis had been completed, yielded the following result:

с 61.3% н 10.2%

A sample of this compound was stored in a tightly stoppered flask for two weeks, and was then completely crystalline. This solid was recrystallized from acetone and from ethanol, and gave pure **6**-pyrogallitol, m.p. 147 -148°.

A solid sample of the β -pyrogallitol acetal deteriorated very slowly on standing in a tightly-stoppered test tube. After a few weeks, the pure acetal, which was originally quite white (m.p. 50.2 - 51°), became very light brown in color.

Attempted preparation of the benzoate esters of isopropylidene-β- and -Ö-pyrogallitol, XLVI and XLVII

The acetals employed, XXVII and XXX, were prepared using hydrochloric acid gas as the catalyst.

The acetal, 5.0 g. (0.03 mole), was dissolved in 15 ml. of chloroform and 15 ml. of pyridine, and benzoyl chloride, 5 ml. (6 g., 0.04 mole) was added to the solution. The mixture was allowed to stand at room temperature for twenty-four hours. Crystals occasionally deposited during this period, but these were not isolated. The addition of 10 ml. of hydrochloric acid caused two layers to separate, and when 30 ml. of acetone were added to the mixture these layers did not coalesce. This liquid mixture was heated gently under reflux for one-half hour, and the two phases did not unite under this treatment.

The mixture was neutralized with sodium bicarbonate solution, and approximately two-thirds of the solvents were distilled <u>in vacuo</u> (water pump). The residue was extracted three times with 50 ml. portions of benzene; the combined extracts were washed with water, and the benzene was evaporated. The oily residue crystallized, and was recrystallized several times from 40 or 50% aqueous ethanol. Although a high yield of the crude product, 7.4 g., (92% of theory) was obtained, large losses occurred in the recrystallizations. After three recrystallizations, the product obtained from the δ -pyrogallitol acetal consisted of white needles, 1.0 g., m.p., 72.7 - 73.7°. On being stored under ordinary conditions, this melting point changed to 71.5 - 76°. A small sample which was sublimed at 0.02 mm. had m.p. 72 - 75.5°, and the sample for analysis melted at 71.5 - 73.1°

Calc'd for $C_{16}H_{20}O_4$: C 69.52% H 7.31% Found : C 69.50% H 7.48%

The empirical formula $C_{16}H_{80}O_4$ corresponds to an isopropylidene-1,2,3-cyclohexanetriol monobenzoate.

After five recrystallizations from aqueous ethanol, the white product obtained when the β -pyrogallitol acetal was the starting material melted at 101.5 - 103.5°; the yield of this substance, in the form of rather broad needles, was 3.5 g., or 43% of the theoretical amount. For analysis, a small sample resublimed at 0.02 mm., m.p. 102.0 - 103.5° was prepared.

Calc'd for $C_{1eH_{20}O_4}$: C69.52%H7.31%Found: C69.21%H7.37%

Both of these substances were soluble in benzene, acetone, chloroform, alcohol, petroleum ether, and were insoluble in water.

Synthesis of the Monomethyl Ethers of β - and δ -Pyrogallitol, XXXI and XXXII

The isopropylidene acetal of each triol, prepared by both procedures outlined previously, was methylated by the Purdie method (66). A total of four methylations were therefore carried out. The reaction product was treated with acid under appropriate conditions to remove the acetone residue, and leave a monomethoxy cyclohexanediol. Only a single typical experiment is described in detail.

The isopropylidene acetal of the β - or **6**-pyrogallitol, 2.5 g., was dissolved in 20 g. of methyl iodide and 5 g. of freshly precipitated and dried silver oxide was added to the solution. These quantities corresponded to a large excess of the theoretical amount necessary for complete methylation of the acetal. The mixture was heated under very gentle reflux with stirring, for eight hours. At the end of this time, the mixture was extracted twice with hot methanol, and filtered. The yellow filtrate was acidified with 2 ml. of concentrated hydrochloric acid, and heated under reflux for one hour. The solution was cooled and neutralized carefully with basic lead carbonate. The precipitate was removed by filtration, washed with hot methanol, and solvents were distilled from the yellow filtrate. The brown residue was distilled at 0.02 mm. The average yield of crude product was 1.2 g., or 57% of the theoretical

amount.

The δ -pyrogallitol monomethyl ether was sublimed twice at 65°/0.02 mm., and was then recrystallized twice from petroleum ether, b.p. 60 - 70°. The products obtained from both methylations consisted of white needles, m.p. 69.5 - 71°; the average yield of this recrystallized material was 1.0 g. A mixed melting point of the two products was also 69.5 - 71°.

Calc'd for $C_7H_{14}O_3$: C 57.49% H 9.65% Found : C 57.79% H 9.38%

The β -pyrogallitol monomethyl ether did not crystallize on distillation. The clear, colorless oil, b.p. 66 - 67°/0.02 mm., analyzed as follows:

Calc'd for C₇H₁₄O₈ : C 57.49% H 9.65% Found : C 56.31% H 9.83%

This analysis indicated a slightly moist product, and when the ether was kept in a vacuum desiccator over phosphorous pentoxide, complete crystallization to a white solid occurred, and this was analyzed.

> Calc'd for C₇H₁₄O₈ : C 57.49% H 9.65% Found : C 57.10% H 9.58%

This solid was extremely hygroscopic. The m.p., taken in a highly evacuated pyrex tube of diameter 3 mm. was $36 - 37^{\circ}$ for the product prepared from β -isopropylidene pyrogallitol synthesized by the method of Newman and Renoll (39), and 35.5 - 37° for the sample prepared from β -isopropylidene pyrogallitol synthesized using hydrochloric acid as the catalyst. The mixed m.p. was 35.5 - 37°.

These compounds were soluble in water, alcohol, benzene and acetone. The δ -monomethyl ether was slightly soluble in petroleum ether, but the β -monomethyl ether absorbed moisture when shaken with this solvent and remained insoluble.

The δ -monomethyl ether, XXXII, and both samples of the β -monomethyl ether, XXXI, were oxidized with lead tetraacetate at 20.0°. The procedures employed in this kinetic study were the same as those adopted by Christian (1), except that only five ml. samples of the oxidation solution were withdrawn, and these were titrated with 0.008989 N instead of approximately 0.02 N sodium thiosulfate solution. In all three oxidations, the initial concentration of lead tetraacetate was 0.005705 moles/l. The results are shown in Table III, and are plotted in Figure 1.

Preliminary Experiments in the 1,2,4-Cyclohexanetriol Series

Synthesis of p-methoxy phenol, LXIII (with R. Y. Moir)



- 84 -

TABLE III

- 85 -

OXIDATION OF THE β - AND δ -PYROGALLITOL MONOMETHYL ETHERS WITH Pb(OAc) AT 20.0°

β-monomethyl ether^a, XXXI, 0.002347 moles/l. (plot 3, Fig. 1)

Time hrs.	ml. 0.008989 N Na _s SgO _s	Moles reacted per mole original glycol	$\frac{K \times 10^{3}}{1./mole/sec^{c}}.$	
0 0.33 0.75 1.50 2.72 4.00 6.11 11.0 23.0 50.0	6.35 5.95 5.63 5.18 4.71 4.48 4.34 4.00 3.90 3.68	0 0.153 0.276 0.448 0.628 0.716 0.770 0.900 0.939 1.02	- 25 22 22 21 19 15 14 8.3	
β-monomet	hyl ether ^b , XX	XI, 0.002437 moles	/1. (plot 2, Fig. 1)	
0 0.33 0.75 1.50 2.72 4.00 6.11 11.0 23.0 50.0	6.35 5.93 5.63 5.10 4.65 4.36 4.06 3.89 3.72 3.50	0 0.155 0.266 0.461 0.627 0.734 0.845 0.907 0.970 1.05	26 21 23 21 20 20 15 11	
8-monomet	hyl ether, XXX	II, 0.002703 moles	/1. (plot 1, Fig. 1)	
0 0.33 0.75 1.50 2.72 4.00 6.11 11.0 23.0 50.0	6.35 5.70 5.16 4.61 4.20 3.92 3.68 3.56 3.49 3.26	0 0.216 0.396 0.579 0.715 0.808 0.889 0.928 0.928 0.951 1.03	48 41 36 30 28 26 18 10	
a. prepa: thesis b. prepa:	red from the c zed according red from the c	orresponding isopr to the procedure of orresponding isopr	opylidene acetal, syn of Newman and Renoll (opylidene acetal, syn	39).
c. calcu	lated using hydr	e formula k = $\frac{2.30}{1000}$	$\frac{3}{b}\log \frac{b(a-x)}{a(b-x)}$, for a bi	-
molecub = instarts	ular reaction, nitial concent	where $a = initial$ ration of the ethe	r, and x has its usua	0Ac) ₄ , 1

This compound was prepared by methylating hydroquinone with dimethyl sulphate according to the procedure of Helfer (67). The yield of the light brown solid, m.p. 53.5 - 55° was 40% of theory; Helfer's yield was 55% of material melting at 53°. This product was suitable for hydrogenation.

Hydrogenation of p-methoxy phenol (with R. Y. Moir)

p-Methoxy phenol, 771.8 g., was hydrogenated with 100 g. of Raney Nickel catalyst, at 180 - 200°, with 2,800 pounds initial pressure of hydrogen. The gas uptake was extremely rapid, especially at the beginning of the reduction, and close to the theoretical amount of gas was absorbed. The product was filtered twice to separate the catalyst, and the nearly colorless liquid was distilled. The distillate, b.p. 85 - $120^{\circ}/7$ mm., was a slightly yellow oil, weight 665.7 g. (83%), and suitable for the next reaction.

Dehydration of 4-methoxycyclohexanol (68) (with R. Y. Moir)



4-Methoxy cyclohexanol, 603.6 g., was distilled in three runs, in the presence of 1 ml. of concentrated sulfuric acid and 1 ml. of water. Distillation occurred over the range 100 - 138°; the bath temperature was 205 -210°, except at the end of the reaction when it was permitted to rise to 225°. Water was separated from the distillate, and the wet residue was distilled through a Vigreux column. The following fractions were collected:

(1) B.p. up to 100°, weight 45.9 g., mainly cyclohexadienes. This fraction distilled with an equal volume, i.e., 45 ml., of water.

(2) B.p. 135.5 - 136.5°/760 mm., weight 257.0 g., pure
4-methoxy cyclohexene.

The residue in the distilling flask, a brown oil weighing 105 g., was again distilled in the presence of 1 ml. of concentrated sulfuric acid and 1 ml. of water. Fractionation of the product yielded 6.0 g. of a fraction corresponding to fraction 1 (see above) and 42.0 g. of 4methoxy cyclohexene. The residue from this distillation was not further examined. The total yield was 58% of theory.

This compound, LIII, has not been described in the literature. It is soluble in benzene, ethanol, acetone, and insoluble in water. The density d_{20}^{20} was 0.9025 and the refractive index n_D^{20} , 1.4566.

Calc'd for C₇H₁₈O : C 74.94% H 10.79% M.R. 33.39 Found : C 74.66% H 10.39% M.R. 33.80

This compound reacted with bromine in carbon tetrachloride instantaneously, and decolorized dilute potassium permanganate.

Hydrogenation of hydroquinone (with R. Y. Moir)

Hydroquinone, 525 g., was dissolved in ethanol (total volume of solution, 1100 ml.) and the solution was hydrogenated in the presence of 80 g. of Raney nickel catalyst. Hydrogen uptake occurred rapidly at 3,000 pounds pressure, at 170°. The solution obtained was filtered to separate the catalyst, and the solvent in the filtrate was removed by distillation. The residue boiled at 140 - 143°/ 8 mm., and crystallized at once to a white solid, a mixture of <u>cis-</u> and <u>trans-1,4-cyclohexanediols</u>. Yield, 527.5 g., or 96% of theory.



- 88 -

1,4-Cyclohexanediol, 527.5 g., was distilled in the presence of 1 ml. of concentrated sulfuric acid and 1 ml. of water over a period of two and one-half hours. The temperature of distillation was 100 - 155° and the bath temperature 190 - 220°. The water layer in the distillate was separated, and the oil was dried over anhydrous magnesium sulfate. On distillation of this oil through a Vigreux column at atmospheric pressure, three fractions were collected:

(a) B.p. up to 110°, weight 85.4 g., after some water had been separated.

(b) B.p., 110 - 154°, weight 22.5 g.

(c) B.p., 154 - 157°, weight 168 g.

The residue in the distilling flask, weighing 52.9 g., was discarded.

The three fractions were combined, kept over anhydrous magnesium sulfate for twenty-four hours, and redistilled, to give:

(a) B.p., up to 100°, 31 g. of an oil, and considerable water.

(b) B.p., 100 - 155°, 4.9 g. of an oil, slightly wet.

(c) B.p., 155 - 161°, 126.4 g. of an oil, slightly wet.

The large residues were strongly acid, and even the distillates were acid to indicator paper; it seemed evident

that further dehydration was occurring during the fractional distillation. Fraction (c) was allowed to stand over solid sodium bicarbonate over-night and was again fractionated. This distillation yielded 87.2 g. of 4-hydroxy cyclohexene, b.p. 164 - 165°, the same b.p. that is recorded in the literature (68). This yield was 19% of theory.

There is little doubt that much of the desired product was lost because the original distillate was not neutralized. The low boiling fractions, probably a mixture of cyclohexadienes, were combined and set aside.

Benzoylation of 4-hydroxy cyclohexene to give LIV

To a solution of 87.2 g. of 4-hydroxy cyclohexene (0.89 mole) in 200 ml. of pyridine and 350 ml. of chloroform was added slowly, with cooling, 128 g. of benzoyl chloride (0.91 mole). The clear, pale yellow solution was allowed to stand at room temperature for sixteen hours. The solution was washed with saturated aqueous sodium bicarbonate, and then with water. The solvents were distilled in vacuo, and the oil remaining was fractionated twice through a Vigreux column. The benzoyl ester of 4-hydroxy cyclohexene boiled at 149 - 150°/12 mm; yield, 172 g., or 96% of theory. This new compound is soluble in benzene, alcohol, acetone, chloroform and is insoluble in water; it decolorized bromine in carbon tetrachloride, and dilute aqueous potassium permangan-The density d_{20}^{20} was 1.085, and the refractive index ate.

 $n_{\rm D}^{20}$ 1.5360.

Calc'd for $C_{13}H_{14}O_{2}$: C77.18%H6.98%M.R.57.63Found: C77.25%H6.94%M.R.57.20

- 92 -

SUMMARY

1. Although the hydrogenation of pyrogallol over Raney nickel catalyst was known to give the acetone insoluble or <u>cis-cis-cis-</u> β pyrogallitol (1,2,3-cyclohexanetriol) in fair yield, only minor amounts of the acetone soluble β - (<u>cis-cis-trans</u>) and α - (<u>cis-trans-cis</u>) forms were produced. Their separation depended on the comparative insolubility of the β -tribenzoate in ethanol. The principal object of this research was to find better methods of obtaining and separating the inaccessible β and α isomers.

2. The syntheses commenced with the oxidation of cyclohexene to 3-cyclohexenol acetate with selenium dioxide or lead tetraacetate. The reaction of 3-cyclohexenol acetate with hydrogen peroxide in tert-butyl alcohol, acetic acid, and formic acid, with the appropriate catalyst when necessary, gave β -pyrogallitol in an average overall yield of 23%, but that of the a-isomer averaged only 1.2%. The synthesis, which involved the directed trans hydroxylation of the double bond in 3-cyclohexenol acetate, was considered successful only as far as the β -pyrogallitol was concerned.

3. Careful scrutiny showed that in the usual separation of the three isomeric pyrogallitols, small amounts of the acetone soluble β and α isomers were lost in the acetone insoluble fraction containing the δ isomer. The usual conditions of benzoylation often failed to give quantitative yields of the ethanol insoluble β -tribenzoate and the soluble α -tribenzoate. - 93 -

It was found, however, that much of the β -triol could be separated from a lesser amount of the α -isomer by fractional recrystallization from a mixture of ethyl acetate and ethanol.

4. p-Toluenesulfénic acid was more effective than hydrogen chloride (0.1 or 1% by weight) as a catalyst in the condensation of acetone with β - and δ -pyrogallitols. Isopropylidene**ö**-pyrogallitol was a very readily hydrolyzable oil, b.p. 113 -115°/18 mm., which yielded a crystalline monobenzoate, m.p. 71 - 76° and a monomethyl ether. Acid hydrolysis of the latter resulted in 3-cis-methoxy-cis-1,2-cyclohexanediol, m.p. 69.5 - 71°, whose structure followed from the fact that the adjacent glycol group it contained was readily oxidized by lead tetraacetate. In parallel work, isopropylidene- β pyrogallitol was found to be a crystalline solid, m.p. 50.2 -51°; the monobenzoate had m.p. 102 - 103.5°, and the monomethyl ether on acid hydrolysis yielded 3-trans-methoxy-cis-1,2cyclohexanediol as an exceedingly hygroscopic solid of m.p. 36 - 37°. As expected, the above new isopropylidene derivatives contained a five-membered ring derived from a cis-1,2glycol.

5. A crude mixture of the three pyrogallitols was condensed with acetone and the product was distilled in the hope of separating less volatile, unchanged a-pyrogallitol quantitatively from the more volatile isopropylidene derivatives of the β and isomers. The <u>cis-trans-cis</u>, or a isomer, however, also formed an isopropylidene derivative and the proposed separation was incomplete. Owing to lack of material, this derivative was not isolated. This unexpected condensation of acetone with either a <u>trans</u> 1,2 or a <u>cis</u> 1,3 glycol unit was supported by the preparation in 67% yield of a new isopropylidene-<u>trans</u>-1,2-cyclohexanediol, b.p. 77 -78°/20 mm., n_D^{20} 1.4468, using p-toluenesulfonic acid as the reaction catalyst.

6. Hydrogen peroxide in formic acid hydroxylated cyclohexene mainly to the <u>trans</u>-1,2 diol monoformate which was successfully converted to the known monobenzoate. Successful syntheses were also devised for 4-methoxy cyclohexene, b.p. 135.5 - 136.5°/760 mm., n_D^{20} 1.4566, and for the benzoate of 4-hydroxy cyclohexene, b.p. 149 - 150°/12 mm., n_D^{20} 1.5360. The availability of the latter substances opens a route to directed syntheses of the four isomeric 1,2,4-cyclohexanetriols.

CLAIMS TO ORIGINAL RESEARCH

1. A directed "trans" hydroxylation of 3-cyclohexenol acetate eventually gave a 23% overall yield of β -pyrogallitol, which therefore was rendered an accessible substance. The yield of the α -isomer, however, was only about 1% and was considered too small to be practical. A separation of much of the β isomer by fractional crystallization from ethyl acetate and ethanol was achieved for the first time. Certain defects in the earlier procedures for the separation of the α -, β -, and δ -pyrogallitols from mixtures of the three were demonstrated.

2. Cyclohexene was hydroxylated with hydrogen peroxide in formic acid to yield <u>trans-1,2-cyclohexanediol monoformate</u> as the main reaction product. The latter was converted into the known monobenzoate.

3. The following new compounds were prepared and characterized: isopropylidene-<u>trans</u>-1,2-cyclohexanediol; isopropylidene- β -pyrogallitol, and its monobenzoate; isopropylidene- δ -pyrogallitol, and its monobenzoate; 3-<u>trans</u>-methoxy-1,2-<u>cis</u>-cyclohexanediol; 3-<u>cis</u>-methoxy-1,2-<u>cis</u>-cyclohexanediol; 4-methoxy cyclohexene, (with R. Y. Moir); the benzoate of 4-hydroxy cyclohexene. Owing to lack of material, isopropylidene- α -pyrogallitol, whose existence was proven, was not characterized.

- 95 -

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