STUDIES IN THE POLYOXYPHENOL SERIES

V. PREPARATION FROM PYROGALLOL OF THE ISOMERIC CYCLOHEXANE-1,2,3-TRIOLS AND -1,2-DIOLS, AND OF SEVERAL ISOPROPYLIDENE AND MONOMETHYL DERIVATIVES¹

By W. R. Christian,² C. J. Gogek,³ and C. B. Purves

Abstract

A study of the high pressure hydrogenation of pyrogallol over nickel, copper – chromium oxide, and palladium catalysts showed that yields of 35% to about 60% of cis-cis-cyclohexane-1,2,3-triol were attainable, but that the cis-cistrans and cis-trans-cis isomers were formed only in minor amount. Partial hydrogenolysis of these primary products incidentally yielded some cis-cyclohexane-1,2-diol, a smaller amount of the trans form, but none of the 1,3-diols. The following derivatives were prepared apparently for the first time: *cis-cis*-isopropylidene-*cis*-cyclohexane-1,2,3-triol, an oil, and its monobenzoate, m.p. 103°C.; *cis-cis*-isopropylidene-*trans*-cyclohexane-1,2,3-triol, m.p. 51°C., and its monobenzoate, m.p. 72° to 76°C.; *cis*-monomethyl-*cis-cis*-cyclohexanetriol, m.p. 71°C., and its *bis*-3,5-dinitrobenzoate, m.p. 100°C.; *trans*-monomethyl-*cis*-*cis*-cyclohexanetric, and *i*-*cis*-*cis*-cyclohexanetriol, m.p. 71°C., and *i*-*cis*-*cis*-*cis*-*cis*-*cyclohexanetriol*, m.p. 71°C., and *i*-*cis*cis-cis-cyclohexane-1,2,3-triol, m.p. 37°C.; and isopropylidene-trans-cyclohexane-1,2-diol, an oil. Formation of the latter compound occurred when p-toluenesulphonic acid, and not the customary hydrogen chloride, was used as catalyst in the condensation of the trans diol with acetone.

Introduction

The high pressure hydrogenation of pyrogallol led Lindemann and de Lange (15) to the three isomeric cyclohexane-1,2,3-triols (Structures I. II, III) which were separated and characterized in a satisfactory way for the first time.



These authors realized that the *cis-cis-trans* isomer could be identified because it was the only one capable of being resolved into D and L forms, but their failure to establish this fact decisively made their allocations of structure doubtful. In 1944 McRae and Moir (17) reviewed the literature and arrived

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Contribution from the Division of Industrial and Cellulose Chemistry, McGill University, and the Pulp and Paper Research Institute of Canada, Montreal, Que. Abstracted from Ph.D. Theses submitted in September 1946 (W.R.C.) and in April 1947 (C.J.G.). ² Present address: Colgate-Palmolive-Peet Company, Jersey City, N.J.

Present address: Corn Products Refining Company, Argo, Ill. 3

at the correct allocations by applying modern theory to the published data. This review will be given in a forthcoming article. In 1947 Posternak and Ravenna (23) published the first direct experimental proof of the configurations and their work included a resolution of the *cis-cis-trans* raceme by microbiological methods. The object of the present work was to determine the yields, unreported by Lindemann and de Lange, of cyclohexanediols and -triols obtainable by hydrogenating pyrogallol, and to study the possibility of separating the triols by the selective formation of their cyclic isopropylidene acetals. Posternak and Ravenna sought in vain to prepare such derivatives. Their data on the relative rates with which lead tetraacetate and the periodate ion oxidized the three triols were also supplemented by larger-scale experiments, since these rates differentiated the *cis-cis-cis* from the *cis-trans-cis* form.

A series of comparable high pressure hydrogenations of pure pyrogallol in ethanol were carried out at $100^{\circ} \pm 3^{\circ}$ C. over Raney nickel instead of over the nickel-copper-cobalt catalyst used by Lindemann and de Lange (15). After various times aliquots of the filtered solutions were used to estimate unreacted pyrogallol. Destruction of the latter in the remainder of the products by air and alkali then left black liquors from which fractional distillation at 0.15 mm. pressure recovered the cyclohexanediols (b.p. 85° to 90°C.) and -triols (b.p. 119° to 123°c.). The yields were corrected for distillation losses but could not be regarded as precise. Fig. 1 (filled circles) shows that the maximum yield of cyclohexanetriols (42%) occurred after about 1.6 hr., or when about 70% of the pyrogallol had reacted. The formation of cyclohexanediols passed through a clearly marked induction period (open circles)



FIG. 1. High pressure hydrogenation of pyrogallol over Raney nickel at $100 \pm 3^{\circ}C$. to cyclohexane-1,2,3-triols and -1,2-diols.

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and the molar ratio of triols alone to diols *plus* triols, when plotted against the percentage of pyrogallol reacted, gave a nearly linear relationship (squares). A somewhat questionable extrapolation of this ratio suggested that its value was unity at zero time, or that diols were not then present. These observations made it extremely likely that pyrogallol was first reduced to the cyclohexane-triols, and that the latter then underwent hydrogenolysis of hydroxyl groups to yield the diols. More volatile fractions, not recovered quantitatively, contained cyclohexanol (triangles). The difficulty of hydrogenolysis was encountered in an acute form by Packendorff (22), whose platinum oxide catalyst gave cyclohexane and cyclohexanol as the main products from catechol, resorcinol, and pyrogallol.

In larger-scale preparations at 130° to 140°C. in a bigger autoclave, it was found convenient to isolate the crude cyclohexanetriols by first evaporating the alcohol from the filtered hydrogenated liquor, and then extracting products of hydrogenolysis and unchanged pyrogallol with ether from an aqueous solution of the residue. As Lindemann and de Lange (15) reported, dilution of the re-distilled product with acetone separated much of the *cis-cis-cis*cyclohexanetriol in crystalline form, and the pure *cis-cis-trans* and *cis-trans-cis* isomers could be isolated as crystalline tribenzoates from the mother liquors. Trial showed that these separations were not clean-cut and mother liquors had to be re-worked by benzoylation and debenzoylation in a very tedious manner. The final yields (Table I) were nevertheless sufficiently accurate

TABLE 1	E
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YIELDS OF THE CYCLOHEXANE-1,2,3-TRIOLS FROM HYDROGENATED PYROGALLOL*

		As tribenzoates		
Catalyst, 100–145°C.	<i>cis-cis-cis</i> M.p. 108°C. %	cis-cis-trans M.p. 184°C.	cis-trans-cis M.p. 142°C. %	
Raney Ni** Ni – Supercel*** Cu – Cr – O† Pd – SrCO3††	12-24 6.3 17 70-77	$0.3-60.86.8\sim 5^{\dagger}^{\dagger}^{\dagger}^{\dagger}$	0-1.1 0.7 3.2 0†††	

* Hydrogenated at 2400 to 3100 p.s.i. initial pressure until residual pyrogallol was 10 to 30%.

* Five runs using 25 to 316 gm. of pyrogallol at 100° to 140°C.

*** Used at 140°C

† Experiment at 140° to 145°C. by C. Gleason.

tt Experiment in pure 1,4-dioxane at 130° to 135°C. by J. F. C. Dixon.

††† Larger-scale separations by N. S. Whittall.

to confirm the fact that the hydrogenation of pyrogallol with nickel catalysts was a practical preparative method for *cis-cis-cis*-cyclohexanetriol. Such catalysts, however, were of doubtful utility for the other two isomers, which were recovered in improved, but still unsatisfactory, yields by hydrogenating over copper – chromium oxide. A new palladium-strontium carbonate catalyst (19) promoted comparatively little hydrogenolysis but the crude cyclohexanetriols consisted overwhelmingly of the *cis-cis-cis* isomer and none of the *cis-trans-cis* isomer was isolated from special larger scale experiments carried out recently in this laboratory by Mr. N. S. Whittall.

The preponderance of the *cis-cis-cis* form in all the hydrogenations studied could be accounted for by the "normal" or "one-sided" addition of hydrogen to pyrogallol molecules adsorbed plane to the flat surface of a crystalline catalyst (12). The occurrence of the *trans* forms, however, would seem to require either a multi-stage hydrogenation of the aromatic ring, or a keto-stage, or a thermal isomerization. Although such a thermal isomerization actually took place when *cis*-1,2-dimethyl cyclohexane was passed over nickel at 170°C. (18, 27), a keto-stage mechanism seemed more probable in the present case because Coussemant and Jungers (6) isolated up to 18% of cyclohexanone as an intermediate in the high pressure hydrogenation of phenol. The recovery of *cis-cis-cis*-cyclohexanetriol exclusively from the hydrogenation of optically active *cis*-2,3-dihydroxycyclohexanone over platinum oxide (23), however, raised an objection to this analogy.

On one occasion the entire cyclohexanediol fraction was found to reduce the amount of periodate calculated for the exclusive presence of 1,2-diols (see below). Cyclohexane-1,3-diols, which would be stable to periodate, were therefore present, if at all, in extremely small amount, as was expected from the known tendency for hydrogenolysis to eliminate hydroxy groups in a β , rather than an α , position to others (1, p. 69). The predominance of *cis*-1,2-diol over the *trans* form (mole ratio 2: 1) reflected the much greater amount of *cis*-cis triol initially produced by the hydrogenation.



FIG. 2. Rates of oxidation, in glacial acetic acid at $18.6^{\circ}C.$, of 0.0025 M solutions of the cyclohexane-1,2,3-triols and -1,2-diols; triols with 0.00665 M, and diols with 0.005 M, lead tetraacetate. Plot for the cis diol (not shown) was superposable on that for the cis-cis-cis triol. Similar oxidations of the monomethyl ethers at $20^{\circ}C.$

Criegee's (7) oxidations of the cyclohexanediols with lead tetraacetate at 18°C. proceeded with second order rate constants of $10^3 K = 80$ and 25 (liters/mole/sec.), respectively, for the cis and trans forms. A repetition of this work (Fig. 2 and Table II) gave a divergent result for the cis diol, but such rates were shown to be sensitive to small amounts of water in the lead

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Second	ORDER	RATE	CONSTANT	S FOR	OXIDATIONS	WITH
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	Pb(C	K104***		
Substance	$C \times 10^{3*}$	103 K**	10 ³ K**	
Cyclohexanediols cis	4.98	54 80†	1.5	
trans	5.00	27 25†	0.22	
Cyclohexanetriols cis-cis-cis	$3.30 \\ 6.63 \\ 13.1$	36 36 30	120	
cis-cis-trans	$3.30 \\ 6.63 \\ 13.1$	14 14 12	0.59	
cis-trans-cis	6.69	1.0	0.12	
3-Methoxycyclohexane-1,2,-diols†† cis-cis-cis	5.7	21		
cis-cis-trans	5.7	48-26		

Concentration C in mole per liter at 18.6°C. Glycol 0.003 M in all cases. Second order rate constant K in liter/mole/sec. A 0.004 M solution at pH 11.6 and 20.0°C.; glycol concentration 0.0025 M. Criegee's results as 18.0°C. (Ref. 7). ***

tŧ At 20°C. for 0.0024 M glycol solutions.

tetraacetate-acetic acid solution (8). The cis form was also oxidized much more rapidly than the trans form by aqueous sodium periodate at pH 11.6, as Price and Knell (24) had previously shown, although the figure they used to publish their data did not lend itself to a quantitative comparison with the present results (Fig. 3 and Table II). The oxidations of the cyclohexane-1,2,3-triols were carried out with the same experimental conditions and the *cis-cis-cis*, *cis-cis-trans*, and *cis-trans-cis* isomers reacted at diminishing rates, both with lead tetraacetate and sodium periodate, as expected from the work of Posternak and Ravenna (23). Although each mole of triol should in theory consume two moles of either oxidant and liberate one mole of formic acid, the utilization of the second mole was slow and the oxidations in their later stages failed to follow the second order rate constants noted in Table II. It is apparent from Fig. 3 that traces of the cis-cis-cis and cis-cis-trans forms could be removed from the *cis-trans-cis* triol by a selective oxidation with periodate, although no use was made of this observation in the present research.



FIG. 3. Rates of oxidation, by 0.004 M aqueous periodate at pH 11.6 and $20^{\circ}C$., of 0.003 M solutions of the cyclohexane-1,2,3-triols and -1,2-diols.

By condensing glycols, usually in presence of hydrogen chloride as a catalyst and anhydrous sodium sulphate as a dehydrating agent (Method B) Böeseken (3) established the generalization that cyclic isopropylidene derivatives would form only with 1,2-diols in which the contiguous hydroxy groups were in favorable proximity and in the same plane as the carbon atoms to which they were attached. This rule explained the existence of isopropylidene derivatives from cis-1,2,-cyclopentanediol and cis-1,2-cyclohexanediol, but not from the corresponding trans isomers. The cyclohexanediols were separated very efficiently on several occasions (2, 9, 26) by taking advantage of this circumstance. An attempt was made to apply the same principle of separation to a mixture of the cyclohexanetriols, but the condensation with acetone happened to be carried out with p-toluenesulphonic acid as catalyst and a continuous azeotropic distillation with ligroin as the means of dehydration (21) (Method A). Acid hydrolysis of the mixed isopropylidene derivatives, however, yielded a little *cis-trans-cis*-cyclohexanetriol and it was plain that this all-*trans* isomer had unexpectedly undergone the condensation. It then transpired that Method A readily produced a 67% yield of the hitherto unknown isopropylidene acetal from trans-cyclohexane-1,2-diol as an oil with a strong peppermint odor, whereas Method B yielded not more than 3%. The attempts of Maan (16) to obtain isopropylidene acetals from several substituted transcyclohexane-1,2-diols resulted in traces of volatile oils which were assumed, probably in error, to be condensation products of acetone itself. cis-cis-cis-Cyclohexanetriol, however, gave with both methods nonquantitative yields of uncrystallized, very readily hydrolyzed acetals (Ia, R = H) which were separately methylated with silver oxide and methyl iodide. Since some



hydrolysis of the labile acetal bonds probably occurred during this process, the crude monomethyl derivatives (Ia, $R = CH_3$) were straightway hydrolyzed with dilute acid, and yielded one and the same crystalline monomethyl cyclohexanetriol. The behavior of the *cis-cis-trans*-cyclohexanetriol was similar, although in this case the isopropylidene derivative (IIa, R = H) was crystalline and the crystalline monomethyl ether of the triol was distinguished by its great hygroscopicity. Both of the cyclohexanetriols yielded crystalline isopropylidene monobenzoates. The ready oxidation of the *cis-cis-cis* monoether with lead tetraacetate (Fig. 2) proved that it still contained an unsubstituted 1,2-glycol group and confirmed the structure (Ia, $R = CH_2$) assigned to its isopropylidene derivative. Moreover, since the glycol unit in this case was obviously *cis*, and since the oxidation proceeded almost as quickly with the monomethyl ether of *cis-cis-trans*-cyclohexanetriol (Table II, Fig. 2) the latter also retained the unsubstituted *cis*-1,2-glycol unit. This argument checked the validity of the structures (IIa).

It was, of course, recognized many years ago that an occasional *trans*-1,2-glycol, such as that from cycloheptane (4, 9), yielded an isopropylidene derivative when condensed with acetone according to the general method A. The present work shows that with *trans*-cyclohexanediol Method B succeeded and Method A failed, and that in consequence Böeseken's generalizations about the formation of isopropylidene derivatives may not apply with the same force when the method of condensation is radically changed.

Experimental

Hydrogenation of Pyrogallol With Raney Nickel Catalyst (20)

(a). The data summarized in Fig. 1 were based on uniform hydrogenations each employing 25.2 gm. of resublimed pyrogallol, 150 cc. of absolute ethanol and 5.0 gm. (wet with ethanol) of catalyst. A Parr high pressure hydrogenation apparatus with a 500 cc. stainless steel bomb was used. After flushing out the system several times with hydrogen, the pressure was adjusted to 2400 p.s.i., the bomb was rapidly heated to 100°C. and maintained within $\pm 3^{\circ}$ C. of that temperature. As the temperature reached 100°C, the shaking device was set in motion and hydrogenation was assumed to have begun at

that moment. After four hours or less, the bomb was rapidly quenched in cold water, the contents were filtered to remove the catalyst, and filtrate and washings were made up to 280 cc. with ethanol.

Gardner and Hodgson's method (11) was used to determine the unreduced pyrogallol in 0.1 cc. aliquots of the above solution. Each aliquot was added to 25 cc. of 0.1 N iodine – potassium iodide solution and strong caustic soda was then added drop by drop until the mixture just failed to give a blue color with a starch indicator. Thirty minutes later 100 cc. of water and 5 cc. of concentrated hydrochloric acid were added, and the liberated iodine was titrated with 0.1 N sodium thiosulphate. If the reagent blank was x cc., the titer of the original pyrogallol solution, y cc., and that of the solution after the hydrogenation, z cc., then the residual pyrogallol was 100 (x-z)/(x-y)%of the original amount. Control experiments showed that the estimation was reliable to $\pm 5\%$ even in the presence of ethanol, cyclohexanediols and triols, and the substances arising from the alkaline oxidation of pyrogallol (see below). The amount of iodine required by one mole of pyrogallol, however, was almost 5 moles; not 3 moles, as stated by Gardner and Hodgson, or 3.85 moles as calculated from the example they gave.

The remainder of the hydrogenation liquor was diluted with three 50 cc. volumes of strong aqueous ammonia, added over a period of five hours while oxygen gas was bubbled through the mixture to destroy any pyrogallol. Evaporation of solvents from the resulting black liquor, followed by fractional distillation at 15 mm. pressure, yielded the cyclohexanediol fraction, b.p. 85° to 90° C. and the triol fraction, b.p. 119° to 123° C. Both fractions gave a negative ferric chloride test for phenols. Trials with known mixtures showed that the loss of cyclohexanediols in the fractionation was about 2%, and that of the triols about 6%. The data in Fig. 1 were corrected accordingly.

(b). Hydrogenations on a larger scale (Table I) were carried out in a 2-liter Aminco stainless steel bomb and with a more convenient method of isolation. In a typical run, 316 gm. (2.5 moles) of pyrogallol dissolved in 1000 cc. of ethanol were hydrogenated over 50 gm. (wet) of Raney nickel for three hours at 140°C. and 3000 p.s.i. of hydrogen. The hydrogen absorbed was 8.5 moles, instead of the 7.5 moles required for a quantitative conversion to cyclohexane triols. After removal of the catalyst and the ethanol, distillation of the residue yielded 290 gm. of a clear, partly crystalline fraction boiling at 90°to 135°C. at 0.05 mm. pressure. A solution, 500 cc., of this product in water was then extracted continuously with ether to remove cyclohexanediols and also 30 gm. (10%) of unreduced pyrogallol. Evaporation and fractional distillation of the aqueous residue then yielded 90.7 gm. (33%) of cyclohexanetriols boiling at 120° to 140°C. at 0.02 mm. pressure.

With Copper – Chromium Oxide Catalyst (5)

The catalyst, 20 gm., was added to 63 gm. (0.05 mole) of pure pyrogallol dissolved in 200 cc. of pure 1,4-dioxane and hydrogenation was with 3100 p.s.i. of hydrogen at 140° to 145°C. for 150 min. Hydrogen absorbed was 1.68 moles,

or about 10% in excess of theory. The crude cyclohexanetriols, isolated as in (b) and weighing 20.2 gm. (30.6%) were separated as described below into the three isomers, all with correct melting and mixed melting points (Table I).

With a Palladium – Strontium Carbonate Catalyst

As the originators noted (19), this catalyst was very readily inactivated by adventitious impurities, which had to be rigorously eliminated from the reagents. Inactivation uniformly occurred in a 2-liter Aminco stainless steel bomb but not in one of 500 cc. capacity, even when the rates of heating were equalized and the same solutions and catalyst were used. The catalyst, 12 gm. containing 2% of palladium, 33.3 gm. of pyrogallol; 200 cc. of dioxane, and hydrogen initially at 2400 p.s.i. were kept at 75° to 80°C., little or no hydrogen being absorbed at a lower temperature. After two hours of hydrogenation the theoretical amount had been absorbed and the reaction apparently ceased. Much of the *cis-cis-cis*-cyclohexanetriol formed was found to have crystallized and concentration of the mother liquor raised the recovery to 17.6 gm. (50%). The residues when worked up as in (b) yielded a further 27% of the mixed *cis-cis-cis* and the *cis-cis-trans* isomers. In larger scale experiments the residual mixture was benzoylated, but extensive fractional crystallization of the tribenzoates revealed no trace of the *cis-trans-cis* form.

Separation of the Cyclohexanetriols

The method of Lindemann and de Lange (15) was followed in principle. A crude cyclohexanetriol fraction, 84 gm., b.p. 135° to 140°C. at 0.25 mm. pressure, was heated under reflux with 1400 cc. of acetone for 10 min. and the mixture was then kept at -15°C. Next day the undissolved portion (45.5 gm.) on recrystallization from an acetone-ethanol mixture yielded 31.7 gm. of the *cis-cis-cis* isomer with the correct melting point of 147° to 147.5°C. In other runs the recrystallizations were more advantageously carried out from ethyl acetate-acetone mixtures. Small amounts of the other two isomers were recovered as the tribenzoates from the final mother liquors.

The acetone-soluble portion, about 40 gm., after recovery was heated on the steam bath for one hour with benzoyl chloride, 110 cc., and pyridine 100 cc. Solution of the semisolid benzoates in 750 cc. of hot ethanol, followed by cooling overnight to room temperature, caused the deposition of the crude crystalline *cis-cis-trans* tribenzoate, which was extracted with 250 cc. of hot ethanol. The tribenzoate, 35.8 gm., was then nearly pure and was conveniently recrystallized to the proper melting point of 182°C. (uncorr.) from glacial acetic acid. The alcohol mother liquors from the crude tribenzoate were kept overnight at -15°C. to bring about the crystallization of the crude *cis-trans-cis* isomer (12.1 gm.). Two recrystallizations from methanol, preferably containing about 5% of water, yielded 5.4 gm. of this isomer with the correct melting point of 139° to 140°C. Mother liquors from all the above crystallizations were then combined, de-benzoylated, and recycled to yield a further 15.1 gm. of *cis-cis-cis*-cyclohexanetriol, 14.1 gm. of the *cis-cis-trans-* tribenzoate, and 0.8 gm. of the *cis-trans-cis*-tribenzoate. The final residues from another run were shown to contain a trace of *trans*-cyclohexanediol, which was isolated as the isopropylidene derivative.

The hydrolyses of the two tribenzoates with five volumes of 10% methanolic potassium hydroxide at 45° C. was allowed to continue for several hours after solution was complete, and the products were isolated as Lindemann and de Lange described. A yield of 78% of *cis-cis-trans-cyclohexanetriol*, with the correct melting point of 124° C. was obtained after recrystallization from ethyl acetate. The *cis-trans-cis* isomer (73% yield) melted at 110° to 110.5° C. after recrystallization from ethyl acetate, whereas the recorded m.p. was 108° C. Unlike the other two isomers, the *cis-trans-cis* form was noticeably hygroscopic.

Separation of cis and trans Cyclohexanediols

The crude diol fraction, melting at 76° to 85° C., when triturated with benzene left a residue of the crude *cis* isomer, which could be recrystallized to the proper m.p. of 99° C. from a hot solution of the same liquid. After recovery from the benzene mother liquors, the residue on recrystallization from a 1:2.5 acetone-ligroin mixture deposited the crude *trans* diol, which attained the correct m.p. of 103° to 104° C. when recrystallized from ethyl acetate. The identity of the *cis* and *trans* cyclohexanediols was confirmed by mixed melting points with authentic specimens obtained by oxidizing cyclohexene with potassium permanganate (16) and hydrogen peroxide (26) respectively.

A much more satisfactory method was to separate the *cis* as its more volatile isopropylidene derivative from the *trans* diol, according to the procedure of Rothstein (25). A 46.9 gm. sample of the mixed diols from a large-scale hydrogenation of pyrogallol yielded 39.9 gm. of isopropylidene *cis*-1,2-cyclohexanediol boiling at 70° to 71°C. (12 mm.), together with a still residue from which 13.8 gm. of pure *trans* diol was recovered by crystallization from hot benzene. Hydrolysis of the isopropylidene derivative by heating for two hours with 100 cc. of acetone and 10 cc. of concentrated hydrochloric acid gave 28.5 gm. of the *cis* diol, which was recrystallized from an acetone – petroleum ether mixture cooled to -15° C.

Condensations with Acetone

Method A

A 5 gm. to 7 gm. sample of the pure diol or triol was heated under reflux with about 0.1 gm. of p-toluenesulphonic acid monohydrate, 150 cc. of purified acetone and 150 cc. of petroleum ether (b.p. 30° to 60°C.). The apparatus, similar to that of Newman and Renoll (21), consisted of a 500 cc. roundbottomed flask attached by a glass joint to a condenser half-filled with water This condenser returned acetone vapor to the flask but permitted the water formed in the reaction to pass (as an azeotrope with petroleum ether) into a second, more efficiently cooled condenser and to be removed by a trap from the system. The condensation was judged to be complete when water ceased to accumulate in the trap. A small amount of anhydrous sodium acetate was added to the residual liquors to neutralize the sulphonic acid before they were evaporated under reduced pressure.

Method B

Five gm. of the diol or triol and 3 gm. of anhydrous sodium sulphate were mechanically shaken with 300 cc. of pure acetone containing 1% or less of dry hydrogen chloride (3), usually for 24 hr. The acid was neutralized with basic lead carbonate; the filtrate from this operation was made definitely alkaline with dry ammonia gas and was evaporated *in vacuo*.

cis-cis-Isopropylidene-cis-Cyclohexanetriol

Method A after two days of heating under reflux gave a still residue which was extracted with benzene. Fractional distillation of the extract returned a 92% yield of the product as a clear colorless oil boiling at 113° to 115°C. (18 mm. pressure). Method B using 1% hydrogen chloride gave a 69% yield (b.p. 111° to 114°C. at 16 mm.), but toward the end of the fractionation white crystals, presumably of regenerated triol, appeared in the neck of the distillation flask. The product from both preparations was soluble in common organic liquids but was practically insoluble in water. All attempts to crystallize the oil failed. Its instability was such that a sample kept for two weeks in a tightly stoppered flask had hydrolyzed completely to the cyclohexanetriol with the correct m.p. of 148°C. after recrystallization. Incipient decomposition was probably the cause of difficulties encountered in the combustion of the isopropylidene derivatives, the best of several results being C, 62.4; H, 8.9%. Calcd. for C₉H₁₆O₂: C, 62.8; H, 9.4%.

cis-cis-Isopropylidene-trans-Cyclohexanetriol

After 60 hr. of heating under reflux, the product from Method A was an oil boiling at 128° to 131°C. at 19 mm. pressure. The oil crystallized completely and recrystallization from ligroin left a 53% yield of fine white needles melting at 50° to 51°C., not depressed by admixture with the product from Method B (0.2% hydrogen chloride). This specimen was initially isolated in 70% yield but two recrystallizations from ligroin at less than 0°C. reduced the amount of pure material, m.p. 51°C., to 45%. Found: C, 63.0; H, 9.5%. Calcd. for C₉H₁₆O₃: C, 62.8; H, 9.4%.

The compound had the solubilities of the *cis* isomer but was much more stable, a sample stored in a tightly stoppered tube deteriorating only very slightly during several weeks.

Isopropylidene-trans-Cyclohexanediol

Method A and 60 hr. of heating yielded 67% of a colorless oil boiling at 77° to 78°C. at 20 mm. pressure, with a density, d_4^{20} , 0.9787 and a refractive index, n_D^{20} 1.4468. Found: C, 69.6; H, 10.3%; mol. refraction, 42.65. Calcd.

for $C_9H_{16}O_2$: C, 69.2; H, 10.3%; mol. refraction, 42.66. Unreacted *trans*-cyclohexanediol was recovered in 9% yield from a benzene extract of the still residue.

The isopropylidene derivative could not be induced to crystallize, had a strong peppermint odor, and was freely soluble in common organic liquids. A 1-gm. sample, when heated under reflux for one hour with 50 cc. of ethanol and 3 cc. of concentrated hydrochloric acid, gave 0.73 gm. (98%) of *trans*-cyclohexanediol with the proper melting point of 103° to 104°C., not depressed by admixture with an authentic specimen.

Method B with 0.1% hydrogen chloride and shaking for five days gave a product which was extracted with 100 cc. of low-boiling petroleum ether. Three recrystallizations of the residue from benzene recovered 54% of unchanged *trans* diol in a pure condition. The petroleum ether extract, when distilled at 23 mm. pressure, gave 3% of a colorless oil boiling at 76° to 78°C. and having the strong odor characteristic of the isopropylidene *trans* diol. Hydrolysis as described above removed the isopropylidene group and left 2.2% of the *trans* diol, whose purity and identity were confirmed by a mixed melting point. A similar condensation, employing 1% hydrogen chloride in acetone, yielded 11% of volatile material, from which only 0.7% of the original *trans* diol was recovered after acid hydrolysis.

cis-Monobenzoyl-cis-cis-Isopropylidene Cyclohexanetriol

A solution of the acetal, 5 gm., in 15 cc. of chloroform, 15 cc. of pyridine, and 5 cc. of benzoyl chloride was worked up by customary methods after standing at room temperature for 24 hr. After five recrystallizations from ethanol, the melting point of the 3.5 gm. of product (43%) became constant at 101.5° to 103.5°C. The portion analyzed was sublimed at 0.02 mm. pressure and then melted at 103.5°C. Found: C, 69.2; H, 7.4%. Calcd. for $C_{16}H_{20}O_4$: C, 69.5; H, 7.3%. The benzoate was soluble in common organic liquids but not in water.

trans-Monobenzoyl-cis-cis-Isopropylidene Cyclohexanetriol

A repetition of the above benzoylation with 5 gm. of the isomeric isopropylidene acetal yielded 7.4 gm. (92%) of crude product but large losses occurred during several recrystallizations from 50% aqueous ethanol. These recrystallizations yielded 1 gm. of white needles which failed to melt sharply, a typical observation being m.p. 71.5° to 76°C. Sublimation at 0.02 mm. pressure gave a sample with m.p. 72° to 75.5°C. Found: C, 69.5; H, 7.5%. Calcd. for $C_{16}H_{20}O_4$: C, 69.5; H, 7.3%. This monobenzoate, like its isomer, was soluble in organic liquids but not in water.

cis-Monomethyl-cis-cis-Cyclohexanetriol

A 2.5 gm. sample of *cis-cis*-isopropylidene-*cis*-cyclohexanetriol was dissolved in 20 gm. of methyl iodide and 5 gm. of freshly prepared, dry silver oxide was added. After being warmed under gentle reflux for eight hours, the mixture was extracted twice with hot methanol. Hydrolysis of the isopropylidene ether contained in the filtered extract was brought about by adding 2 cc. of concentrated hydrochloric acid and by heating under reflux for one hour. Neutralization, filtration, and evaporation left a brown residue that distilled at 0.02 mm. pressure. The distillate soon solidified. After sublimation at 65°C. and 0.02 mm. pressure and two recrystallizations from petroleum ether the average yield was 1.0 gm. or 47%. Specimens were prepared from isopropylidene derivatives made from the cyclohexanetriol by each of the Methods A and B. Each of these specimens melted at 69.5° to 71°C. and a mixed melting point was not depressed. Found: C, 57.8; H, 9.4%. Calcd. for C₇H₁₄O₃: C, 57.5; H, 9.7%. The monomethyl cyclohexanetriol was soluble in water, alcohol, benzene, and acetone but dissolved very sparingly in petroleum ether.

bis-(3,5-Dinitrobenzoate) of cis-Monomethyl-cis-cis-Cyclohexanetriol

The monomethyl ether, 0.752 gm., was heated under reflux with 3,5dinitrobenzoyl chloride, 0.752 gm., and pyridine, 3.5 cc., for 30 min. Recrystallization of the product from 30 cc. of ethanol and 20 cc. of ethyl acetate left 0.5 gm. of pure product, m.p. 190°C. Found: C, 46.9; H, 3.5; N, 10.6%. Calcd. for C₂₁H₁₈O₁₈N: C, 47.2; H, 3.4; N, 10.5%. An attempt to crystallize the corresponding dibenzoate failed.

This compound was prepared by R. Y. Moir and was analyzed by Marie A. Moir.

trans-Monomethyl-cis-cis-Cyclohexanetriol

The substance was prepared from the corresponding isopropylidene derivative, 2.5 gm., as already described for the *cis*-monomethyl isomer, and in 57% yield. The clear, colorless gum, distilled at 66° to 67° C. at 2 mm. pressure, crystallized completely as white needles when kept *in vacuo* over phosphorus pentoxide. Unlike the *cis* isomer, the present product was extremely hygroscopic and the melting point of 36° to 37° C. had to be taken in a highly evacuated Pyrex tube of 3 mm. diameter. No depression was observed in a mixed melting point of samples prepared from isopropylidene cyclohexanetriols made by Methods A and B. Found: C, 57.1; H, 9.6%. Calcd. for C₇H₁₄O₃: C, 57.5; H, 9.7%.

Determination of Rates of Oxidation

With Lead Tetraacetate

A stock 0.1 \dot{M} solution of the tetraacetate in redistilled, aldehyde-free glacial acetic acid was prepared and standardized iodometrically with 0.02 N sodium thiosulphate according to the directions of Hockett and McClenahan (13). The oxidations were carried out, exactly as described by these authors (14), with 100 cc. volumes 0.00025 M with respect to the diol or triol and about 0.005 M with respect to the lead tetraacetate. Blanks were run and temperature controlled to $18.6 \pm 0.5^{\circ}$ C. When a and b were the initial molar

concentrations of the tetraacetate and the glycol, the rate constant K for a second order reaction was given by

$$K = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

The data (Table II) fitted this equation up to consumptions of 0.89 and 0.22. 0.91, 0.91, and 0.15 moles of tetraacetate, respectively, per mole of cis and trans cyclohexanediol, cis-cis-cis, cis-cis-trans, and cis-trans-cis triol, the slower reactions not being followed to completion. The monoethers of the *cis-cis-cis* and *cis-cis-trans* triols consumed 0.94 and 0.97 moles of tetraacetate per mole in 23 hr. at $20 \pm 0.1^{\circ}$ C. and 1.02, 1.05 mole after 50 hr.

With Sodium Periodate

The procedure was adapted from the oxidations of the cyclohexanediols by Price and Knell (24). Twenty cubic centimeters of a stock 0.02 M solution of recrystallized periodic acid was mixed in a 100 cc. volumetric flask with 5.0 cc. of 0.045 N sodium hydroxide and 54 cc. of distilled water. At 18.6°C. and zero time, 20 cc. of an aqueous solution containing 0.00030 mole of the cyclohexanediol or -triol was added and the solution (pH 11.6) was made up to the mark with water and rapidly mixed. After various times, 10 cc. aliquots were titrated for remaining periodate by Fleury and Lange's sodium arsenite – iodine method (10). The data fitted the second order rate equation until the molar consumptions by the *cis* and *trans* diols, the *cis-cis-cis*, *cis-cis-cis*. trans, and cis-trans-cis triols were at least 0.63 and 0.24, 0.99, 0.41, and 0.51 moles of periodate, respectively.

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