Summary

The Fries reaction is discussed and an explanation of the mechanism is given based upon some experimental evidence. The reaction is shown not to be intramolecular. It has been applied to the production of some acyl salicylic esters and acids, many of which are new substances.

The alkyl salicylic acids are produced from the acyl salicylic acids by the Clemmensen reduction method. Although these acids show a higher toxicity than the parent substance, salicylic acid, they also possess by virtue of the alkyl group higher phenol coefficients.

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[CONTRIBUTION NO. 54 FROM THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, RESEARCH LABORATORY OF ORGANIC CHEMISTRY]

THE OXIDATION OF META-XYLORCINOL[1]

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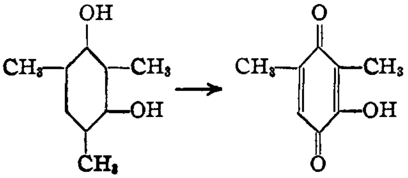
RECEIVED JULY 30, 1929 PUBLISHED JANUARY 8, 1930

When tribromoresorcinol is oxidized with aqueous chromic acid[2] it does not yield a *m*-quinone, but loses a bromine atom from the position para to one of the hydroxyl groups and yields oxidized and brominated substances which are derivatives of diphenoquinone. We have wished to determine whether a methyl group in the para position would be similarly lost, and have accordingly studied the oxidation of *m*-xylorcinol in which both positions para to hydroxyl are occupied by methyl groups. A similar substance has been studied by Knecht,[3] who found that the action of hot ferric chloride solution on mesorcinol removed a methyl group from the para position and produced a derivative of benzoquinone, thus



It is apparent from Knecht's result that one of the methyl groups is more easily removed by oxidation than is the hydrogen of one of the hydroxyl groups. When tribromoresorcinol is oxidized, the bromine in one of the para positions is similarly removed and one of the hydroxyl groups remains unaffected. *m*-Xylorcinol differs from mesorcinol in having a hydrogen instead of a methyl in the position between the two hydroxyl groups, and it is to be expected that this particular hydrogen atom would be oxi-

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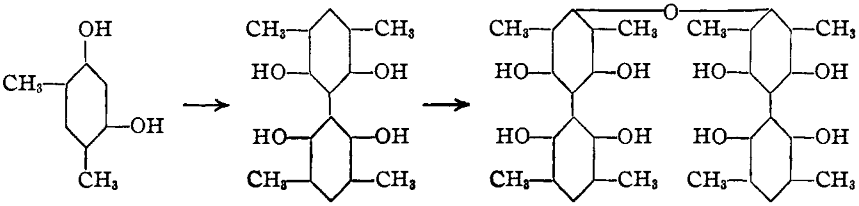
[1] A summary of the Doctor's Dissertation of Joseph Frederic Walker, Massachusetts Institute of Technology, June, 1929.

[2] Davis and Hill, THIS JOURNAL, **51**, 493 (1929).

[3] Knecht, *Ann.*, **215**, 96 (1882).

dized fairly easily, surely more easily than a methyl group. We find, in fact, that the methyl and hydroxyl groups of *m*-xylorcinol are not affected by dilute aqueous ferric chloride solution at laboratory temperature. One hydrogen atom, presumably the hydrogen which is present in *m*-xylorcinol but is lacking in mesorcinol, is, however, removed from the nucleus, and two nuclei combine to form di-*m*-xylorcinol. This product, soluble in water, is oxidized by the further action of ferric chloride to form an insoluble substance which appears to be di-(di-*m*-xylorcinol) ether.



m-Xylorcinol has been studied but little, probably because of the difficulty of its preparation. In the course of our work we have prepared from more than 2 kilos of *m*-xylene, a total of 15 g. of *m*-xylorcinol. We have checked the work of previous investigators and have substantiated the formula by determinations of molecular weight in benzene and in camphor. The substance is a vigorous reducing agent. If a 1% aqueous solution of *m*-xylorcinol is mixed with its own volume of 0.1 *N* silver nitrate, the liquid after about three minutes becomes colored from colloidal silver, and on longer standing deposits a silver mirror on the walls of the tube. Cresorcinol, in which there is a methyl group para to only one of the hydroxyl groups, under similar conditions shows no effect until about fifteen minutes have elapsed, and resorcinol itself shows none after twenty-four hours.

When a drop of ferric chloride solution is added to a dilute aqueous solution of *m*-xylorcinol a deep blue coloration is produced which disappears in a few minutes and leaves a pale green turbidity. On standing a voluminous greenish precipitate settles out. This behavior—similar to that observed by Dianin,[4] who reported that ferric chloride gave with solutions of α- and β-naphthol a color which vanished almost instantly with the appearance of a white precipitate—suggests that the hydrogen atom which is oxidized is that which occupies the position next to an hydroxyl group, or, in our case, between the hydroxyl groups, for Walder[5] and Fosse[6] later showed that the products from Dianin's experiments are dinaphthols in which the residues are linked through the position ortho to the hydroxyl group.

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[4] Dianin, *J. Russ. Phys.-Chem. Soc.*, **6,** 187 (1873).

[5] Walder, *Ber.*, **15,** 2166 (1882).

[6] Fosse, *Bull. soc. chim.*, [3] **21,** 650 (1899).

The first product of the oxidation is a crystalline substance, soluble in water, and was obtained by extracting the filtered liquid with ether, or in better yields by shaking an ether solution of *m*-xylorcinol with an aqueous solution of ferric chloride. It is dinuclear and forms a tetra-acetate. It dissolves readily in sodium hydroxide solution, but not in sodium bicarbonate, and it gives Liebermann's nitroso reaction for *m*-diphenols. It precipitates metallic silver from ammoniacal silver nitrate, and with ferric chloride it yields the insoluble material which we believe to be di-(di-*m*-xylorcinol) ether. When distilled with zinc dust it yields a substance which is probably dixylyl. When di-*m*-xylorcinol is heated for three minutes at 160° with phthalic anhydride and a drop of concd. sulfuric acid, it gives a melt which dissolves in alkali to form a practically colorless solution. We infer from this fact that it probably contains no hydrogen atom either ortho or para to an hydroxyl group, and hence that the two nuclei are probably linked through the position between the two hydroxyl groups.

m-Xylorcinol contains one hydrogen atom which is readily replaceable by bromine, but this same atom appears to be lacking from di-*m*-xylorcinol and is evidently the atom through the removal of which the two nuclei are joined. *m*-Xylorcinol brominates easily in chloroform solution to form the monobromo-*m*-xylorcinol which was described by Luther.[7] When this substance is heated gently with a trace of sulfuric acid, it evolves hydrogen bromide vigorously—a fact which suggests that the bromine atom is in a position ortho to an hydroxyl group. Di-*m*-xylorcinol reacts with bromine in boiling chloroform solution to yield colorless needles of a product which analyses and molecular weight determinations show to be not a simple bromine substitution product. The product dissolves slowly in caustic alkali and reprecipitates on acidification; the solution after acidification contains no ionized bromine. It does not give Liebermann's reaction for *m*-diphenols. It reduces ammoniacal silver nitrate slowly in the cold, and rapidly when the liquid is heated. Its analysis, etc., correspond, unexpectedly and unexplainably, to di-*m*-xylorcinol in which two of the hydroxyl groups have been replaced by bromine atoms. In confirmation of the belief that the hydroxyl groups are involved in the reaction with bromine, we find that the tetra-acetate of di-*m*-xylorcinol does not react when boiled with two molecules of bromine in chloroform solution.

When a drop of ferric bromide solution is added to a dilute aqueous solution of monobromo-*m*-xylorcinol, a momentary violet coloration is produced which is followed by a white turbidity. After a few minutes a white precipitate settles out. The appearance of the reaction suggests that the changes are analogous to those which occur with *m*-xylorcinol,

[7] Luther, *Arch. Pharm.*, **244,** 561 (1906).

but such is not the case. The crystalline product does not give Liebermann's reaction and does not yield an acetate by the usual procedure. It dissolves readily in dilute sodium hydroxide to form a solution which contains ionized bromine. It liberates a small amount of iodine from alcoholic potassium iodide to which a drop of hydrochloric acid has been added, and it reduces ammoniacal silver nitrate immediately in the cold. Analysis and molecular weight determinations show that it contains two bromine atoms, but it does not have the composition of dibromo-di-*m*-xylorcinol, and is not identical with the substance obtained by the action of bromine on di-*m*-xylorcinol.

Under the conditions in which *m*-xylorcinol is oxidized by ferric chloride to di-*m*-xylorcinol in maximum yield, cresorcinol yields no oxidation product and is recovered unchanged.

Experiments

Preparation of *m*-Xylorcinol.—*m*-Xylene was nitrated according to the method of Maltese and Errera[8] and the 4,6-dinitroxylene-1,3 was separated by fractional crystallization from alcohol as light yellow needles with a faint greenish glow, m. p. 93°. Maltese and Errera reported a yield of about one-third, but we were not able to obtain more than a 12% yield of the pure product. The other steps in the synthesis were slight modifications of the procedure originally employed by Pfaff.[9] Reduction in the usual way with hydrogen sulfide and alcoholic ammonia gave 4-nitro-6-aminoxylene-1,3, orange needles from alcohol, m. p. 122–123° (90%), and this by the diazo reaction gave 4-nitro-6-hydroxyxylene-1,3 as yellow needles from ligroin, m. p. 95° (65%). The nitrophenol was reduced with tin and hydrochloric acid and the 4-amino-6-hydroxyxylene-1,3 was isolated in the form of its hydrochloride (70%). In the diazo reaction for the replacement of the second amino group by hydroxyl it was found that the use of copper sulfate as a catalyst increased the yield from about 47 to 60%. The *m*-xylorcinol, obtained by extracting the boiled and filtered diazo solution with ether, decolorizing the product in water solution with decolorizing carbon and finally purifying by sublimation at 120° and 3 mm., consisted of colorless needles, m. p. 124.5–125.2°. The yields indicated above are the yields in our best experiments and correspond to an over-all yield of 2.95% of the theoretical amount of *m*-xylorcinol from *m*-xylene. When the product was heated at 160° for three minutes with phthalic anhydride and a drop of sulfuric acid, it gave a melt which dissolved in alkali to give a dark brown solution possessing a deep green fluorescence. A similar experiment without phthalic anhydride gave, contrary to the report of Pfaff, a faint mauve-colored solution which showed only a very slight fluorescence.

Molecular weight. Subs., 0.0866, 0.1922 g.; benzene, 17.27, 17.27 g.; ΔT, 0.099°, 0.215°. Calcd. for $C_8H_{10}O_2$: 138. Found: 135, 138. Subs., 0.0141 g.; camphor, 0.1158 g.; ΔT, 35.7°. Mol. wt. found: 136.

The Oxidation.—When ferric chloride was added to an aqueous solution of *m*-xylorcinol, a momentary blue color was followed by a turbidity which increased until a voluminous precipitate had settled out. The precipitate was very sparingly soluble in water, for a 0.01% solution of *m*-xylorcinol gave a distinct turbidity when a drop of ferric chloride was added, although the first blue color was not visible with so dilute

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[8] Maltese and Errera, *Gazz. chim. ital.*, II, **33,** 277 (1903).

[9] Pfaff, *Ber.*, **16,** 616, 1136 (1883).

a solution. The precipitate had an olive-green color, evidently due to accidental traces of iron. Two samples, thoroughly washed and dried, contained, respectively, 0.24 and 0.56% of iron. The compound which might be formed from one atom of iron and three molecules of *m*-xylorcinol would contain 12% of the metal. By repeatedly dissolving in benzene and precipitating with ligroin, the pure substance was obtained as a faintly yellow amorphous powder which contained no iron. The aqueous filtrate from the original precipitate reduced many times as much permanganate as corresponded to the total possible ferrous chloride, a fact which suggested that it contained either *m*-xylorcinol or some water-soluble oxidation product of that substance. Extraction with ether gave di-*m*-xylorcinol. When an aqueous solution of this substance was treated with ferric chloride, it yielded the familiar olive-green precipitate.

Experiments in which known amounts of *m*-xylorcinol were treated in aqueous solution at laboratory temperature with ferric chloride in slight excess showed that the first product of the oxidation, the water-soluble di-*m*-xylorcinol, was formed rapidly but oxidized slowly and gradually decreased in amount, while the amorphous insoluble product of the further oxidation increased in amount as the solution was allowed to stand. Titration of an aqueous solution of *m*-xylorcinol with standard ferric chloride solution, ammonium thiocyanate on a spot plate being used as an indicator, showed that the reaction took place in two stages. The ferric chloride was at first reduced almost instantly until a fairly sharp change of rate occurred, after which the reduction proceeded slowly until finally no more ferric chloride was reduced. A fairly good end-point could be measured for the first stage of the reaction and was found to correspond to one molecule of ferric chloride per molecule of *m*-xylorcinol, 0.533 g. of *m*-xylorcinol (0.0039 mole) consuming 23 cc. of 0.16 *M* ferric chloride solution (0.0037 mole). The end-point, however, did not represent an abrupt boundary between the two stages of the oxidation, for a small amount of precipitate had already formed and a corresponding small amount of *m*-xylorcinol evidently remained unoxidized.

Since di-*m*-xylorcinol, the first product of the oxidation, was found to be soluble in ether as well as in water, it was hoped that it might be obtained in better yield if the oxidation was carried out in the presence of ether, by which it would be taken up and removed from the influence of the oxidizing agent. The expectation was verified. Ether solutions of *m*-xylorcinol were shaken in the shaking machine with aqueous solutions of ferric chloride in large excess, and after a known time interval the ether phase was removed and worked up for di-*m*-xylorcinol. Results were as shown in Table I.

TABLE I

TWO-PHASE OXIDATION, EFFECT OF TIME AND CONCENTRATION

m-Xylorcinol, g.	Ether, cc.	Ferric chloride, cc. 1 *N*	Time, hours	Di-*m*-xylorcinol, weight per cent.
1.000	150	100	2	32.9
1.000	150	100	2.5	35.5
1.000	150	100	3	34.0
0.619	200	50	2	17.6
.619	200	50	6	30.2
.502	50	50	1	33.0

The first three experiments show that the yield of di-*m*-xylorcinol increases with increasing duration of shaking until it drops off again after a maximum has been reached. The series shows that the best yields are probably to be obtained by the long shaking of dilute solutions.

In one experiment 0.533 g. of *m*-xylorcinol yielded 0.200 g. of di-*m*-xylorcinol and 0.326 g. of the amorphous oxidation product, a total of 0.526 g. or very nearly the weight of the original material which was oxidized.

Di-*m*-xylorcinol.—The ether solution from the two-phase oxidation was evaporated just to dryness and the residue, recrystallized from benzene, yielded colorless needles of di-*m*-xylorcinol, m. p. 242–243° with slight decomposition. The first mother liquors contained traces of *m*-xylorcinol and a small quantity of the amorphous oxidation product. Di-*m*-xylorcinol is much less soluble in water than *m*-xylorcinol. It is practically insoluble in cold benzene, but about 0.93 g. dissolves in 100 cc. of the boiling solvent. Small quantities were sublimed unchanged both at reduced and at atmospheric pressure. When distilled with zinc dust it yielded a substance which had an odor resembling that of diphenyl, and melted at 81–94°, but was too small in amount for further examination. A chloroform solution of this material, which was evidently dixylyl, gave a violet coloration when poured upon a fresh sublimate of aluminum chloride.

Anal. Subs., 40.23, 40.95 mg.: CO_2, 104.19, 105.44 mg.; H_2O, 24.24, 24.43 mg. Calcd. for $C_{16}H_{18}O_4$: C, 70.04; H, 6.62. Found: C, 70.66, 70.24; H, 6.47, 6.68.

Molecular Weight. Subs., 0.0115, 0.0124 g.; camphor, 0.1045, 0.1161 g.; ΔT, 17.4°, 21.2°. Calcd. for $C_{16}H_{18}O_4$: 274. Found: 252, 249.

Di-*m*-xylorcinol tetra-acetate was prepared by refluxing di-*m*-xylorcinol with acetic anhydride and anhydrous sodium acetate, as colorless crystals from ligroin, m. p. 158–159°. It was not soluble in warm caustic soda solution, and was recovered unchanged after refluxing for several minutes with a chloroform solution of a large excess of bromine. It gave no color with ferric chloride solution.

Anal. Subs., 41.52, 33.18, 36.84 mg.: CO_2, 99.26, 79.38, 87.96 mg.; H_2O, 21.75, 17.52, mg. Calcd. for $C_{24}H_{26}O_8$: C, 64.99; H, 5.91. Found: C, 65.22, 65.27, 65.14; H, 5.86, 5.91.

Molecular Weight. Subs., 0.0241, 0.0211 g.; camphor, 0.1103, 0.0776 g.; ΔT, 20.7°, 24.5°. Calcd. for $C_{24}H_{26}O_8$: 443. Found: 421, 431.

The Amorphous Oxidation Product, Probably Di-(di-*m*-xylorcinol) Ether.—This substance was prepared by adding an excess of ferric chloride to an aqueous solution of *m*-xylorcinol and allowing it to stand until precipitation was complete. The greenish precipitate, after washing and drying, was purified by repeatedly dissolving in benzene and precipitating with ligroin, and yielded the pure material in the form of a pale yellow amorphous powder which charred gradually when heated above 250°. It dissolved readily in caustic alkali solution and was reprecipitated by acid. It reduced ammoniacal silver nitrate and did not liberate iodine from a solution of potassium iodide acidified with hydrochloric acid. It dissolved readily in benzene, chloroform, alcohol and ether, but was insoluble in cold ligroin and petroleum ether.

Anal. Subs., 38.81, 37.31 mg.: CO_2, 97.56, 93.64 mg.; H_2O, 20.87, 20.10 mg. Calcd. for $C_{32}H_{34}O_9$: C, 68.30; H, 6.09. Found: C, 68.58, 68.47; H, 6.02, 6.04.

Molecular Weight. Subs., 0.0186, 0.0109 g.; camphor, 0.1161, 0.0514 g.; ΔT, 12.6°, 16.0°. Calcd. for $C_{32}H_{34}O_9$: 563. Found: 505, 530.

Bromination of *m*-Xylorcinol.—Two grams of *m*-xylorcinol was dissolved in 100 cc. of chloroform, 2.32 g. of bromine in 40 cc. of chloroform added and the mixture refluxed for an hour, at the end of which time hydrogen bromide was no longer given off. The residue from the evaporation was purified by sublimation at 110° and 1 mm. and yielded pure monobromo-*m*-xylorcinol in almost theoretical amount as colorless needles, m. p. 119–119.5°. An excess of bromine was found to reduce the yield.

When bromine was added to a chloroform solution of monobromo-*m*-xylorcinol, hydrogen bromide was given off and a reddish-brown solution resulted which yielded a brown amorphous powder on evaporation. In one experiment, where a large excess of bromine was used, small dark blue crystals were deposited on the walls of the test-tube. These were too small in amount for further study but were notable because of their similarity in appearance to a substance which was produced by the action of an excess of bromine on di-*m*-xylorcinol.

Aqueous solutions of *m*-xylorcinol and of monobromo-*m*-xylorcinol both decolorized bromine water with the production of a white precipitate; both substances yielded the same products with an excess of bromine water. We have isolated three crystalline substances from the white precipitate, but all in insufficient quantity for analysis. They melted, respectively, at 71–72, 173 and 194°, and all decomposed above the melting point, giving off large quantities of gas in which bromine was detected by iodo–starch paper. The first, m. p. 71–72°, liberated iodine from acidified alcoholic potassium iodide; the others did not.

Oxidation of Monobromo-*m*-xylorcinol.—The white precipitate produced by the action of an excess of ferric bromide on an aqueous solution of monobromo-*m*-xylorcinol was found to contain an amorphous substance, m. p. 128–135°, and a crystalline material, insoluble in water, sparingly soluble in cold benzene but readily in hot, as small faintly yellowish needles which did not melt but charred gradually between 265 and 278°. The yield of the crystalline product was 26.2–26.5% of the weight of the original monobromo-*m*-xylorcinol.

Anal. Subs., 22.86, 25.12 mg.: CO_2, 41.43, 45.71 mg.; H_2O, 7.95, 8.57 mg. Subs., 18.98, 19.03 mg.: AgBr, 14.59, 14.50 mg. Found: C, 49.44, 49.64; H, 3.89, 3.82; Br, 32.40, 32.67.

Molecular Weight. Subs., 0.0135, 0.0139, 0.0078 g.; camphor, 0.1053, 0.0715, 0.0541 g.; ΔT, 9.6°, 16.1°, 11.6°. Found: 531, 480, 497.

If the substance contains one bromine atom, the molecular weight calculated from the found percentage of bromine would be 246; if two atoms of bromine, 492; if three, 738. We conclude then that it contains two bromine atoms, but the corresponding calculated empirical formula, $C_{20}H_{19}Br_2O_4$ (corresponding to carbon 49.70%, hydrogen 3.96%, bromine 33.08%, and molecular weight 483.1), does not appear to represent any probable oxidation product of monobromo-*m*-xylorcinol.

Bromination of Di-*m*-xylorcinol.—When di-*m*-xylorcinol was treated with two moles of bromine in chloroform solution, there was no apparent action at room temperature, but hydrogen bromide was given off on boiling and, after a few minutes, fine silky colorless crystals appeared in the liquid. The solution was chilled and the crystals removed. The chloroform mother liquors were reddish colored and on evaporation gave a small amount of dark blue crystals. The colorless needle crystals, recrystallized from benzene, melted with decomposition at 274–277° and amounted to 29–30% of the weight of the original di-*m*-xylorcinol. The simple introduction of two bromine atoms into di-*m*-xylorcinol would produce 161 weight per cent. of product. Analysis and molecular weight determinations gave results which correspond fairly closely to di-*m*-xylorcinol in which two of the hydroxyl groups have been replaced by bromine atoms.

Anal. Subs., 27.13, 23.29 mg.: CO_2, 46.96, 40.28 mg.; H_2O, 9.70, 7.06 mg. Subs., 18.65, 9.54 mg.: AgBr, 14.21, 8.66 mg. Calcd. for $C_{16}H_{16}O_2Br_2$: C, 48.01; H, 4.03; Br, 39.95. Found: C, 47.22, 47.18; H, 4.00, 3.39; Br, 39.25, 38.63.

Molecular Weight. Subs., 14.21, 10.96 mg.: camphor, 63.26, 63.21 mg.; ΔT, 20.8°, 17.7°. Calcd. for $C_{16}H_{16}O_2Br_2$: 400. Found: 429, 396.

Summary

m-Xylorcinol (4,6-dihydroxyxylene-1,3), when oxidized with ferric chloride in aqueous solution, first yields di-*m*-xylorcinol in which the two nuclei are evidently joined through the position between the hydroxyl groups.

The further action of ferric chloride converts di-*m*-xylorcinol into an

insoluble amorphous tetranuclear substance which is probably di-(di-*m*-xylorcinol) ether.

The action of bromine on *m*-xylorcinol, on monobromo-*m*-xylorcinol and on di-*m*-xylorcinol, and the oxidation of monobromo-*m*-xylorcinol by means of ferric bromide in aqueous solutions have also been investigated.

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[CONTRIBUTION NO. 186 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

SYNTHETIC GLYCERIDES. II. REFRACTIVE INDICES OF GLYCERIDES OF KNOWN CONSTITUTION

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RECEIVED JULY 31, 1929 PUBLISHED JANUARY 8, 1930

In a previous paper,[1] methods for the synthesis of symmetrical and unsymmetrical triglycerides containing two fatty acids were given in detail and data for their melting points were included. It was pointed out that the melting point of the symmetrical isomer in each of the sets of isomeric triglycerides made was slightly higher than that of the unsymmetrical isomer. In continuing a study of the relation between their molecular structure and physical properties, a study of the refractive indices of these isomers has been made.

Although the refractive index is one of the most widely used physical constants for the identification of natural glycerides (oils and fats), very little is known of the relation of this property to the constitution of the component glycerides. Furthermore, as stated by Myddleton and Barry,[2] "at present it is not known whether the refractive index of a mixed triglyceride is the same as the corresponding mixture of simple glycerides." In this paper data are also given for the comparison of three sets of isomers with equivalent mixtures of the corresponding simple triglycerides.

It was expected that any differences in the refractive indices of the isomers would be small. Apparatus was, therefore, devised by means of which a constant temperature could be held for a considerable length of time and which permitted the use of an immersion refractometer.

Apparatus.—The constant temperature bath was a round three-liter flask with the original neck shortened and three other necks, each one inch in diameter. These contained, respectively, the immersion refractometer, leads for the heating element, a standardized thermometer and a Liebig condenser.

A Zeiss immersion refractometer was used, fitted with an auxiliary prism and a metal beaker. The metal beaker made the enclosed sample air and water tight. As

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[1] H. P. Averill, J. N. Roche and C. G. King, THIS JOURNAL, **51**, 866 (1929).

[2] W. W. Myddleton and T. H. Barry, "Fats, Natural and Synthetic," Ernest Benn, Ltd., London, **1924**, p. 93.